Derek S. Wheeler
Hector R. Wong
Thomas P. Shanley
Editors

Pediatric Critical Care Medicine

Volume 2: Respiratory, Cardiovascular and Central Nervous Systems

Second Edition

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For Cathy, Ryan, Katie, Maggie, and Molly

"You don't choose your family. They are God's gift to you…"

Desmond Tutu

Foreword to the First Edition

The practitioner of *Pediatric Critical Care Medicine* should be facile with a broad scope of knowledge from human developmental biology, to pathophysiologic dysfunction of virtually every organ system, and to complex organizational management. The practitioner should select, synthesize and apply the information in a discriminative manner. And finally and most importantly, the practitioner should constantly "listen" to the patient and the responses to interventions in order to understand the basis for the disturbances that create life-threatening or severely debilitating conditions.

Whether learning the specialty as a trainee or growing as a practitioner, the pediatric intensivist must adopt the mantle of a perpetual student. Every professional colleague, specialist and generalist alike, provides new knowledge or fresh insight on familiar subjects. Every patient presents a new combination of challenges and a new volley of important questions to the receptive and inquiring mind.

A textbook of pediatric critical care fills special niches for the discipline and the student of the discipline. As an historical document, this compilation records the progress of the specialty. Future versions will undoubtedly show advances in the basic biology that are most important to bedside care. However, the prevalence and manifestation of disease invariably will shift, driven by epidemiologic forces, and genetic factors, improvements in care and, hopefully, by successful prevention of disease. Whether the specialty will remain as broadly comprehensive as is currently practiced is not clear, or whether sub-specialties such as cardiac- and neurointensive care will warrant separate study and practice remains to be determined.

As a repository of and reference for current knowledge, textbooks face increasing and imposing limitations compared with the dynamic and virtually limitless information gateway available through the internet. Nonetheless, a central standard serves as a defining anchor from which students and their teachers can begin with a common understanding and vocabulary and thereby support their mutual professional advancement. Moreover, it permits perspective, punctuation and guidance to be superimposed by a thoughtful expert who is familiar with the expanding mass of medical information.

Pediatric intensivists owe Drs. Wheeler, Wong, and Shanley a great debt for their work in authoring and editing this volume. Their effort was enormously ambitious, but matched to the discipline itself in depth, breadth, and vigor. The scientific basis of critical care is integrally woven with the details of bedside management throughout the work, providing both a satisfying rationale for current practice, as well as a clearer picture of where we can improve. The coverage of specialized areas such as intensive care of trauma victims and patients following congenital heart surgery make this a uniquely comprehensive text. The editors have assembled an outstanding collection of expert authors for this work. The large number of international contributors is striking, but speaks to the rapid growth of this specialty throughout the world.

We hope that this volume will achieve a wide readership, thereby enhancing the exchange of current scientific and managerial knowledge for the care of critically ill children, and stimulating the student to seek answers to fill our obvious gaps in understanding.

Chicago, IL, USA — Thomas P. Green
New Haven, CT, USA — George Lister

Preface to the Second Edition

The specialty of pediatric critical care medicine continues to grow and evolve! The modern PICU of today is vastly different, even compared to as recently as 5 years ago. Technological innovations in the way we approach the diagnosis and treatment of critically ill children have seemingly changed overnight in some cases. Efforts at prevention and improvements in care of patients prior to coming to the PICU have led to better outcomes from critical illness. The outcomes of conditions that were, even less than a decade ago, almost uniformly fatal have greatly improved. Advances in molecular biology have led to the era of personalized medicine – we can now individualize our treatment approach to the unique and specific needs of a patient. We now routinely rely on a vast array of condition-specific biomarkers to initiate and titrate therapy. Some of these advances in molecular biology have uncovered new diseases and conditions altogether! At the same time, pediatric critical care medicine has become more global. We are sharing our knowledge with the world community. Through our collective efforts, we are advancing the care of our patients. Pediatric critical care medicine will continue to grow and evolve – more technological advancements and scientific achievements will surely come in the future. We will become even more global in scope. However, the human element of what pediatric critical care providers do will never change. "For all of the science inherent in the specialty of pediatric critical care medicine, there is still art in providing comfort and solace to our patients and their families. No technology will ever replace the compassion in the touch of a hand or the soothing words of a calm and gentle voice [1]." I remain humbled by the gifts that I have received in my life. And I still remember the promise I made to myself so many years ago – the promise that I would dedicate the rest of my professional career to advancing the field of pediatric critical care medicine as payment for these gifts. It is my sincere hope that the second edition of this textbook will educate a whole new generation of critical care professionals, and in so-doing help me continue my promise.

Cincinnati, OH, USA — Derek S. Wheeler, MD, MMM

Reference

1. Wheeler DS. Care of the critically ill pediatric patient. Pediatr Clin North Am 2013; 60:xv–xvi. Copied with permission by Elsevier, Inc.

Preface to the First Edition

Promises to Keep

The field of critical care medicine is growing at a tremendous pace, and tremendous advances in the understanding of critical illness have been realized in the last decade. My family has directly benefited from some of the technological and scientific advances made in the care of critically ill children. My son Ryan was born during my third year of medical school. By some peculiar happenstance, I was nearing completion of a 4-week rotation in the Newborn Intensive Care Unit. The head of the Pediatrics clerkship was kind enough to let me have a few days off around the time of the delivery – my wife Cathy was 2 weeks past her due date and had been scheduled for elective induction. Ryan was delivered through thick meconium-stained amniotic fluid and developed breathing difficulty shortly after delivery. His breathing worsened over the next few hours, so he was placed on the ventilator. I will never forget the feelings of utter helplessness my wife and I felt as the NICU Transport Team wheeled Ryan away in the transport isolette. The transport physician, one of my supervising 3rd year pediatrics residents during my rotation the past month, told me that Ryan was more than likely going to require ECMO. I knew enough about ECMO at that time to know that I should be scared! The next 4 days were some of the most difficult moments I have ever experienced as a parent, watching the blood being pumped out of my tiny son's body through the membrane oxygenator and roller pump, slowly back into his body (Figs. 1 and 2). I remember the fear of each day when we would be told of the results of his daily head ultrasound, looking for evidence of intracranial hemorrhage, and then the relief when we were told that there was no bleeding. I remember the hope and excitement on the day Ryan came off ECMO, as well as the concern when he had to be sent home on supplemental oxygen. Today, Ryan is happy, healthy, and strong. We are thankful to all the doctors, nurses, respiratory therapists, and ECMO specialists who cared for Ryan and made him well. We still keep in touch with many of them. Without the technological



Fig. 1

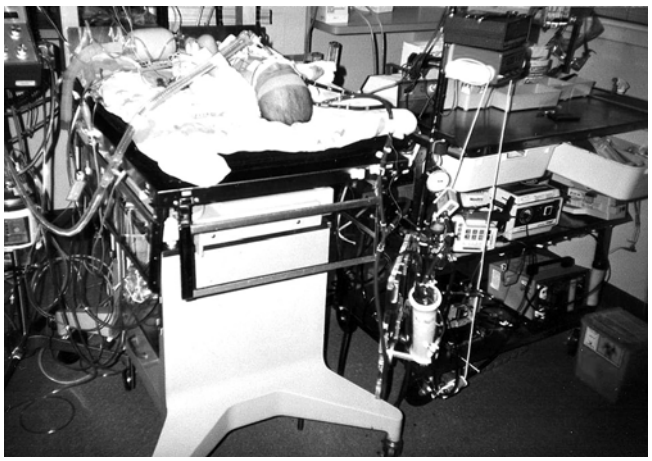


Fig. 2

advances and medical breakthroughs made in the fields of neonatal intensive care and pediatric critical care medicine, things very well could have been much different. I made a promise to myself long ago that I would dedicate the rest of my professional career to advancing the field of pediatric critical care medicine as payment for the gifts that we, my wife and I, have been truly blessed. It is my sincere hope that this textbook, which has truly been a labor of joy, will educate a whole new generation of critical care professionals, and in so-doing help make that first step towards keeping my promise.

Cincinnati, OH, USA Derek S. Wheeler, MD

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With any such undertaking, there are people along the way who, save for their dedication, inspiration, and assistance, a project such as this would never be completed. I am personally indebted to Michael D. Sova, our Developmental Editor, who has been a true blessing. He has kept this project going the entire way and has been an incredible help to me personally throughout the completion of this textbook. There were days when I thought that we would never finish – and he was always there to lift my spirits and keep me focused on the task at hand. I will be forever grateful to him. I am also grateful for the continued assistance of Grant Weston at Springer. Grant has been with me since the very beginning of the first edition of this textbook. He has been a tremendous advocate for our specialty, as well as a great mentor and friend. I would be remiss if I did not thank Brenda Robb for her clerical and administrative assistance during the completion of this project. Juggling my schedule and keeping me on time during this whole process was not easy! I have been extremely fortunate throughout my career to have had incredible mentors, including Jim Lemons, Brad Poss, Hector Wong, and Tom Shanley. All four are gifted and dedicated clinicians and remain passionate advocates for critically ill children, the specialties of neonatology and pediatric critical care medicine, and me! I want to personally thank both Hector and Tom for serving again as Associate Editors for the second edition of this textbook. Their guidance and advice has been immeasurable. I have been truly fortunate to work with an outstanding group of contributors. All of them are my colleagues and many have been my friends for several years. It goes without saying that writing textbook chapters is a difficult and arduous task that often comes without a lot of benefits. Their expertise and dedication to our specialty and to the care of critically ill children have made this project possible. The textbook you now hold in your hands is truly their gift to the future of our specialty. I would also like to acknowledge the spouses and families of our contributors – participating in a project such as this takes a lot of time and energy (most of which occurs outside of the hospital!). Last, but certainly not least, I would like to especially thank my family – my wife Cathy, who has been my best friend and companion, number one advocate, and sounding board for the last 22 years, as well as my four children – Ryan, Katie, Maggie, and Molly, to whom I dedicate this textbook and all that I do.

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Part I

The Respiratory System in Critical Illness and Injury

Applied Respiratory Physiology

1

J. Grant McFadyen, Douglas R. Thompson, and Lynn D. Martin

Abstract

Understanding and managing respiratory failure remains a cornerstone of critical care practice, as over half of all admissions to pediatric critical care units are related to respiratory issues. The unique aspects of a developing pulmonary system demand an in-depth knowledge of these changes and their impact on diagnostics and therapeutics. Only by understanding the normal function of the respiratory system is the critical care physician able to begin to formulate mechanisms for supporting a failing physiology.

In this chapter, we describe the developmental anatomy of the lung, with emphasis on the fact that the number of alveoli continues to increase long after birth. We describe the developmental mechanics of breathing, with particular reference to elastic properties of the lung and chest wall, compliance of the lung and chest wall, airway resistance, and lung volumes. Next, we describe the physiologic effects of mechanical ventilation. Factors that affect the maintenance of oxygenation are discussed, and the alveolar gas equation is introduced. We describe the maintenance of alveolar ventilation with a discussion of the included components of tidal volume, dead space and respiratory frequency. This knowledge is applied to a simplified model of the lung allowing an examination of the mechanics of ventilation. Using the single compartment model of the lung, the derivation of the equation of motion for the respiratory system and its implications for artificial mechanical ventilation are explored. Developmental anatomy and physiology of the pulmonary circulation is reviewed including physiologic and pharmacologic factors affecting pulmonary vascular pressures, resistances and the resultant changes in blood flow. A brief discussion of ventilation and perfusion relationships including the difference between shunt and venous admixture concludes this chapter.

Keywords

Mechanics of breathing • Alveolar gas equation • Equation of motion • Work of breathing • Ventilation perfusion relationships

Introduction

Understanding and managing respiratory failure remains a cornerstone of critical care practice, as over half of all admissions to pediatric critical care units are related to respiratory issues. The unique aspects of a developing pulmonary system demand an in-depth knowledge of these changes and their impact on diagnostics and therapeutics. Only by understanding the normal function of the respiratory system is the

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critical care physician able to begin to formulate mechanisms for supporting a failing physiology. This chapter will serve to introduce the developmental aspects of anatomy and physiology as they relate to the respiratory system, discuss pulmonary circulation and ventilation/perfusion inequality, and discuss the physiologic effects of mechanical ventilation.

Developmental Anatomy

During the embryonic period, the airways first appear as a ventral outpouching of the primitive foregut. The lung develops through five stages (Fig. 1.1), beginning with the embryonic stage in the 4th week during which the two main bronchi are formed. By the end of the pseudoglandular stage (week 16) all major conducting airways have formed, including the terminal bronchioles [1]. The canalicular stage is characterized by the development of respiratory bronchioles and the initiation of surfactant production [2]. During the saccular and alveolar stages the respiratory system continues to mature, with decreased interstitial tissue, thinning distal airway walls, the formation of alveoli and increasing surfactant production. The pulmonary vasculature develops in tandem with the airways, eventually resulting in the completion of the extensive pulmonary capillary network by the alveolar stage. Since the process of lung development is a continuum beginning early in embryonic life and progressing through to adolescence, factors that interfere with any of the phases of development may result in altered lung function and/or increased risk of disease in later life [3].

Close to term, the human fetal lung secretes approximately 0.5 L of fluid a day. The lung contains approximately 30 mL/kg of fetal lung liquid just prior to birth [4]. At birth, the lung epithelium switches from a secretory to absorptive epithelium. This switch involves increased expression of the epithelial sodium channel and of the sodium pump, and also changes in expression of lung aquaporins [5]. At birth, most of the lung fluid is expelled mechanically, but some will remain to be absorbed during the first postnatal days. In premature infants this ability of lung to reabsorb water is often impaired.

Over the remainder of childhood, the lung will continue to grow and mature and the 20 million alveolar saccules present at birth [6], will increase to 300 million alveoli by 8 years of age [7]. The increase in alveoli parallels the increase in alveolar surface area from 2.8 m^2 at birth, to 32 m^2 at 8 years of age, and 75 m^2 by adulthood [7]. Alveolar

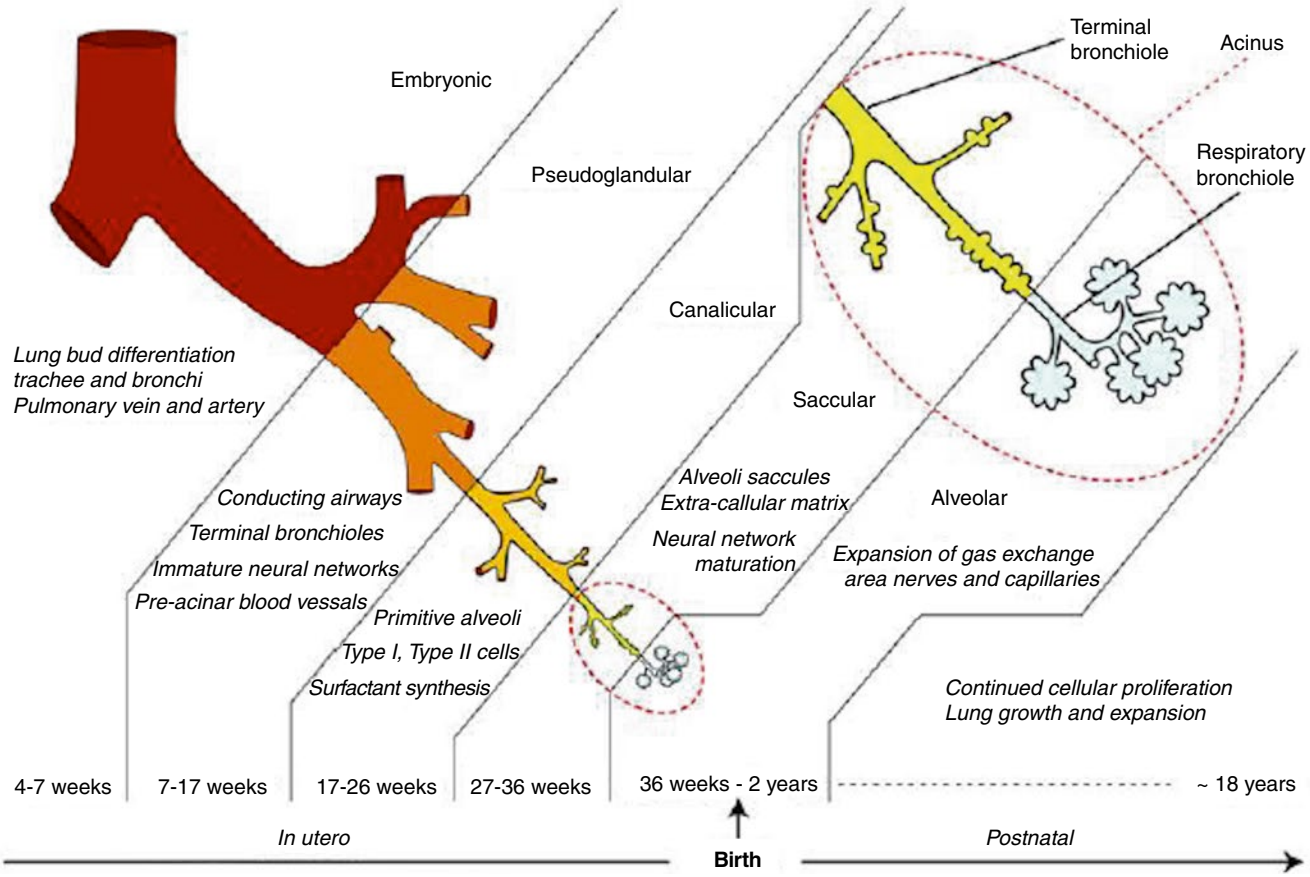


Fig. 1.1 Stages of lung development (Reprinted from Kajekar [3]. With permission from Elsevier)

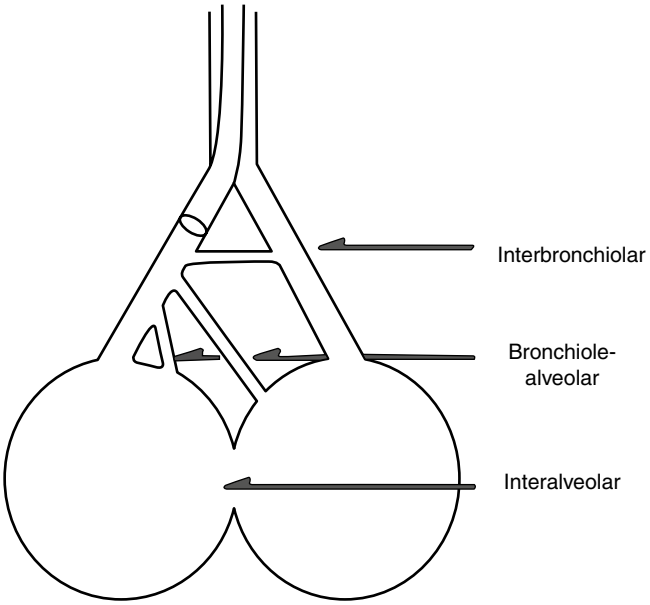


Fig. 1.2 The various pathways for collateral ventilation (Reprinted from Menkes [50]. With permission of the American Thoracic Society. Copyright © 2012 American Thoracic Society. Official journal of the American Thoracic Society)

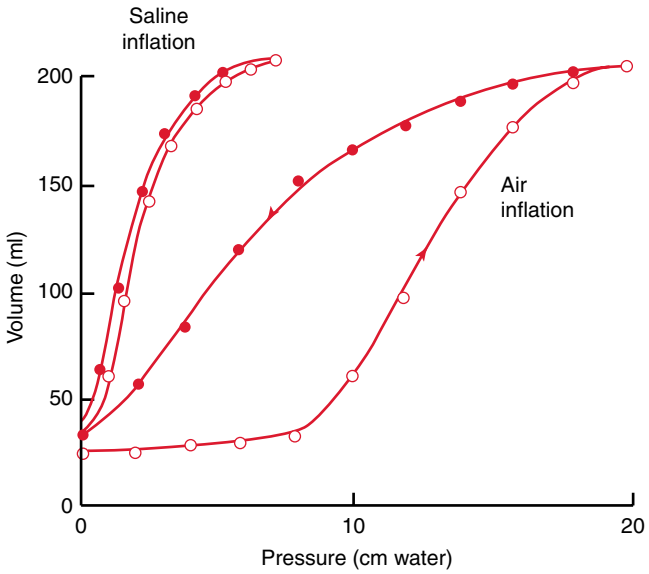


Fig. 1.3 Pressure-volume curves of air and saline. *Open circles* represent inflation and *closed circles* represent deflation. The compliance of the saline filled lung is greater than the air filled lung (Reprinted from West [14], p. 84. With permission from Wolters Kluwers Health)

multiplication appears to be the major mechanism for lung growth, although some growth has also been attributed to the growth of individual alveoli.

The adult lung contains anatomic channels that permit ventilation distal to an area of obstruction (Fig. 1.2). Two channels have been identified in normal human lungs: interalveolar (pores of Kohn) and bronchioalveolar (Lambert's channels). Inter-bronchiolar channels are not found in healthy lungs, but develop during disease processes. Pores of Kohn appear as holes in alveolar walls in the first and second year of life [8]. Lambert's channels are found after 6 years of age [9]. The absence of these collateral pathways places infants and children at risk for the development of atelectasis and resulting ventilation/perfusion inequality [10].

Developmental Mechanics of Breathing

Elastic Properties of the Lung and Chest Wall

The lung is an elastic structure and has a natural tendency to decrease its size. The chest wall, which, in contrast to the lung, pulls outward at low volumes and inward at high volumes, counteracts this tendency [11]. Lung recoil has been shown to increase with age in children over 6 years of age [12] and may relate to elastin deposition [13]. The presence of an air-liquid interface increases the elastic recoil of the lung, due to surface tension. Surface tension is the force that acts across the surface of a liquid, since the attractive forces between liquid molecules are stronger than the forces between liquid and gas molecules [14]. In early surface tension experiments in the 1920s, Von Neergaard demonstrated that saline filled lung units, in which the surface tension forces had been abolished, were far more compliant than air filled lung units (Fig. 1.3). It is likely that the decrease in surface tension forces resulted in a reduction in lung elastic recoil [14]. Surfactant, a phospholipid-protein complex, has been shown to lower surface tension profoundly. The intermolecular repulsive forces oppose the normal attractive forces and this effect is amplified at lower lung volumes, with compression of the surfactant complex. Traditional understanding of surface tension notes the significant role that surfactant plays in lung stabilization in accordance with the law of Laplace, stating that the pressure across a surface (P) is equal to 2 times the surface tension (T) divided the radius (r):

$$P = 2T / r$$

However, this probably does not explain lung stabilization in its entirety. The interdependence model of the lung, in which lung units share planar rather than spherical walls, gives credence to tissue forces playing a role (Fig. 1.4). In all likelihood, lung stability results from a combination of these two forces.

Compliance of the Lung and Chest Wall

The pressure-volume curve of the air-filled lung is depicted in Fig. 1.3. The slope of the curve, volume (V) change per

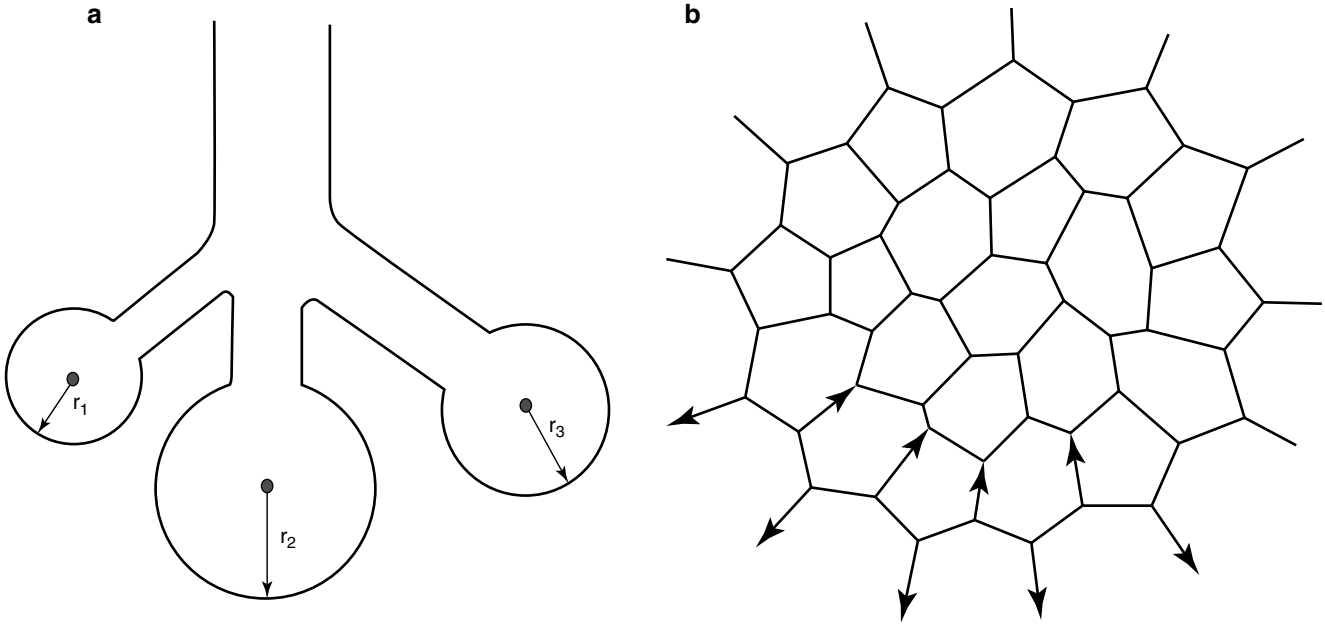


Fig. 1.4 (**a**) Classic model of the distal lung, in which individual alveoli are controlled by Laplace's law. Small alveoli would empty into large alveoli. (**b**) Interdependence model of the lung, in which alveoli share common planar and not spherical walls. Any decrease in the size of one alveolus would be stabilized by the adjacent alveoli (Reprinted from Weibel [51]. With permission from The American Physiological Society)

unit pressure (P), is equal to the compliance (C) of the lung ($C = \Delta V/\Delta P$). Normally the lung is quite compliant. However, at the extremes of lung inflation and deflation, as seen from the graph, that compliance is reduced. Lung compliance depends both on the elasticity of the tissue and the original lung volume before inflation, as much larger pressures are needed to inflate lungs from lower lung volumes. Compliance measured at zero airflow is termed static compliance. Lung compliance may also be measured during slow breathing; this value is termed dynamic compliance. Dynamic compliance also reflects the intrinsic elastic properties of the lung, though it is influenced by the respiratory rate and level of airway resistance [15].

$$C_{static} = \frac{\text{Tidal Volume}(\text{corrected})}{\text{Plateau Pressure} - \text{Positive End Expiratory Pressure}}$$

$$C_{dynamic} = \frac{\text{Tidal Volume}(\text{corrected})}{\text{Peak Inspiratory Pressure} - \text{Positive End Expiratory Pressure}}$$

The compliance of the respiratory system depends both on the compliance of the lung as well as the compliance of the chest wall. During the first year of life, the compliance of the respiratory system (C_T) increases by as much as 150 % [16]. The increase in lung compliance is responsible for the majority of the gain, outstripping the decrease in chest wall compliance. The compliance of the chest wall (C_{CW}) is measured by examining the difference between the esophageal/pleural pressure (P_{PL}) and atmospheric pressure (P_A) per change in volume ($C_{CW} = V/([P_A - P_{PL}])$). The infant chest wall is remarkably compliant and chest wall compliance decreases with increasing age. The elastic recoil of an infant's chest wall is close to zero and with age it increases due to the progressive ossification of the rib cage and increased intercostal muscle tone [17]. In addition, the moving of the abdominal compartment caudally with the attainment of an upright posture has also been theorized to play a role in increasing outward recoil of the adult chest. The decreased recoil of the infant chest wall increases the possibility of lung collapse in the setting of lung disease. The excessive compliance of the infant chest wall requires the infant to perform more work than an adult to move a proportionally similar tidal volume. During an episode of respiratory distress an infant will develop severe chest wall retractions during its efforts to maintain ventilation and oxygenation. However, a significant portion of the energy generated is wasted through the distortion of the highly compliant rib cage during negative pressure generation from diaphragmatic contraction [18]. It has been observed that some infants will stop breathing from fatigue when faced with excessive respiratory demands. This clinical impression of diaphragmatic fatigue and failure has been confirmed through electromyographic measurements of the diaphragms of fatiguing infants who become apneic in the face of increased work of breathing [19].

Airway Resistance

In order for air to move in and out of the lungs, gas must flow from an area of higher pressure to one of lower pressure. According to Ohm's law, the pressure gradient (P) that faces a substance (gas or liquid) is equal to the product of the flow rate (V) times the resistance to flow (R). ($P = V \times R$). The components of pulmonary resistance to gas flow include: (i) the inertia of the respiratory system (effectively negligible); (ii) the frictional resistance of the chest wall tissue (negligible); (iii) the frictional resistance of the lung tissue (20 % of pulmonary resistance); and (iv) the frictional resistance of the airways to the flow of air (majority of pulmonary resistance) [20].

The extent of the pressure drop and its relationship to the airflow rate depend on the pattern of flow, either laminar or turbulent. In laminar flow, air travels down a tube in parallel to the side of the tube; however, when variation in the flow rate develops due to a sudden rise in gas flow rate, a narrowing of the tube or the encountering of an acute angle, the flow becomes turbulent. Laminar flow of air is governed by the Hagen-Poiseuille law (also known as Poiseuille's law), where $P = (V)\ (8l\eta/\pi r^4)$; in this equation, l is the length of the tube, r is the radius of the tube and η is the viscosity of the gas. Through rearranging the terms, it can be noted that resistance is mostly determined by the radius of the tube, in that $R = P/V = 8l\eta/\pi r^4$. Turbulent flow has different properties to laminar flow, as it is proportional to the square of the flow rate: $P = KV^2$ and becomes more dependent on the gas density instead of the viscosity [21]. Clinical attempts to exploit the properties of turbulent gas flow have been made in the patients with both upper and lower airway obstruction (i.e., croup and asthma). In both of these settings, the introduction of helium-oxygen admixtures is an attempt to introduce helium, a gas with a lower density than oxygen, in order to promote airflow in turbulent airways.

The main site of airway resistance in the adult is the upper airway; however, it has been shown that peripheral airway resistance in children under 5 years of age is four times higher than in adults [22]. This may explain the high incidence of lower airway obstructive disease in infants and young children, especially when considering Poiseuille's law and the dramatic increase in resistance that is seen with only a small amount of airway obstruction. Within the bronchial tree, direct measurements of the pressure drop have found that the major site of resistance is the medium-sized bronchi and that little of the total resistance to airflow is determined by the smaller airways. The resistance of these bronchi is determined by the presence of exogenous materials, autonomic regulation of bronchial smooth muscle, and lung volume. As lung volume increases, radial traction is imparted to the surrounding lung tissue, which increases the intraluminal caliber of these bronchi and reduces their resistance (Fig. 1.5) [23].

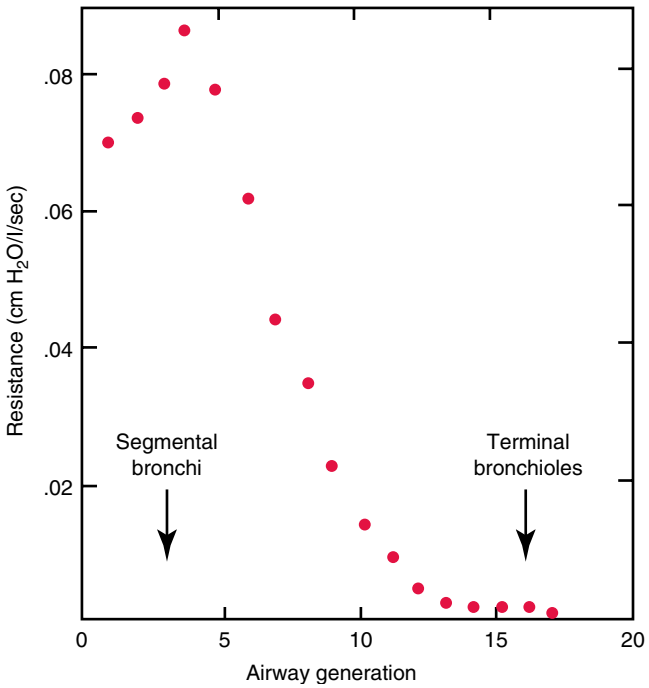


Fig. 1.5 The relationship of airway resistance (AWR) with lung volume. Conductance, the reciprocal of AWR, is a straight line (Reprinted from West [14], p. 84. With permission from Wolters Kluwers Health)

During illness, airway resistance can be increased from either intraluminal obstruction or extrinsic compression. Extrinsic compression can occur from a variety of etiologies, including the occurrence of airway collapse during forced expiration, secondary to dynamic compression of the airway. During normal exhalation there is a pressure drop from the alveolus to the mouth, which allows for air flow. A continued favorable transmural pressure gradient and cartilaginous support maintain airway patency (transmural pressure gradient = intraluminal pressure − pleural pressure). On the contrary, during a forced expiration maneuver, the pleural pressure raises significantly, decreasing the transmural pressure gradient, causing the airway caliber to narrow. At some location along the airway during the forced expiration maneuver, the intraluminal pressure will equal the intrapleural pressure. This is termed the equal pressure point (EPP). Beyond this point, forces favoring airway collapse exceed those favoring patency (tethering action of lung tissue and rigid cartilage), resulting in airway collapse [24]. In the presence of bronchopulmonary dysplasia, bronchomalacia and tracheomalacia, these mechanisms are amplified, leading to earlier symptoms of airway collapse [25].

Lung Volumes

An understanding of static lung volumes and the developmental impacts are critical to evaluating and subsequently

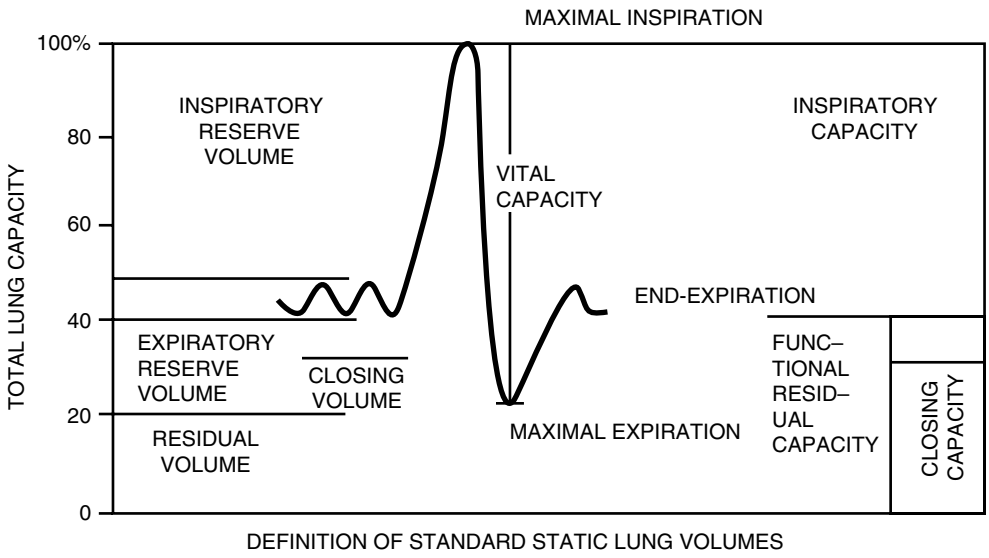


Fig. 1.6 Typical spirometric tracing that depicts tidal breathing followed by a maximal inspiration and then a maximal expiration. Five volumes and five capacities are shown (Reprinted from Smith and Nelson [52]. With permission from Charles C. Thomas Publishers, Ltd)

treating infants and children with respiratory disease. Volumes and capacities of the lungs are affected by several factors, specifically muscle strength, static-elastic characteristics of the chest wall and lungs, and patient age [26]. A traditional spirometric tracing is shown in Fig. 1.6, depicting tidal breathing followed by maximal inspiratory and expiratory efforts. There are five lung volumes depicted on the figure. Tidal volume is defined as the amount of gas moved during normal breathing and residual volume is defined as the amount of gas that remains in the lung after a maximal expiration. Four capacities, which are composed of multiple volumes, are also shown on the figure. Vital capacity is defined as the volume of gas that may be exhaled from the lung following a maximal inspiration. Functional residual capacity (FRC) is defined as the gas that remains in the lung at the end of a tidal breath. This gas serves as a reservoir of oxygen during expiration and accordingly is a very important construct in the understanding of respiratory pathophysiology and will now be considered at length.

FRC in a normal lung is the same as the end expiratory lung volume (EELV); however, in diseased or injured lung, EELV may be greater or less than FRC. FRC is determined by the static balance between the outward recoil of the chest wall and the inward recoil of the lung. However, in infants, the outward recoil is quite small, while the inward recoil is only slightly less than that in adults [27]. Accordingly, the static balance of forces results in a low ratio of FRC to total lung capacity (TLC) (approximately 10–15 %), limiting gas exchange. However, when measured in the dynamic state, that ratio of FRC/TLC in infants approximates the adult value of 40 % [28]. Therefore, the dynamic end-expiratory lung volume of infants is much greater than that predicted by the static balance of forces.

The mechanism for this difference in static versus dynamic FRC/TLC ratio in infants relates to the mechanism of breath termination. Adults cease expiration at low flow rates, while infants will abruptly terminate expiration [29] at high flow rates (Fig. 1.7). Infants utilize two mechanisms to end expiration; post-inspiratory activity of the diaphragm and expiratory laryngeal braking [30, 31]. The expiratory braking mechanism is an active process in which the resistance in the upper airway is increased by laryngeal narrowing during expiration. This generates positive end-expiratory pressure (PEEP), which results in an EELV that is above FRC and prevents lung derecruitment during times of acute respiratory illness. These mechanisms are dependent on both sleep state and gestational age. During REM sleep in premature infants, both post-inspiratory activity of the diaphragm and laryngeal braking are reduced, though braking appears preserved during non-REM sleep [32, 33]. This may exacerbate the loss of oxygen stores, resulting in apnea that presents with the clinical findings of significant desaturation and bradycardia in premature infants.

The final volume and capacity to consider are closing volume and closing capacity. The closing capacity is comprised of residual volume and closing volume and is defined as the volume of gas that remains in the lung when small alveoli and airways in dependent regions of the lung are collapsed or considered closed. When closing capacity exceeds FRC, by definition, some lung units are closed during a portion of tidal breathing. If closing capacity exceeds tidal volume, then these lung units will be closed during all phases of tidal breathing. These concepts are important in pediatrics, as children younger than 6 years of age have a closing capacity greater than FRC in the supine position [34]. This finding has been attributed to reduced inward recoil of the lung. This concept becomes clinically important in critically ill infants and children, in which elevated closing capacity leading to areas of collapse results in ventilation and perfusion inequality, resulting in pathophysiologic intrapulmonary shunting,

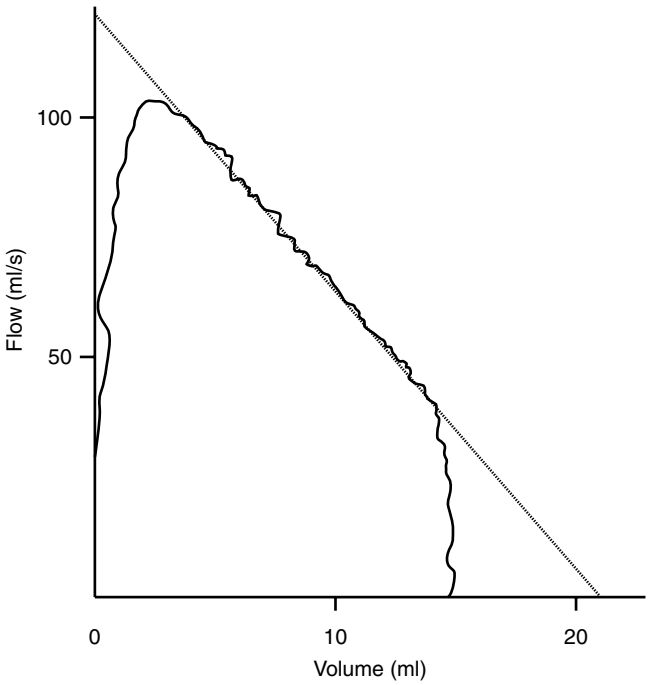


Fig. 1.7 Passive flow-volume curve in an infant, that demonstrates the abrupt onset of inspiration much above passive FRC (Reprinted from Le Souef et al. [29]. With permission of the American Thoracic Society. Copyright © 2012 American Thoracic Society. Official journal of the American Thoracic Society)

especially in the supine position in bed. Ventilation/perfusion (V/Q) matching will be discussed at length later in the chapter.

Physiologic Effects of Mechanical Ventilation

Since the introduction of mechanical ventilation into the intensive care unit, there has been an explosion of new ventilators and ventilatory techniques to treat patients with respiratory failure. Physicians contemplating the use of mechanical ventilation must be familiar with these therapeutic options and their potential benefits and associated risks. A detailed understanding of the physiologic and pathophysiologic effects of mechanical ventilation is crucial to improve the outcomes of patients with respiratory failure.

Maintenance of Oxygenation

The partial pressure of oxygen in the alveolus (PAO_2) is one of the primary determinants of arterial oxygen tension and is the chief target of alterations in mechanical ventilation. The PAO_2 is determined by the alveolar gas equation: $PAO_2 = PiO_2 - PACO_2$, where PiO_2 is the partial pressure of inspired oxygen and $PACO_2$ is the partial pressure of alveolar carbon dioxide. The PiO_2 is determined by the fraction of inspired oxygen, the barometric pressure ($P_b = 760$ mmHg at sea level), and the partial pressure of water vapor ($P_{H2O} = 47$ mmHg). Thus the $PiO_2 = FiO_2 * (P_b - P_{H2O}) = 150$ mmHg in room air at sea level. For clinical purposes, $PACO_2$ is assumed to equal the partial pressure of arterial carbon dioxide ($PaCO_2 = 40$ mmHg) divided by the respiratory quotient (RQ; determined by the mix of metabolic substrates and usually estimated to be approximately 0.8) resulting in 50 mmHg. Substituting these values for PiO_2 and $PACO_2$, respectively, into the previous equation yields the classic alveolar gas equation: $PAO_2 = FiO_2 * (P_b - P_{H2O}) - PaCO_2/RQ$. The latter equation yields a PAO_2 of 100–120 mmHg at room air and sea level. The alveolar gas equation reveals three etiologies for hypoxemia (Table 1.1): (i) low FiO_2 (i.e., hypoxic gas mixture); (ii) low barometric pressure (i.e., high altitude); and (iii) hypoventilation. The first two are rarely causes of hypoxemia and an important principle of the alveolar gas equation can be gleaned by examining the last situation. A decrease in alveolar ventilation by 50 % in room air at sea level will yield a PAO_2 of 50 mmHg, a clinically significant level of hypoxemia. However, with the administration of 25 % inspired oxygen, the PAO_2 increases to 78 mmHg, a non-hypoxemic concentration. Thus, a very small increase in inspired oxygen tension will easily overcome hypoxemia due solely to hypoventilation.

Table 1.1 Alveolar partial pressures of oxygen under various conditions

Condition	FiO_2 $(P_B - P_{H20}) - PaCO_2/RQ$	$= PAO_2$(mmHg)
Normal	0.21 (760 − 47) − 40/0.8	100
Hypoxic gas mixture at sea level	0.15 (760 − 47) − 40/0.8	57
Normoxic, hypobaric pressure	0.21 (560 − 47) − 40/0/8	58
Normoxic, hypoventilation at sea level	0.21 (760 − 47) − 40/0.8	50
Hypoventilation with supplemental O_2	0.25 (760 − 47) − 80/0.8	78

Adapted from Martin [53], p. 58. With permission from Blackwell Publishing Ltd

The difference between the partial pressure of oxygen in the alveolus (PAO_2) and that in the pulmonary capillary (PaO_2), approximately 10 mmHg under normal conditions, is caused by the diffusion barrier of the alveolar-capillary membrane and the overall V/Q ratio of the lung. While the former is easily overcome by increasing the inspired oxygen concentration and is rarely a cause for clinically significant hypoxemia, the same cannot be said for the latter. The principal etiology for clinically significant hypoxemia is pulmonary pathology associated with decreased lung volumes, reduced lung compliance, and an increased proportion of low V/Q compartments of the lung [35]. Under severe

conditions, areas of the lung may become completely atelectatic and lead to right-to-left intrapulmonary shunting. One of the primary objectives of mechanical ventilation is to restore normal lung volumes and mechanics through the application of continuous positive airway pressure (CPAP). A useful clinical index of the effect of changes of ventilation variables is mean airway pressure (P_{aw}) [36]. Mean airway pressure is defined by the following equation:

P_{aw} = (Peak Inspiratory Pressure (PIP)–Positive End-Expiratory Pressure(PEEP)) * ($T_i/T_i + T_e$) + PEEP, where T_i is inspiratory time and T_e is expiratory time.

Accordingly, alterations in peak inspiratory and end-expiratory pressure, ventilator rate, and inspiratory to expiratory (I:E) ratio can increase P_{aw}, which can recruit atelectatic or poorly ventilated alveolar units, thereby restoring normal V/Q matching and decreasing intrapulmonary shunt [37]. The restoration of lung volumes frequently allows a dramatic reduction in the inspired oxygen concentration as well as improving respiratory mechanics and decreasing the work of breathing. These improvements may allow for the partial or complete restoration of spontaneous ventilation, which is associated with several possible advantages (improved V/Q matching, decreased risk of barotrauma, diminished adverse effects of continuous positive pressure ventilation) [38]. From the previous discussion, the major etiologic factors producing hypoxemia can be listed as: (i) hypoxic gas mixture; (ii) hypoventilation; (iii) ventilation-perfusion mismatch; (iv) diffusion abnormalities of the alveolar-capillary membrane; (v) high altitude and (vi) true shunt related to cyanotic congenital heart disease.

Maintenance of Alveolar Ventilation

A second goal of mechanical ventilation is to augment or control alveolar ventilation. Respiratory failure is frequently defined in terms of $PaCO_2$, which is inversely related to alveolar ventilation (V_A): $PaCO_2 \propto V_{CO2}/V_A$, where V_{CO2} is carbon dioxide production. Alveolar ventilation is also defined (at normal ventilator frequencies) as: $V_A = f^*(V_T - V_D)$, where V_T is tidal volume, V_D is dead space volume, and f is the respiratory frequency. Alterations in V_T and/or f, which are the components of minute ventilation (V_E), will result in changes in $PaCO_2$. Clinicians may fail to account for the third component in these equations, namely V_D. The relationship between V_E and $PaCO_2$ can be described by the following equation: $PaCO_2 = 0.863\ V_{CO2}/[V_E(1 - V_D/V_T)]$, where V_{CO2} is the metabolically produced carbon dioxide at standard temperature and pressure. Most of V_D in normal individuals is the result of the volume of the conducting airways (anatomic V_D). Since the anatomic dead space is relatively constant, with an increasing V_T, V_D/V_T tends to decrease and rarely exceeds 0.3. In patients with intrinsic lung disease undergoing mechanical ventilation, V_D/V_T has been found to exceed 0.6 and is primarily due to continued ventilation of poorly perfused regions of the lungs (alveolar V_D). In this setting, increases in V_T may not decrease V_D/V_T since higher alveolar pressures as a result of increases in V_T may result in a decrease in pulmonary perfusion and therefore increase alveolar V_D. The effect of changes in V_T on V_D/V_T can be assessed with capnography and use of the Bohr equation: $V_D/V_T = (PaCO_2 - P_{ET}CO_2)/PaCO_2$, where $P_{ET}CO_2$ is the partial pressure of carbon dioxide in exhaled gas, commonly referred to as end-tidal carbon dioxide. In summary, three factors must be considered when changes in $PaCO_2$ occur: (i) changes in metabolic V_{CO2}; (ii) alterations in V_E as a result of increases or decreases in V_T and f; and (iii) modifications of V_D.

Mechanics of Ventilation

A simplified single-compartment model of the lungs composed of a single, cylindrical flow-conducting tube (i.e., conducting airways) connected to a single, spherical elastic compartment (i.e., alveoli) is frequently used to describe pulmonary mechanics (Fig. 1.8). In this model, the lungs are considered as a homogeneous assembly of units with uniform pressure-volume (compliance) and pressure-flow (resistance) characteristics derived from this single representative unit. To achieve inflation, a transrespiratory pressure (P_{tr}) composed of two components is required. The first component, the transthoracic pressure (P_{tt}), is defined as the pressure required to deliver the tidal volume against the elastic recoil of the lungs and chest wall, while the second component, the transairway pressure (P_{ta}), is the pressure necessary to overcome airflow resistance. This is described mathematically by the equation $P_{tr} = P_{tt} + P_{ta}$, where P_{tr} = airway minus body surface pressure, P_{tt} = alveolar minus body surface (atmospheric) pressure, and P_{ta} = airway minus alveolar pressure. The pressure required for inspiration may come from the respiratory muscles (P_{rm}) and/or the ventilator (P_{tr}), giving us the equation: $P_{rm} + P_{tr} = P_{tt} + P_{ta}$. Since the ventilator measures pressure relative to atmosphere, P_{tr} is equal to the P_{aw} displayed on the ventilator, allowing the substitution: $P_{rm} + P_{aw} = P_{tt} + P_{ta}$.

The single-compartment model assumes a linear relationship between pressure and volume and between pressure and flow. The change in P_{tt} is directly proportional to the corresponding change in lung volume and the constant of proportionality is the slope ($\Delta P/\Delta V$) of the pressure-volume curve (i.e., the reciprocal of compliance [C]). Similarly, the change in P_{ta} is proportional to the change in flow rate (F) and the constant of proportionality ($\Delta P/\Delta F$) is resistance (R). Substituting $\Delta P/\Delta V$ for P_{tt} and $\Delta P/\Delta F$ for P_{ta} yields the equation of motion of the respiratory system for inspiration:

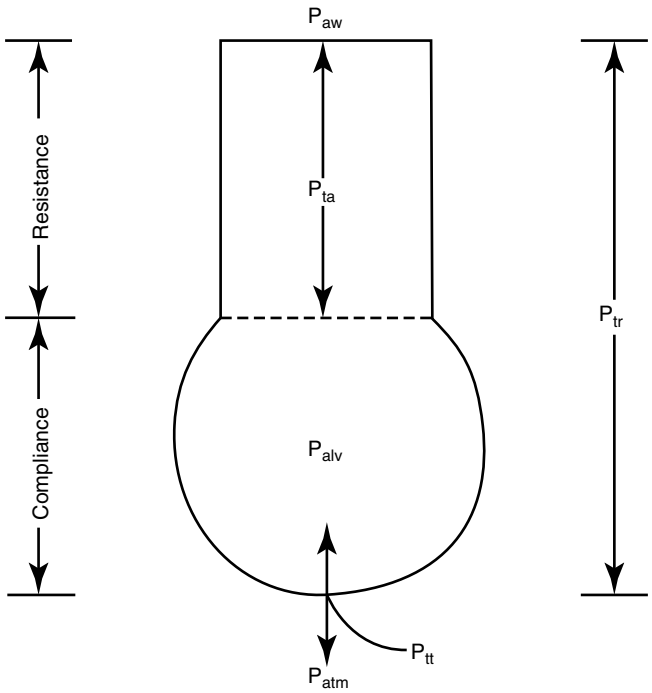


Fig. 1.8 The simplified single compartment model of the lungs composed of a flow-resistive element adjoined in series with a compliance element. P_{aw} airway pressure, P_{alv} alveolar pressure, P_{atm} atmospheric pressure, P_{ta} transairway ($P_{aw}-P_{alv}$) pressure, P_{tt} transthoracic ($P_{alv}-P_{atm}$) pressure, P_{tr} transrespiratory ($P_{aw}-P_{atm}$) pressure. Ventilator manometers are equivalent to P_{tr} (Reprinted from Martin [53]. With permission from Blackwell Publishing Ltd)

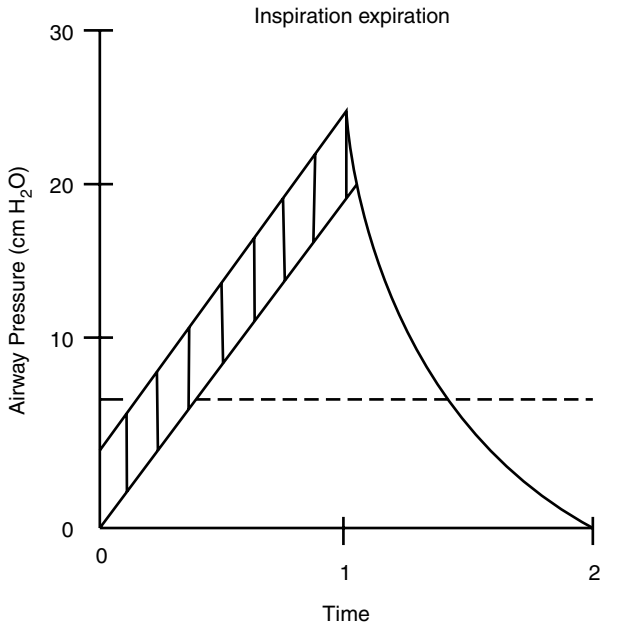


Fig. 1.9 Graphic representation of the equation of motion for constant inspiratory flow (*left*) and constant inspiratory pressure (*right*) breaths. Pressure, volume and flow are measured relative to their respective end-expiratory values. The *shaded areas* represent equal geometric areas proportional to the pressure required to overcome lung elastic recoil. The *dotted line* represents mean airway and lung pressure. Note the higher peak and lower mean airway pressures with the constant inspiratory flow breath (*left*) compared to the constant inspiratory pressure breath (*right*) (Reprinted from Martin [53], p. 62. With permission Blackwell Publishing Ltd)

$P_{rm}+P_{aw}=V/C+(F)*(R)$, where V is the volume inspired or expired, C is the compliance of the respiratory system, F is the inspiratory or expiratory flow rate, and R is the resistance of the respiratory system. For passive expiration, the equation of motion of the respiratory system is defined as: $V/C=-(F)*(R)$, where the elastic components of the lungs ($P_A=V/C$) provides the pressure to drive the expiratory flow rate. In situations where respiratory muscles are relaxed, measurement of pressure, volume and flow allow calculation of total respiratory system compliance and resistance.

The relationships represented in the equation of motion can be graphically represented for both constant inspiratory flow (i.e., volume-limited ventilation) and constant inspiratory-pressure (i.e., pressure-limited ventilation) as shown in Fig. 1.9. During constant inspiratory *flow* ventilation (Fig. 1.9, left), the initial increase in pressure is related to the resistance and flow rate while the slope of the pressure rise is inversely proportional to compliance, tidal volume, resistance, and inspiratory flow rate. Lung pressure (P_L) is expressed as $P_L=(F)*(t)/C$, where F is inspiratory flow rate, t is the inspiratory time, and C is the compliance of the respiratory system. Lung volume (V_L) can be represented as $V_L=(F)*(t)$. During constant inspiratory *pressure* ventilation (Fig. 1.9, right), the P_L, V_L, and F during inspiration are exponential functions of time derived from the equation of motion as $P_L=\Delta P(1-e^{-t/\tau})$, $V_L=C(\Delta P)(1-e^{-t/\tau})$, and $F=\Delta P/R\ (e^{-t/\tau})$, where ΔP is equal to peak inspiratory pressure minus end-expiratory pressure, t is the inspiratory time, e is the natural logarithm (≈ 2.72), and τ is the time constant of the respiratory system.

The time constant (τ) is the product of compliance (volume/pressure) and resistance (pressure x time/volume) and is measured in seconds. Exhalation during any form of mechanical ventilation is passive. Therefore, the P, V, and F can also be derived from the equation of motion as: $P_L=\Delta P(e^{-t/\tau})$, $V_L=C(\Delta P)(e^{-t/\tau})$, and $F=-\Delta P/R\ (e^{-t/\tau})$, where t is the expiratory time and τ is the expiratory time constant. Note that all variables are measured relative to their value at end-expiration, the P_L is pressure above positive-end expiratory pressure (PEEP) and V_L is the volume above end-expiratory volume. When inspiratory and expiratory times are between zero and infinity, the shapes of the lung pressure and lung volume curves are defined by the τ. By plotting these curves over time in units of τ, clinically useful principles emerge (Fig. 1.10). Irrespective of the specific values of resistance and compliance, after 1 τ 63 % of lung inflation or deflation occurs, 95 % after 3 τ, and for all practical purposes, complete equilibration after 5 τ.

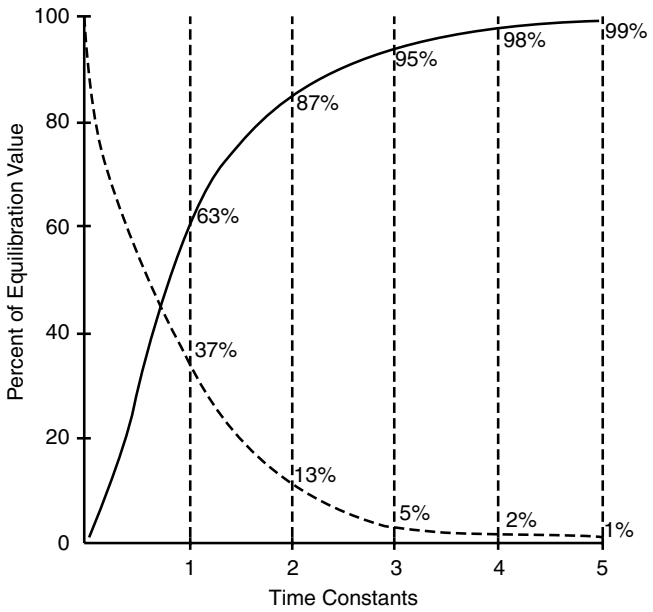


Fig. 1.10 Exponential lung pressure or volume curves as a function of time constant during inspiration (*solid line*) and expiration (*dotted line*) (Reprinted from Martin [53], p. 63. With permission from Blackwell Publishing Ltd)

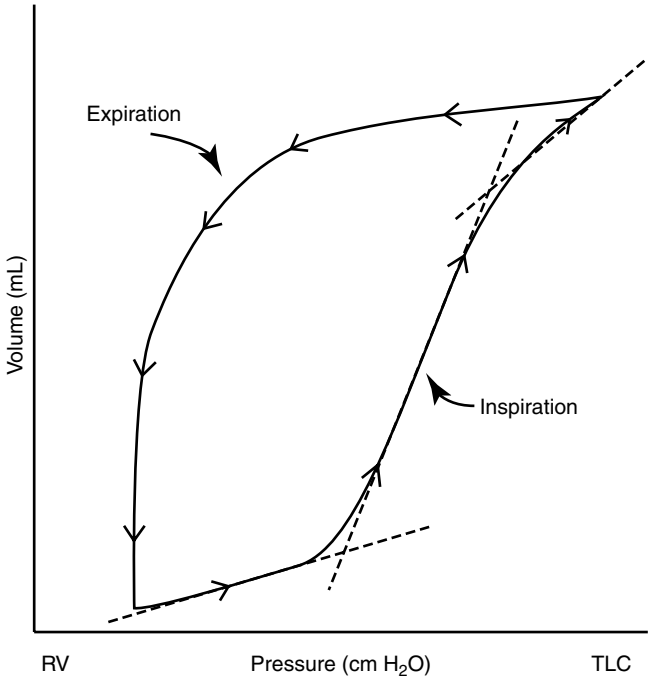


Fig. 1.11 A hypothetical static pressure-volume curve of the respiratory system. Note the sigmoidal shape of the inspiratory limb with high compliance in the midvolume range and low compliance at either high or low lung volumes. Inflection points denote the change from low to high compliance regions (Reprinted from Martin [53], p. 64. With permission Blackwell Publishing Ltd)

The equation of motion is a useful means to more closely examine the differences between constant flow volume-limited ventilation, and constant pressure ventilation with a decelerating inspiratory flow waveform. Peak airway pressures are higher for a constant flow pattern compared to the constant pressure pattern. However, peak alveolar pressures depend only on the compliance and tidal volume, thereby making peak lung pressures independent of the pattern of ventilation. Second, at any point time, airway pressure is equal to the volume/compliance plus the resistance/flow. The pressure required to overcome flow resistance (shaded area in Fig. 1.9) is constant with fixed inspiratory flow while it decreases exponentially with the decelerating flow pattern. In the example depicted, the area is equal for both patterns, since tidal volume and inspiratory times are equal. Third, the more rapid approach to the pressure limit during constant pressure decelerating flow ventilation leads to a higher P_{aw} compared to constant flow ventilation. Since all shaded areas are equal, the total area under the airway curve is equal to the total area under the lung pressure curve for each pattern. Therefore, the P_{aw} is equal to mean P_L, a finding that has been verified in animals [36].

The final feature of pulmonary mechanics that must be appreciated is the sigmoidal shape of the static pressure-volume (compliance) relationship of the respiratory system (Fig. 1.11). The respiratory system is most compliant in the mid-volume range, becoming progressively less compliant at high (near total lung capacity) and low (approaching residual volume) volume extremes. Tidal ventilation near total lung capacity occurs under two conditions: (i) when total lung volume and/or vital capacity are decreased secondary to intrinsic lung disease, and (ii) when end-expiratory volume is decreased. Conversely, ventilation near residual volume with a decrease in compliance also occurs under two conditions: (i) when obesity and/or abdominal distention increase residual volume and encroach on the lower range of vital capacity, and (ii) when intrinsic lung disease results in airway or alveolar closure at end-expiratory volume.

The relationship between end-expiratory lung volume and closing capacity is critical. Conditions that decrease FRC below closing capacity or increase closing capacity above FRC, result in maldistribution of ventilation and perfusion, and adversely affect the mechanics of breathing (Table 1.2). In the school-aged child and in the adult, FRC is normally well above closing capacity. However, the relationship is more precarious in young infants, as noted previously, in whom studies suggest that closing capacity exceeds FRC [39]. A primary goal of mechanical ventilation is restoration of the normal relationship between FRC and closing capacity. Conditions associated with a decrease in FRC (e.g., pulmonary edema, pneumonitis, infant respiratory distress syndrome [(IRDS)] and acute respiratory distress syndrome [(ARDS)] are treated with PEEP to increase FRC back to normal levels. Situations associated with increased closing

Table 1.2 Conditions predisposing to convergence of closing and functional residual capacities

Elevation of closing capacity
Infancy
Bronchiolitis
Asthma
Bronchopulmonary dysplasia
Smoke inhalation (thermal airway injury)
Cystic fibrosis
Reduction of functional residual capacity
Supine position
Abdominal distention
Thoracic or abdominal surgery/trauma
Atelectasis
Pulmonary edema
Acute lung injury/acute respiratory distress syndrome (ARDS)
Near drowning
Diffuse pneumonitis
Aspiration pneumonitis
Idiopathic interstitial pneumonitis
Bacterial pneumonia
Viral pneumonitis
Opportunistic organism (i.e. Pneumocystis carinii)
Radiation

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capacity, such as bronchiolitis and reactive airway disease, are treated with bronchodilators and measures to improve airway clearance in order to reduce closing capacity and maintain airway patency.

Work of Breathing

The pressure-volume (compliance) and pressure-flow (resistance) characteristics of the respiratory system determine the work of breathing which, in actuality, represents the afterload on the respiratory muscles [40]. The work of breathing overcomes two major sources of impedance: (i) elastic recoil of the lung and chest wall (Fig. 1.12, areas A, C and D), and (ii) the frictional resistance to gas flow in the airways (Figs. 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 1.10, 1.11, and 1.12, areas A, B and C). The total work of breathing (Fig. 1.12, areas A through D) is increased by a decrease in respiratory compliance and/or an increase in respiratory resistance properties. When total work of breathing against compliance and resistance is summated and plotted against respiratory frequency, an optimal respiratory frequency exists that minimizes the total work of breathing (Fig. 1.13). In patients with low lung compliance (restrictive lung diseases) such as pulmonary edema, pneumonia, IRDS, or ARDS, the optimal frequency is increased, leading to rapid, shallow breathing. In contrast, in obstructive lung diseases with increased resistance such as

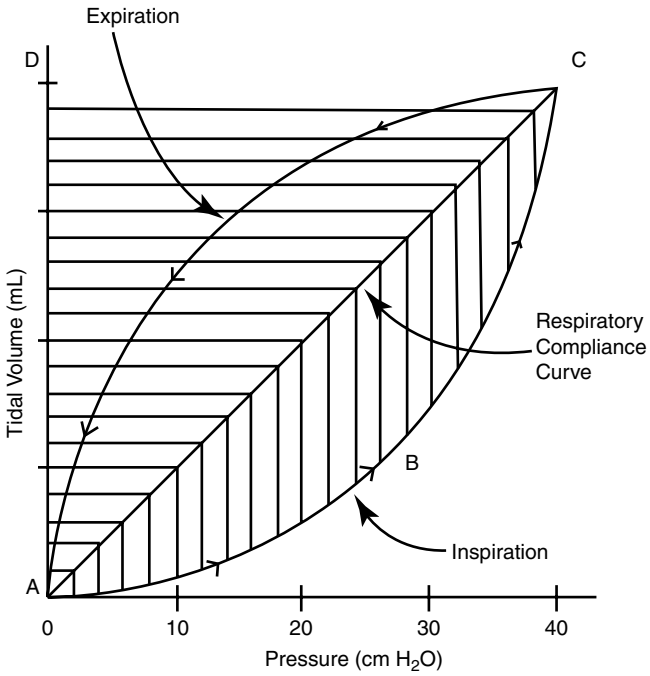


Fig. 1.12 Inspiratory and expiratory pressure-volume curve recorded during a complete respiratory cycle. Total work of breathing (pressure × volume) is defined as the sum of resistive work (area defined by *ABC*) plus the elastic work (area defined by *ACD*). Total work (defined by area *ABCD*) is increased by either an increase in resistive properties of the respiratory system or by a decrease in compliance (slope of line between *A* and *C*) (Reprinted from Martin [53], p. 66. With permission from Blackwell Publishing Ltd)

bronchiolitis or asthma, the optimal frequency is decreased leading to slow, deep breathing.

Developmental Anatomy and Physiology of the Pulmonary Circulation

The development of the lungs and the pulmonary vasculature are closely related, as adequate blood flow is essential for the formation of the lungs, and preacinar arteries develop in utero with conducting airways [41]. The arterial tree undergoes complex remodeling in the peripheral portions of the pulmonary circulation, due in part to changes in wall stress [42]. Muscularization of the pulmonary vasculature occurs throughout infancy and reaches adult levels by adolescence. Pulmonary vascular muscle thickness is a function of gestational age and blood flow which explains why in patients with congenital heart disease, increased pulmonary blood flow leads to long-standing pulmonary hypertension due to smooth muscle proliferation in the pulmonary vessels [43]. Premature infants are born with less arterial smooth muscle than full term infants, this smooth muscle regresses earlier and therefore predisposes to early congestive heart failure in the setting of left-right shunts.

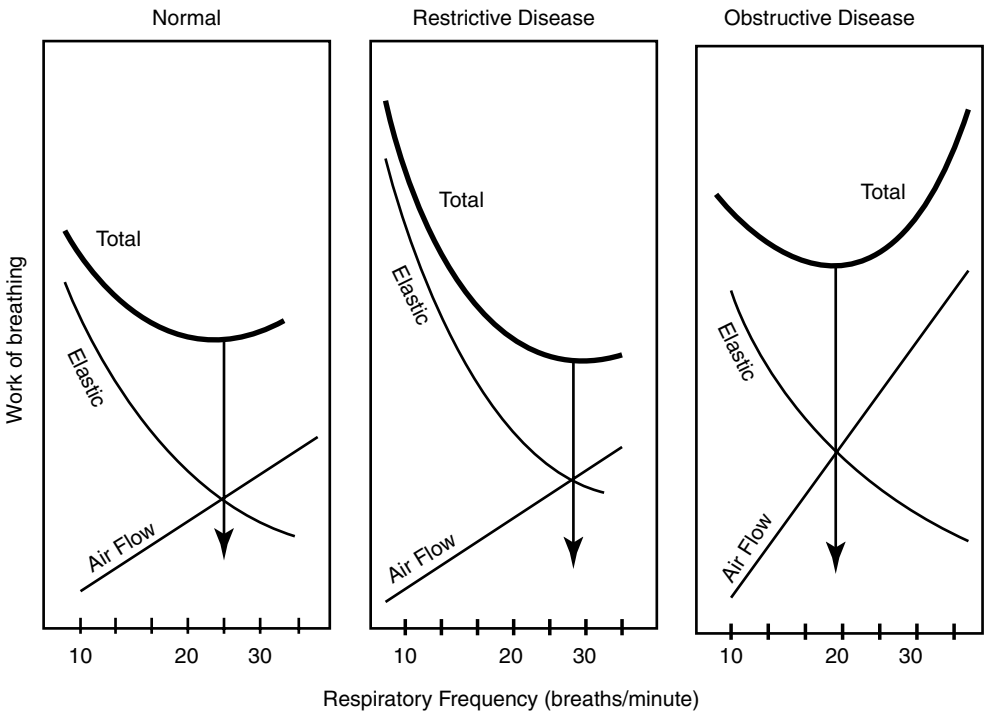


Fig. 1.13 Hypothetical diagrams showing work done against elastic and resistance, separately, and summated to indicate total work at different respiratory frequencies. For a constant minute volume, minimum work is performed at higher frequencies with restrictive (low compliance) disease and at lower frequencies when airflow resistance is increased (Reprinted from Martin [53], p. 67. With permission from Blackwell Publishing Ltd)

Pulmonary Vascular Pressures

Pressures within the pulmonary circulation are quite low, despite the fact that the entire cardiac output is designed to flow through it. Following the initial decrease after birth, pulmonary arterial pressures remain fairly constant in the disease-free state throughout life, with systolic, diastolic and mean pressures of 25, 8 and 15 mmHg, respectively. Pulmonary venous pressure is routinely just above that of left atrial pressure, near 5 mmHg. The transpulmonary pressure is determined by subtracting the left atrial pressure from the mean pulmonary arterial pressure and is approximately 10 mmHg in the healthy subject. The pressure within the pulmonary capillaries is uncertain, though experimental evidence in animals suggests it may range from 8 to 10 mmHg. The pulmonary vascular pressures vary based on gravity and may range from near 0 mmHg at the apex of the lung and increase to 25 mmHg at the base [44]; the consequences resulting from this gradient will be discussed below.

The pressure within the pulmonary capillaries plays an important role in their patency as they are surrounded by gas and receive little support from the alveolar epithelial cells (Fig. 1.14). The pressure within the capillaries is fairly close to alveolar and when the transmural pressure is positive, the capillaries collapse. As the lung expands, the extra-alveolar vessels are pulled open by the radial traction of the elastic lung parenchyma. In addition, this expansion results in a negative intrapleural pressure which also helps maintain the patency of the alveolar vessels (Fig. 1.15).

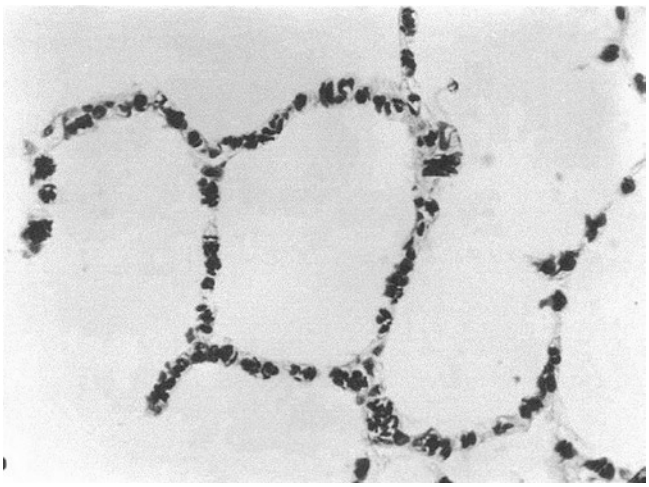


Fig. 1.14 Alveolar vessels. Microscopic section of dog lung showing capillaries in the alveolar walls (Reprinted from West [54]. With permission from Wolter Kluwers Health)

Distribution of Blood Flow

Blood flow in the lung is influenced by gravity whether supine or upright. In the upright lung, blood flow decreases almost linearly from the base to the apex. The uneven distribution is explained by hydrostatic pressure differences within the blood vessels. In order to explain the effects of the hydrostatic forces, one may consider the lung as being comprised of distinct units or zones (Fig. 1.16). At the apex of the lung, zone 1, alveolar pressure exceeds both pulmonary arterial and venous pressure, resulting in collapse of the alveolar

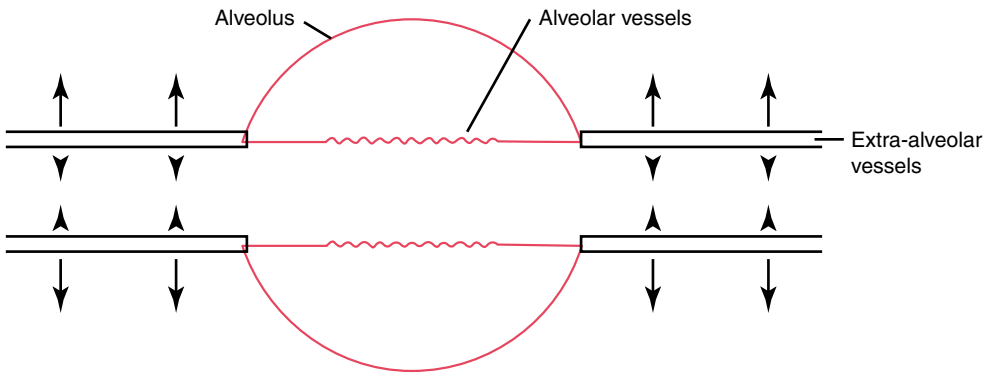


Fig. 1.15 Alveolar and extra-alveolar vessels. Alveolar vessels are predominantly capillaries exposed to alveolar pressure. Extra-alveolar vessels are pulled open by the radial traction of the lung parenchyma, resulting in a lower external pressure that promotes vascular patency (Reprinted from West [14], p. 84. With permission from Wolters Kluwers Health)

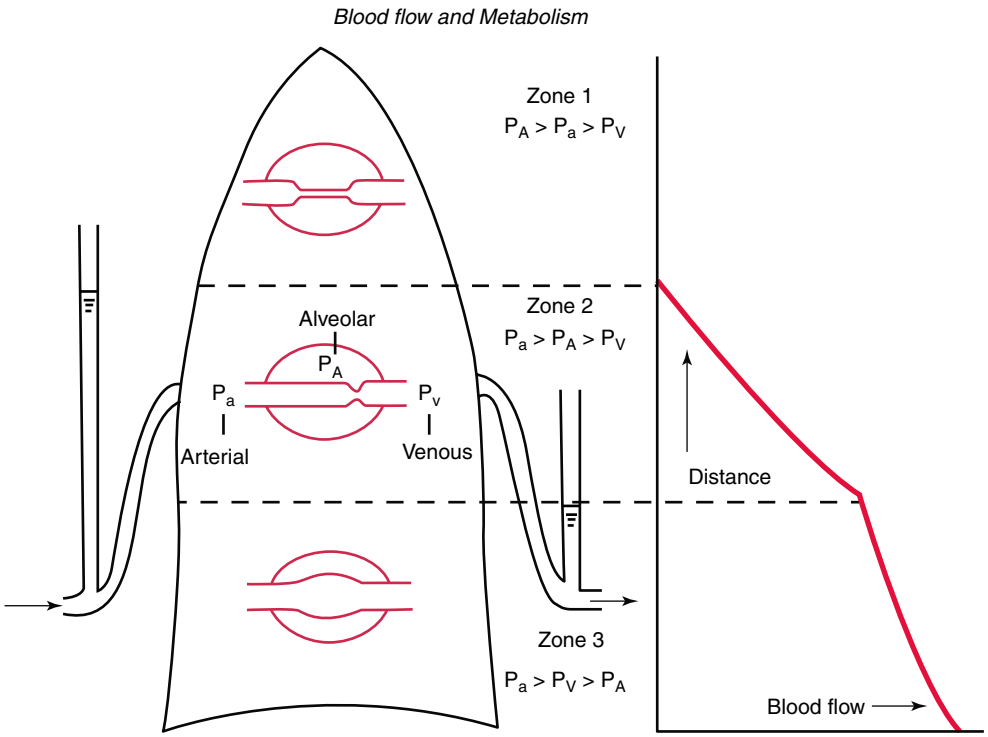


Fig. 1.16 West lung zones. Explanation of uneven distribution of blood flow (Reprinted from West [14], p. 84. With permission from Wolters Kluwers Health)

vessels. This zone is ventilated, but not perfused and is termed alveolar dead space. In the mid-region of the lung, zone 2, pulmonary arterial pressure exceeds alveolar pressure. Blood flow here is determined by the difference between alveolar and arterial pressures in this zone and is not impacted by venous pressure. At the base of the lung, zone 3, venous pressure exceeds alveolar pressure and flow is determined by the usual arterial-venous pressure difference. At low lung volumes, zone 4 arises at the base of the lung where the low lung volume reduces the size of extra-alveolar vessels, increasing their resistance and reducing blood flow.

Pulmonary Vascular Resistance

The resistance within any system may be described by a variation of the previously described Ohm's law, where:

$$\text{Resistance} = \frac{\text{Input pressure} - \text{Output pressure}}{\text{Blood flow}}$$

Decreased pulmonary vascular resistance (PVR) can only occur if there is an increase in the diameter of the blood

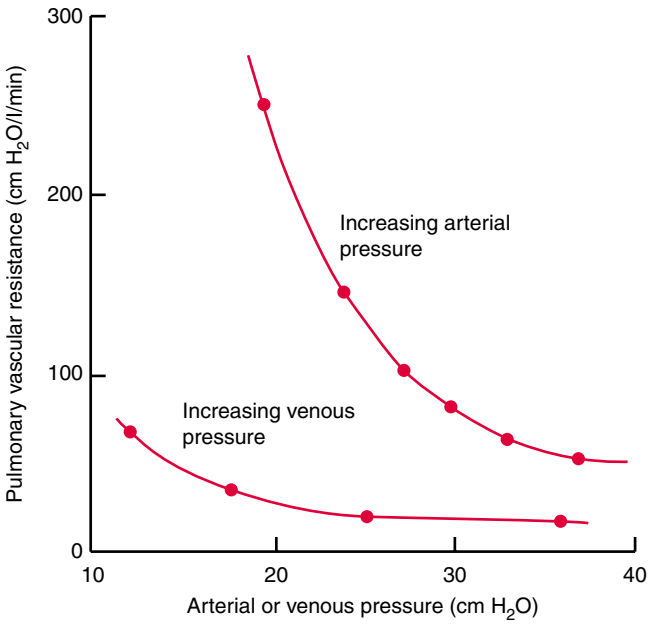


Fig. 1.17 Pulmonary vascular resistance decreases with increases in either pulmonary arterial or venous pressure. During decreases in arterial pressure, venous pressure was held constant and vice versa (Reprinted from West [14], p. 84. With permission from Wolters Kluwers Health)

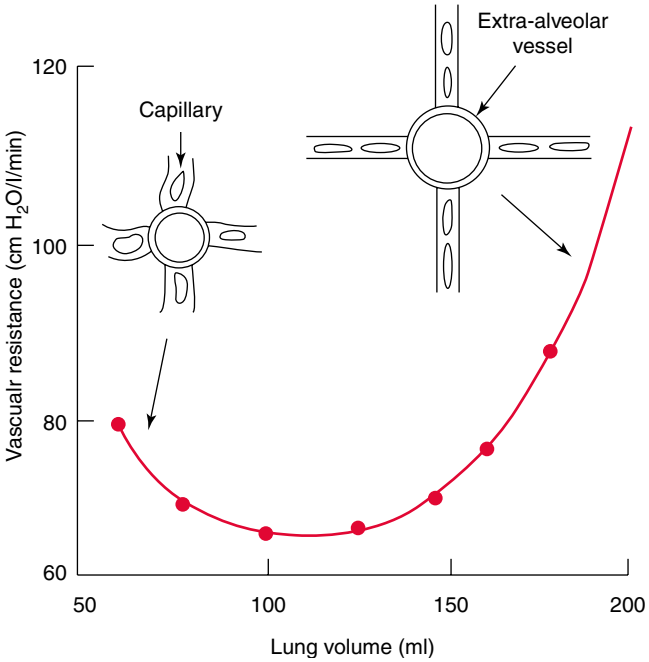


Fig. 1.18 Effects on pulmonary vascular resistance as lung volume changes. At low lung volumes, the extra-alveolar vessels are narrow and at high volumes, the capillaries are stretched, reducing their caliber. Both of these effects, increase pulmonary vascular resistance (Reprinted from West [14], p. 84. With permission from Wolters Kluwers Health)

vessels or there is an increase in the number of blood vessels. This concept is key to understanding the ability of the pulmonary vasculature to decrease its resistance in response to increases in arterial or venous pressure (Fig. 1.17). During periods of increased blood flow, the initial mechanism to reduce resistance, is via the recruitment of capillaries with low or no blood flow. If this mechanism is not sufficient and pressures begin to rise, the pulmonary capillaries then distend, which increases the total cross sectional area that blood may pass through, thereby decreasing the pressure.

An additional mechanism that alters pulmonary resistance is the volume of the lung, though this relationship is complex as illustrated below. A change is lung volume has opposite effects on the resistances of extra-alveolar versus the alveolar vessels. During lung inflation, the radial traction as noted above pulls open extra-alveolar vessels; however, this same increase in lung volume increases the resistance to flow through alveolar vessels (Fig. 1.18). It can be seen from Fig. 1.18 that there is a lung volume where pulmonary resistance is at a minimum. It has been concluded that this lung volume, where pulmonary resistance nadirs, is FRC [45].

Neurogenic stimuli, vasoactive substances, and chemical mediators have been demonstrated to alter PVR in the setting of elevated PVR in adults. However, in adults with normal PVR these agents do not appear to significantly alter resistance. Interestingly, the neonate appears to respond to a variety of vasodilating agents, including acetylcholine, β-adrenergic agonists, bradykinin, prostaglandin E_1, prostacyclin, bosentan, calcium channel blockers, and nitric oxide [46]. The ability of the pulmonary vasculature to constrict is not age dependent and even newborns with only a small amount of arterial muscularization are able to induce significant pulmonary vasoconstriction, as noted in neonates with persistent pulmonary hypertension (PPHN). There are numerous vasoconstrictors, including endothelin, carbon dioxide, leukotrienes, hypoxia and platelet activating factor [47, 48].

Ventilation-Perfusion Relationships

Matching ventilation to perfusion (V/Q) depends to some extent on gravity. Both ventilation and perfusion increase with increasing distance towards the base of the lung; however, perfusion increases more than ventilation which accounts for the variability in V/Q from apex to base (Fig. 1.19). The apical regions are usually underperfused, V/Q = 3, while the base is underventilated in relation to perfusion, V/Q = 0.6 [49]. In the discussion and explanation to follow, it is important to recognize the difference between shunt and venous admixture. Shunt refers to the anatomic shunt that occurs when venous blood travels to the arterial side of the circulation without encountering ventilated lung. Examples include bronchial and Thebesian circulation, right to left shunting in cyanotic congenital heart disease and blood flow through completely atelectatic lung segments.

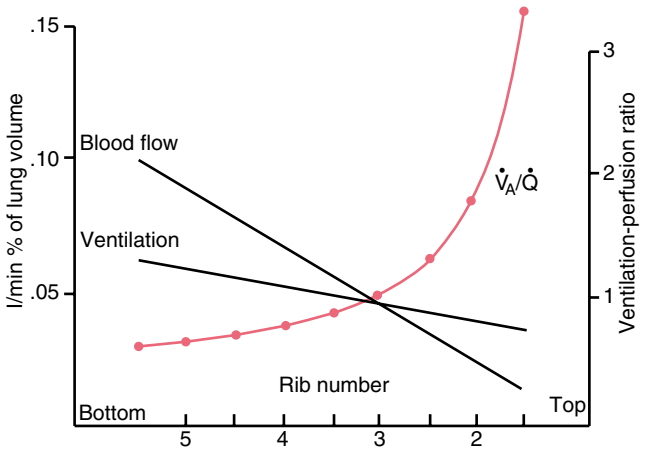


Fig. 1.19 The distribution of pulmonary blood flow, ventilation and the ventilation/perfusion ratio as found between apex and base in an upright lung (Reprinted from West [14], p. 84. With permission from Wolters Kluwers Health)

Venous admixture, in contrast, is the amount of venous blood that needs to be added to the pulmonary end-capillary blood to produce the actual arterial oxygen content. Venous admixture is a calculated value and not an anatomic construct. Lung units with low V/Q ratios contribute to venous admixture. They are differentiated from lung units with V/Q ratios of 0, by the fact that the administration of supplemental oxygen will increase the saturation of blood emerging from their end-capillaries.

V/Q mismatching lowers arterial pO_2 and results in desaturation through the addition of mixed venous blood to pulmonary end-capillary blood. There are two additional reasons that V/Q mismatching results in lower arterial pO_2. (i) More blood will flow through lung units with low V/Q ratios than through high V/Q units, resulting in a greater amount of venous admixture. (ii) Due to the sigmoidal shape of the oxyhemoglobin dissociation curve, lung units with low V/Q ratios have lower pO_2 values and accordingly lie on the steep portion of the curve, and will have a disproportionately greater drop in saturation. This is in contrast to high V/Q units, who reside on the flat part of the curve and even large increases in pO_2 will have minimal impact on saturation. The net result is arterial desaturation, as the slightly higher oxygen content from high V/Q units cannot counteract the significantly lower oxygen content from the low V/Q units.

The difference between mixed venous pCO_2 (46 mmHg) and pulmonary end-capillary pCO_2 (40 mmHg) is not very great. Accordingly, even a significant amount of venous admixture will only produce a very small increase in arterial pCO_2. The presence of dead space ventilation, on the other hand, will have a much larger impact on arterial pCO_2. For example, an infant with bronchiolitis may have a large portion of their lung comprised of lung units with high V/Q ratios. In this setting, additional increases in ventilation will be ineffective at eliminating pCO_2, as these units are already maximally ventilated in relation to their perfusion.

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Life-Threatening Diseases of the Upper Respiratory Tract

2

Derek S. Wheeler

Abstract

Acute airway obstruction is one of the most common causes of acute respiratory failure in children. Left untreated, it can rapidly progress to cardiopulmonary arrest and death. There are several important anatomical differences between pediatric and adult patients that render children more susceptible to acute airway obstruction. In addition, there are several diseases that can cause life-threatening acute airway compromise. An understanding of the developmental anatomy and physiology, as well as the myriad diseases that can cause airway compromise in children is therefore essential for all healthcare personnel that provide care for critically ill children.

Keywords

Acute airway obstruction • Epiglottitis • Croup • Peritonsillar abscess • Bacterial tracheitis • Airway trauma • Post-extubation stridor • Foreign body aspiration

Introduction

Acute airway obstruction is one of the most common causes of acute respiratory failure in children. Left untreated, it can rapidly progress to cardiopulmonary arrest and death. There are several important anatomical differences between pediatric and adult patients that render children more susceptible to acute airway obstruction. In addition, there are several diseases that can cause life-threatening acute airway compromise. An understanding of the developmental anatomy and physiology, as well as the myriad diseases that can cause airway compromise in children is therefore essential for all healthcare personnel that provide care for critically ill children.

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Developmental Anatomy

The airway is divided into the upper respiratory tract, which begins with the nose and lips and extends down to the glottis, and the lower respiratory tract which is the airway below the glottis. The upper respiratory tract begins with the nasal and oral cavities, which together comprise the pharynx. The pharynx is connected to the esophagus and the larynx. The larynx and its unique anatomy continue into the chest in the form of a cylindrical structure called the trachea. The larynx is a unique structure whose primary functions are in speech production and protection of the airway. It is formed by cartilaginous, bony, and connective tissue structures. The glottis is the area around the vocal cords. The subglottis is the area directly below the vocal cords leading into the trachea. The cords are closed during the end of the expiratory phase, and they open at the beginning of the inspiratory phase. The trachea is a cylindrical structure formed by 16–20 U-shaped cartilaginous rings and a muscular/cartilaginous part that completes the tube.

Though basic principles in the management of the airway in children are the same as in adults, there are important developmental characteristics that distinguish the pediatric

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Table 2.1 Major anatomic differences between the airway of infant vs. adult

	Infant	Adult
Head	Large, prominent occiput	Flat occiput
Tongue	Relatively larger	Relatively smaller
Larynx	Cephalad position Opposite to C2–C3	Opposite to C4–C6
Epiglottis	Omega-shaped & soft	Flat and flexible
Vocal cords	Short & concave	Horizontal
Narrowest portion	Cricoid ring, below cords	Vocal cords
Cartilage	Soft	Firm
Lower airways	Smaller, less developed	Larger, more cartilage

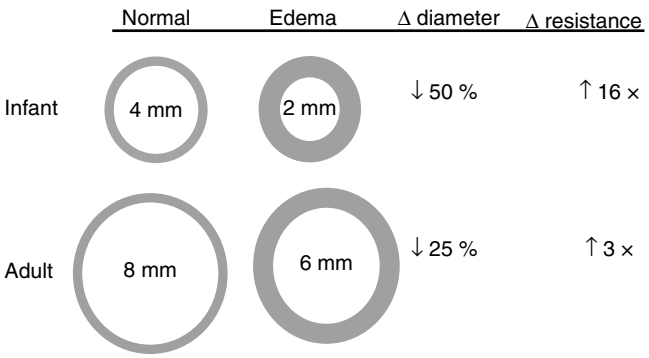


Fig. 2.1 Age-dependent effects of a reduction in airway caliber on the airway resistance and airflow. Normal airways are represented on the *left*, edematous airways are represented on the *right*. According to Poiseuille's law, airway resistance is inversely proportional to the radius of the airway to the *fourth power* when there is laminar flow and to the *fifth power* when there is turbulent flow. One mm of circumferential edema will reduce the diameter of the airway by 2 mm, resulting in a 16-fold increase in airway resistance (cross-sectional area reduced by 75 %). In contrast, an equivalent amount (1 mm) of circumferential edema results in only a 3-fold increase in airway resistance (cross-sectional area reduced by 25 %) in an adult. Note that turbulent air flow (such as occurs during crying) in the infant would increase the resistance by 32-fold

airway from the adult airway (Table 2.1). These affect both mask ventilation and tracheal intubation. In the neonate and infant, important anatomic differences include a proportionately larger head and tongue, narrower nasal passages, an anterior and cephalad larynx, long epiglottis, and a short trachea and neck. These factors contribute to making infants "obligate" nasal breathers. The cricoid cartilage is the narrowest point of the airway in children younger than 10 years of age as opposed to the glottis in the adult. Even minimal edema will have a proportionately greater effect in children because of their smaller tracheal diameters. In older children, prominent adenoidal and tonsillar tissue can obstruct visualization of the larynx. Also, there are specific congenital anatomic airway anomalies that occur in children which makes management of the airway even more complex. As the child becomes older the airway becomes more comparable to the adult anatomy, and by 8 or 9 years of age the airway is considered similar to the adult airway, with the exception of the size of the airway itself.

All parts of the pediatric airway are very small and fragile. Even trauma caused during tracheal intubation can cause significant edema and obstruction of the upper airway. For example, 1 mm of circumferential edema can result in a 16-fold increase in resistance in a 4 mm infant airway (Fig. 2.1). The narrow caliber of the airway results in greater baseline resistance. Any process that narrows the airway further will cause an exponential rise in airway resistance and hence a significant increase in the work of breathing. When the child perceives distress, the resultant increase in respiratory effort will further augment turbulence and increase resistance.

Because the neonate is primarily a nasal breather, any degree of obstruction of the nasopharynx may result in a significant increase in the work of breathing and present clinically as nasal flaring, tachypnea, and retractions. The tongue of infants and small children dominates the overall capacitance of the oropharynx, so any pediatric patient who presents with altered mental status will be at risk for the development of upper airway obstruction secondary to loss of muscle tone affecting the tongue. Occlusion of the oropharynx by the tongue is not uncommon in this setting, but tilting of the head, lifting the chin, or insertion of an oral airway may correct this obstruction (the so-called *triple airway maneuver*).

Older children have tonsillar and adenoidal tissues that are large in proportion to the rest of the upper airway. Although these rarely are the cause of an upper airway catastrophe, they are vulnerable to traumatization and bleeding during clinical interventions such as insertion of an oral or a nasal airway. The pediatric trachea is easily distensible and compressible due to incomplete closure of semiformed cartilaginous rings. Any maneuver that overextends the neck will contribute to compression of this structure and secondary upper airway obstruction. As the cricoid ring represents the narrowest portion of the upper airway in children it is often the site of occlusion in tracheobronchial foreign body aspiration.

Acute Airway Obstruction

Children are at particular risk for acute airway obstruction (AAO) due to the anatomic differences between the pediatric and adult airway discussed above [1, 2]. In fact, children may appear surprisingly well from a clinical standpoint, despite being on the verge of cardiorespiratory collapse. Infants have a high oxygen demand due to a higher metabolic rate relative to body size and weight. Consequently, in the presence of apnea or inadequate ventilation, hypoxemia develops more rapidly in the child than adult, and acute decompensation of

Table 2.2 Common causes of upper airway obstruction in children

Anatomic
Altered level of consciousness (airway muscle laxity)
Post-extubation airway obstruction
Tonsillar hypertrophy
Subglottic stenosis (acquired or congenital)
Macroglossia
Vocal cord paralysis
External or internal compression
Tumor
Hemangioma
Hematoma
Cyst
Papilloma
Vascular rings and slings
Infectious
Laryngotracheobronchitis (Croup)
Peritonsillar abscess
Retropharyngeal abscess
Bacterial tracheitis
Epiglottitis ("Supraglottitis")
Infectious mononucleosis
Miscellaneous
Post-extubation airway obstruction
Angioedema
Foreign body aspiration
Airway trauma

cardiorespiratory status may be swift and often difficult to reverse [3, 4]. Upper airway obstruction (Table 2.2) often leads to acute respiratory failure and is an important cause of out-of-hospital cardiopulmonary arrest, in stark contrast to adults in which primary cardiac disease commonly precipitates cardiopulmonary arrest. Once respiratory arrest progresses to cardiac arrest, outcome is dismal [5–7], and prompt recognition of AAO and appropriate, timely intervention is crucial to assure the best possible outcome.

Physiology of Airway Obstruction

The pediatric airway is highly compliant and the cartilaginous support less well-developed compared to the adult airway and is therefore more susceptible to dynamic airway collapse in the presence of airway obstruction. The normal respiratory dynamics change significantly in the presence of airway obstruction (Fig. 2.2). A forced inhalation that is required to generate airflow in the presence of a partial upper airway obstruction requires a stronger contraction of the diaphragm and respiratory muscles, generating a greater decrease (i.e. more negative relative to atmospheric pressure) in intra-pleural and intra-luminal airway pressures. The larger gradient between atmospheric pressure and the airway pressure leads to dynamic collapse of the extrathoracic trachea just beyond the level of obstruction. This explains why obstruction of the extrathoracic airway is worse during inspiration (Fig. 2.3). Conversely, lower airway or intrathoracic airway obstruction (e.g. aspirated foreign body, asthma, bronchiolitis, etc) results in a ball-valve effect and subsequent air-trapping. Increased respiratory effort during exhalation is required, generating an increase in intra-pleural pressures and leading to dynamic compression of the intrathoracic airways. This explains why obstruction of the intrathoracic airways is worse during expiration (Fig. 2.4).

The movement of a gas (i.e. air) through a partially closed, collapsible tube (i.e. airway) obeys the laws of physics. According to the *Venturi effect*, the pressure exerted by a gas (i.e. air) as it flows through a partially closed tube is equal in all directions except when there is linear movement, which creates additional pressure in the forward vector with a corresponding fall in the lateral vectors. This decrease in lateral pressure (i.e. the distending pressure keeping the collapsible tube open) causes the tube to narrow, leading to partial obstruction. In addition, according to the *Bernoulli principle*, the velocity of a gas increases as it flows through a partially obstructed tube, creating an additional decrease in intraluminal pressure and further exacerbating the obstruction (Fig. 2.5). This pattern of intermittent flow produces audible sounds that are characterized (depending upon the level of partial obstruction) as stertor, gurgling, stridor, wheezes, rhonchi, and rales. For example, stretor is a snoring or snorting sound that is produced by turbulence within the nasopharynx. Gurgling is produced by turbulence within the oropharynx due to the mixture of air and secretions. Stridor is the sound produced by turbulent airflow in a partially obstructed trachea, either due to intrinsic obstruction or extrinsic compression [1, 2, 8–14].

According to Hagen-Poiseuille's law, the change in air flow resulting from a reduction in airway diameter is directly proportional to the airway radius elevated to the fourth power:

$$\mathbf{Q} = \left(\Delta \mathbf{P}\,\pi\,\mathbf{r}^{4}\right) / \left(8\,\eta\,\mathbf{L}\right)$$

where Q is flow, ΔP is the pressure gradient from one end of the airway to the other end, r is the radius of the airway, η is the viscosity of the air, and L is the length of the airway. Therefore, increasing the length of the airway (L), increasing the viscosity of the air (η), or decreasing the radius of the airway will reduce laminar air flow. Changing the airway radius, however, has the greatest effect on flow. Hagen-Poiseuille's law holds for conditions of laminar flow. Laminar flow is highly organized, streamlined, and efficient. Turbulent flow, on the other hand, is highly disorganized, chaotic, and inefficient (Fig. 2.6). Laminar flow is typically found in the peripheral airways, while turbulent flow is found

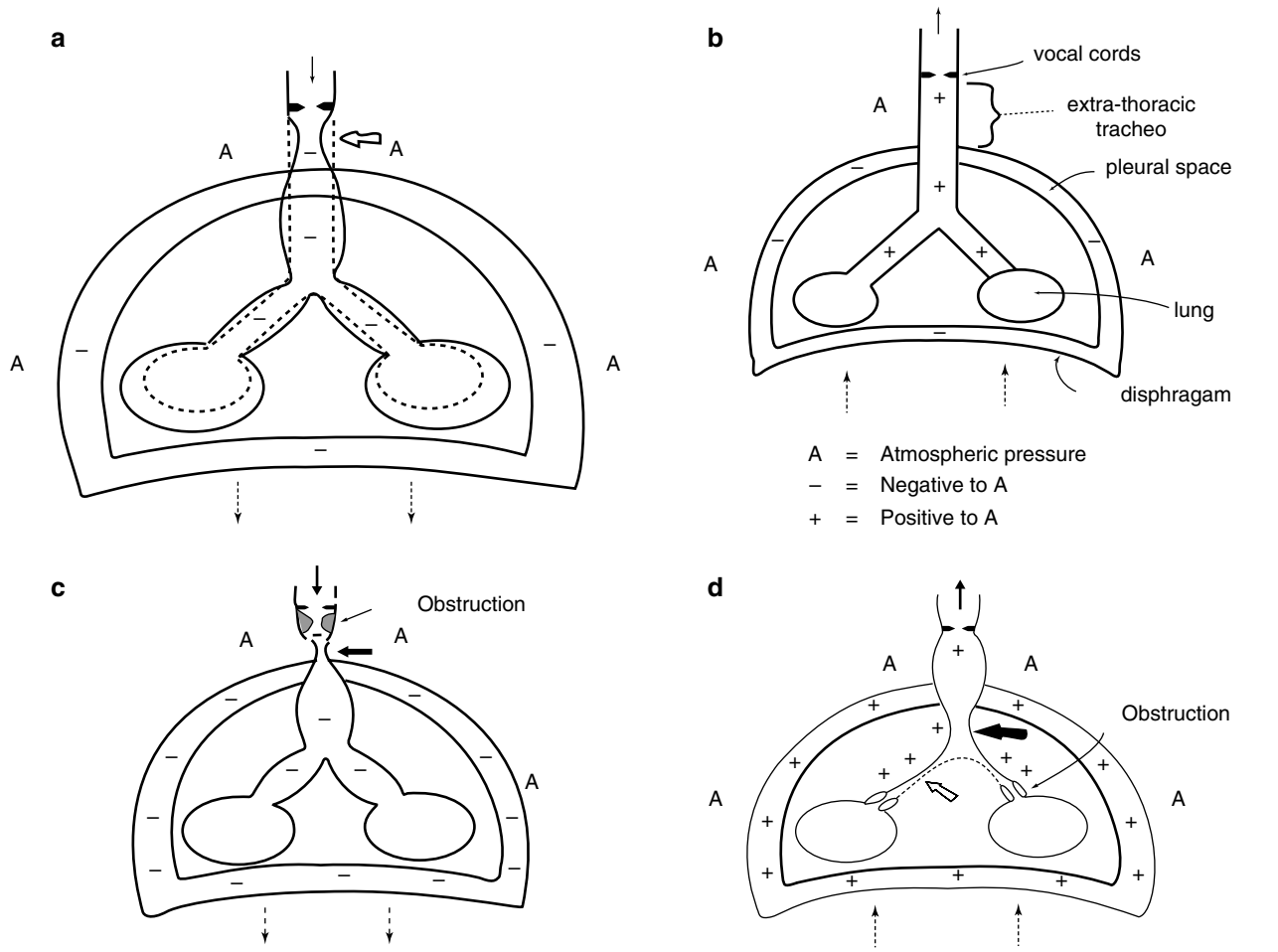


Fig. 2.2 (**a**) Normal Inspiration. At end-expiration, intrapleural pressure is less than atmospheric pressure, so it should maintain airway patency. In infants the highly compliant chest wall does not provide the support required. Thus airway closure occurs with each breath. Descent of the diaphragm and contraction of the intercostals muscles develop a greater negative intrathoracic pressure relative to intraluminal and atmospheric pressure. The net result is a longitudinal stretching of the larynx and trachea, dilation of the intrathoracic trachea and bronchi, movement of air into the lungs, and some dynamic collapse of the extrathoracic trachea due to the increased compliance of the trachea ad the negative intraluminal pressure in relation to atmospheric pressure. (**b**) Normal expiration. Intraluminal pressures are slightly positive in relation to atmospheric pressure, so air is forced out of the lungs. (**c**) Extra-thoracic obstruction (obstructed inspiration). Respiratory dynamics occurring with upper airway obstruction; note the severe dynamic collapse of the extrathoracic trachea below the level of obstruction. This collapse is greatest at the thoracic inlet, where the largest pressure gradient exists between negative intratracheal pressure and atmospheric pressure. (**d**) Intra-thoracic obstruction (obstructed expiration). Respiratory dynamics occurring with lower airway obstruction. Breathing through a partially obstructed lower airway (such as occurs in bronchiolitis or asthma) results in greater positive intrathoracic pressures, with dynamic collapse of the intrathoracic airways (prolonged expiration or wheezing) (Reprinted from Zalzal [11]. With permission from Elsevier)

in the proximal, upper airways. Importantly, the Poiseuille's law assumes conditions of laminar flow. When turbulent flow is present, as occurs during partial airway obstruction, airway resistance is inversely proportional to the radius of the airway to the fifth power! The Reynolds number can be used to determine whether conditions favor laminar versus turbulent flow. It is calculated by the following equation:

$$\mathbf{Re = 2Vr\rho / \eta}$$

Where Re is the Reynolds number, V is the velocity of flow of air, r is the radius of the airway, η is the viscosity of the air, and ρ is the density of the air. Laminar flow is favored when the Reynolds number is less than 2,000, while turbulent flow is favored when the Reynolds number is greater than 4,000. In other words, the higher the Reynolds number, the more likely turbulent flow is present. As such, higher velocities (such as occurs during crying, coughing, agitation, or respiratory distress), larger caliber airways, lower air density, and lower air viscosity all favor turbulent flow [15, 16].

Clinical Manifestations of Airway Obstruction

Careful assessment of the time in the respiratory cycle in which stridor predominates may provide valuable diagnostic clues in determining the site of airway obstruction [2, 8–15].

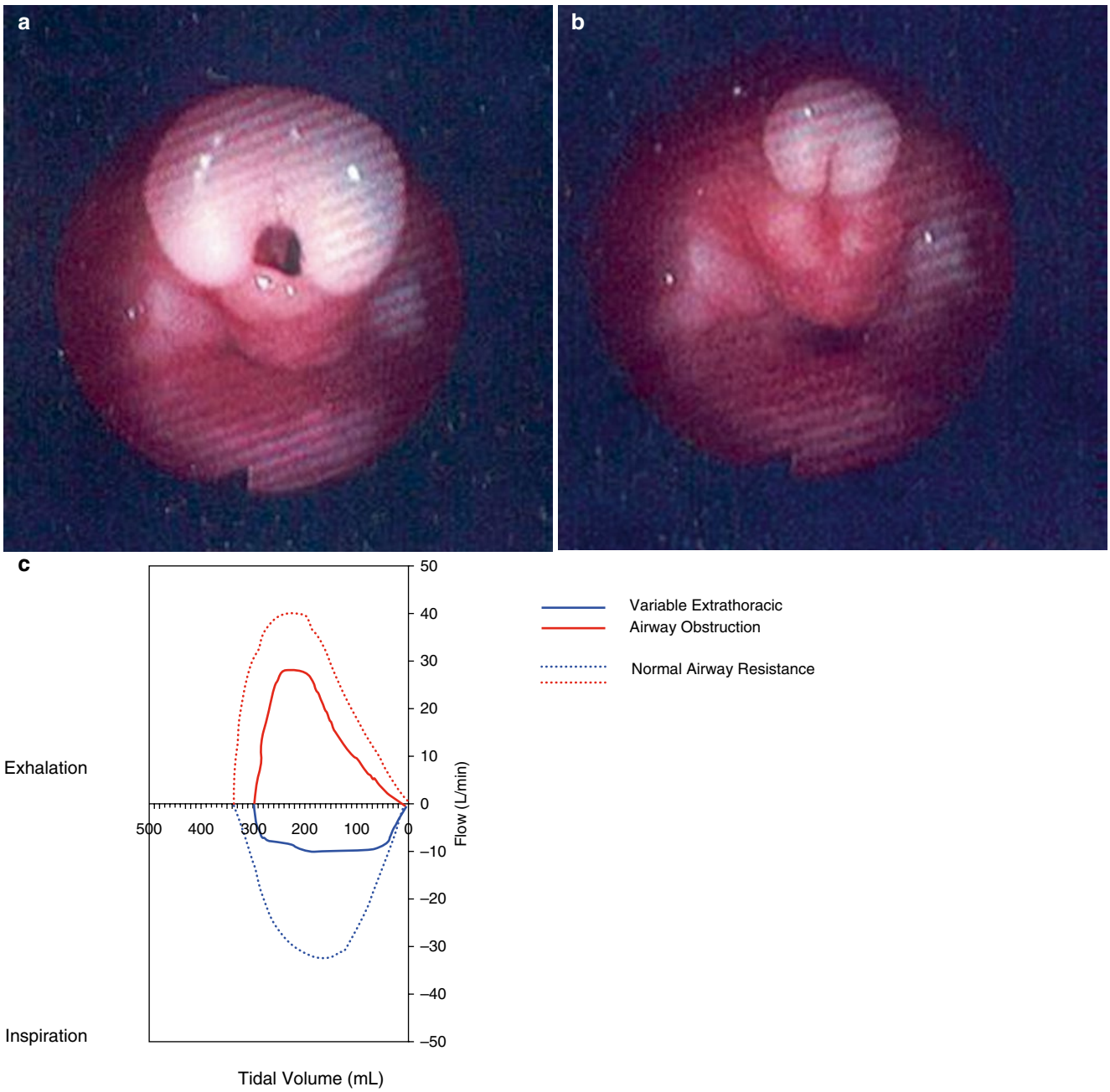


Fig. 2.3 Endoscopic appearance of the larynx in patient with dynamic airway compression secondary to laryngomalacia. (**a**) Severe laryngomalacia during expiration. (**b**) Same patient during inspiration with total collapse of the airway. (**c**) Flow-volume loops further demonstrating evidence of worsening extrathoracic airway obstruction during inspiration

For example, according to the principles discussed in the preceding paragraph, partial obstruction of the extrathoracic, supraglottic airway usually manifests as inspiratory stridor (i.e. occurring during the initial phase of inspiration). Partial obstruction of the intrathoracic, subglottic airway, on the other hand, usually manifests as biphasic (inspiratory AND expiratory) stridor. Changes in the severity of stridor may suggest the presence of an expanding lesion, such as a papilloma or congenital cyst. Wheezing, on the other hand, is produced by partial obstruction in the smaller, peripheral airways.

Initial attention should focus on the child's overall appearance and cardiorespiratory status, as this will influence subsequent decision-making with respect to the necessary speed and sequence of subsequent diagnostic and therapeutic actions [1, 2, 8, 9]. The child's level of consciousness should be assessed immediately, as an obtunded or unconscious child may require immediate control of the airway. Restlessness, anxiety, diaphoresis are usually signs of *air hunger* and hypoxemia. Drooling or the inability to handle oral secretions results from an inability to swallow

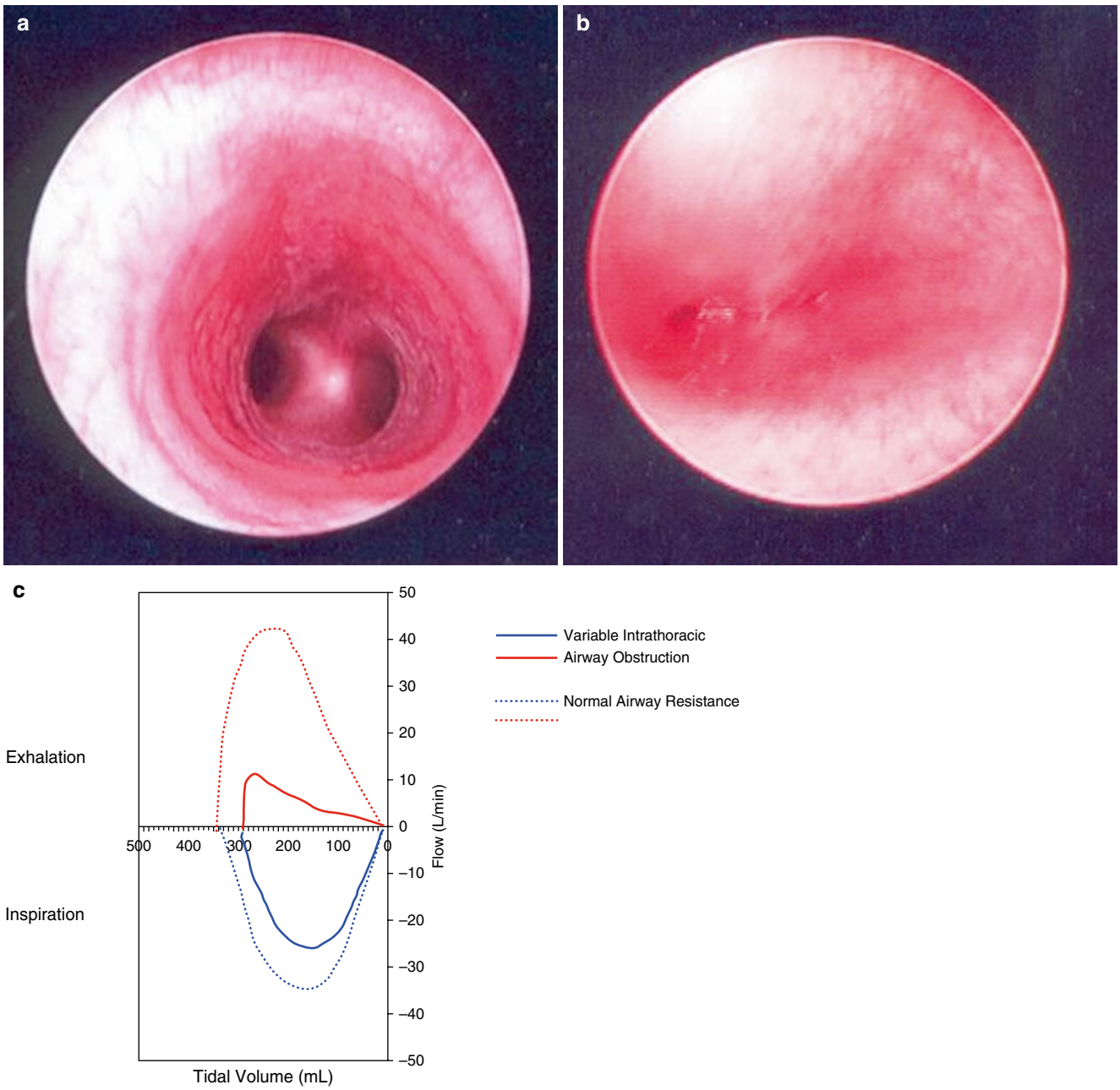


Fig. 2.4 Endoscopic appearance of the trachea in a patient with dynamic airway compression secondary to tracheomalacia. (**a**) Normal trachea. (**b**) Child with severe tracheomalacia demonstrating total collapse of the airway during inspiration. (**c**) Flow-volume loops further demonstrating evidence of worsening intrathoracic airway obstruction during expiration

secondary to pain or swelling of affected tissues and is typically seen with supraglottic pathology (e.g. supraglottitis, retropharyngeal abscess). Accessory muscle use is an additional sign of increased work of breathing and is indicative of compromised gas exchange.

During quiet breathing, airflow is laminar and resistance to airflow is inversely proportional to the fourth power of the airway radius as stipulated by Poiseuille's law. When airflow is turbulent (e.g., during crying) resistance to airflow is inversely proportional to the fifth power of radius such that even a minor reduction in the cross-sectional area of the airway will result in a marked increase in airflow resistance and work of breathing. For these reasons, the infant or child with airway obstruction should be kept calm and as quiet as possible to prevent generation of turbulent airflow, increased airway resistance, and worsening respiratory distress. In general, any child in severe respiratory distress will assume a position that maximizes oxygenation and ventilation and should be allowed to remain in this *position of comfort*. For example, the child with supraglottitis will sit erect with the

head tilted forward in the *sniffing position*, whereas a child with a retropharyngeal abscess will assume a head tilt or opisthotonus posture because of spasm of the muscles supporting the cervical spine [1, 2, 8, 9].

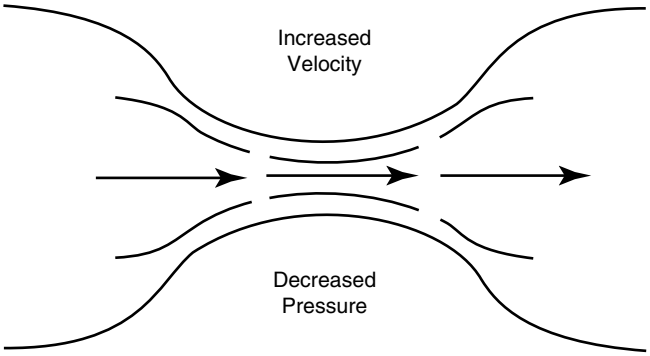


Fig. 2.5 Illustration of the Venturi effect and Bernoulli's principle

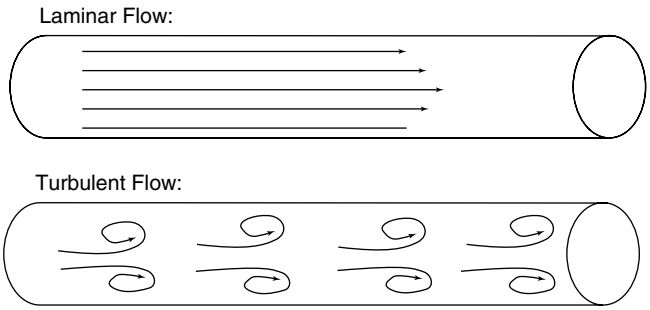


Fig. 2.6 Laminar versus turbulent air flow

Infectious Disorders of the Pediatric Airway

The clinical spectrum of infectious causes of upper airway obstruction has changed dramatically in the last few decades, especially following the introduction of vaccines against diphtheria and *Haemophilus influenzae*. Many of the infectious causes of upper airway obstruction pose less of a threat today as a result of advances in prevention, early diagnosis, and treatment. Nevertheless, infectious causes of upper airway obstruction remain a common cause of upper airway obstruction as well as an important source of morbidity and potential mortality in the pediatric age group [17–19] (Table 2.3).

Viral Laryngotracheobronchitis ("Croup")

Viral laryngotracheobronchitis, or croup, is the most common infectious cause of upper airway obstruction in children with an annual incidence of 18 per 1,000 children in the United States [20]. Croup primarily affects children between the ages of 6 months and 4 years with a peak incidence between 1 to 2 years of age. While sporadic cases may be seen throughout the year, the peak incidence occurs during early fall and winter. Males are affected slightly more commonly than females [17–21]. Croup is caused by an inflammation affecting the subglottic tissues, occasionally affecting the tracheobronchial tree as well, usually due to a viral infection. Croup is most commonly caused by parainfluenza virus type 1, though parainfluenza virus types 2 and 3, influenza A and B, respiratory syncytial virus (RSV), human metapneumovirus, adenovirus, rhinovirus, coronavirus, enterovirus, and *Mycoplasma pneumoniae* are commonly implicated as well [21–25].

Table 2.3 Infectious causes of upper airway obstruction

	Croup	Epiglottitis	Bacterial tracheitis	Retropharyngeal abscess
Onset	Gradual Viral prodrome 1–7 days	Rapid onset 6–12 h	Viral prodrome followed by rapid deterioration	Viral prodrome followed by rapid deterioration
Typical age at onset	6 months–4 years	2–8 years	6 months–8 years	<5 years
Seasonal occurrence	Late fall to winter	Throughout the year	Fall to winter	Throughout the year
Causative agents	Parainfluenza, respiratory syncytial virus, influenza A	*Haemophilus influenzae* type b (classically), *Streptococcus pneumoniae,* GABHS	*Staphylococcus aureus* (classically), GABHS, *Streptococcus pneumoniae*	Anaerobic bacteria, GABHS, *Staphylococcus aureus*
Pathology	Subglottic edema	Inflammatory edema of supraglottis	thick, mucopurulent, membranous tracheal secretions	Abscess formation in the deep cervical fascia
Fever	Low-grade	High fever	High fever	High fever
Cough	"Barking" or "seal-like"	None	Usually absent	Usually absent
Sore throat	None	Severe	None	Severe
Drooling	None	Frequent	None	Frequent
Posture	Any position	Sitting forward, mouth open, neck extended ("tripod position")	Any position	Sitting forward, mouth open, neck extended ("tripod position")
Voice	Normal or hoarseness	Muffled	Normal or hoarseness	Muffled
Appearance	Nontoxic	Toxic	Toxic	Toxic

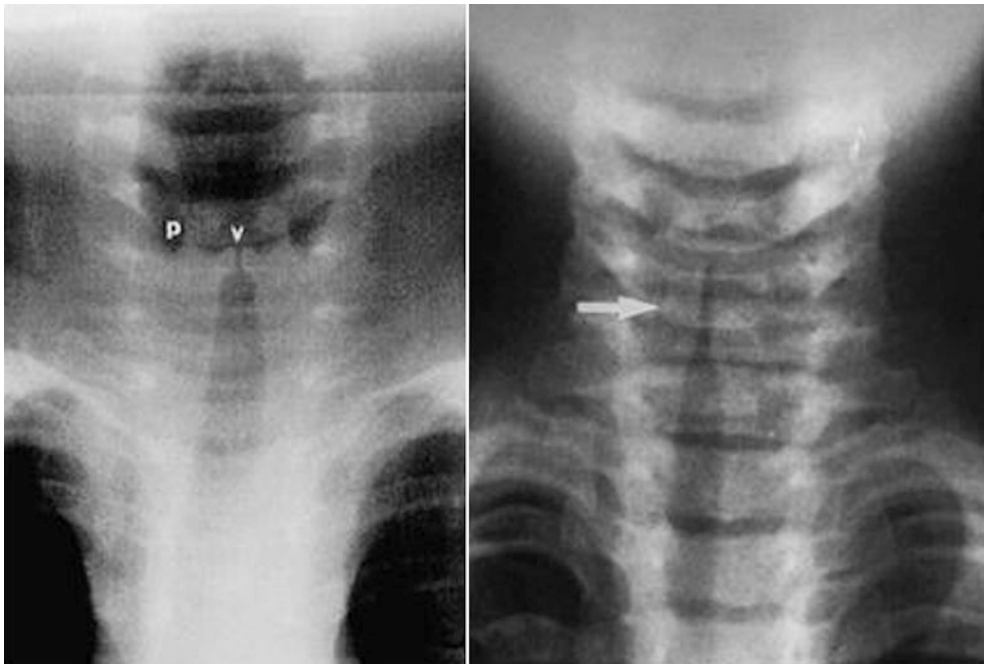


Fig. 2.7 Typical radiographic appearance of croup demonstrating symmetric narrowing of the subglottic region ("steeple sign") (**a**) Normal anatomy *(left)* (*v* vestibule, *p* pyriform sinuses), (**b**) Subglottic narrowing *(arrow)* consistent with croup *(right)*

Most children with croup can be managed in the outpatient setting, though between 1 % to 30 % of children require hospitalization and 2 % of hospitalized children require tracheal intubation and mechanical ventilatory support [26–28]. Children with croup typically present with several days of viral prodromal symptoms (cough, coryza, rhinorrhea, low-grade fever) with progressively worsening hoarseness, the classic "seal-like" or barky cough, and stridor (most commonly inspiratory in nature, though biphasic stridor is indicative of more severe degree of airway obstruction). The absence of drooling (i.e. dysphagia and inability to handle oral secretions) can help differentiate children with croup from those with a more serious bacterial illness, such as supraglottitis. Conversely, children with high fevers, drooling, absence of a cough, and/or a toxic appearance are more likely to have a more serious infection such as bacterial tracheitis, retropharyngeal abscess, or supraglottitis [29]. The classic harsh cough or bark may progress to inspiratory stridor and frank dyspnea in severe cases, and various scales have been devised to quantify the severity of stridor and document the progression of the illness and subsequent response to therapy [30–33].

While radiographic examination is useful to rule out other important causes of airway obstruction (e.g. supraglottitis, foreign body, retropharyngeal abscess, etc), the classic *steeple sign* (Fig. 2.7) may be absent in as many as half of children with croup [21, 34–36]. When visible, the subglottic narrowing is dynamic and is more accentuated during inspiration, because of the more negative intraluminal airway pressure during inspiration [37]. Children with a longstanding history of stridor or those under 4 months of age should be carefully evaluated for anatomical airway obstruction, such as laryngeal cyst or papillomatosis, vocal cord paresis, extrinsic airway compression (e.g. vascular ring), or laryngotracheal stenosis.

Croup is generally self-limited and frequently requires only supportive care. Humidification with continuous cool mist has been the standard accepted treatment for many years [34, 38–40]. The mechanism by which humidified cool mist improves symptomatology is not well understood, and probably reflects a placebo effect [38–40]. In addition, recent studies suggest that continuous cool mist therapy is not effective for croup [40, 41]. Nebulized racemic epinephrine rapidly reduces airway edema and improves symptoms, though the effect is transient and disappears within 2–3 h of administration [32, 42–48]. Both the racemic and L-isomer form of epinephrine appear to be safe and effective, however racemic epinephrine has not been shown to decrease the need for either tracheal intubation or tracheotomy in children with croup [42, 44, 45]. Rebound or worsening of airway obstruction after the drug effect wears off may occur with the use of racemic epinephrine, and for this reason, treated patients should be observed for 4–6 h after administration [48].

Several studies have shown substantial improvement in symptoms following administration of corticosteroids. Administration of corticosteroids appears to improve symptomatology, shorten the duration of hospital stay, and reduce the need for racemic epinephrine [26, 46, 49–55]. A single dose of dexamethasone is usually adequate for mild to moderate croup. The dose of dexamethasone ranges from 0.15 mg/kg of oral preparation to 0.6 mg/kg of parenteral

preparation. Nebulized corticosteroids appear to be effective as well, especially when administered in combination with racemic epinephrine [46, 55–62]. Children with severe croup who are managed in the PICU setting may require a more prolonged course of corticosteroids. Although few adequately controlled, randomized studies exist to suggest any benefit to prolonged administration of corticosteroids in critically ill children with acute respiratory failure secondary to croup, the wealth of anecdotal experience would suggest this to be a reasonable practice. Corticosteroids appear to be advantageous in relieving upper airway obstruction regardless of the route of administration [63–66]. While the precise mechanism of action of corticosteroids in croup is not readily known, the rapid response observed following corticosteroid administration suggests that decreased capillary permeability and peripheral vasoconstriction plays an important role [63]. The anti-inflammatory effects of corticosteroids (via inhibition of pro-inflammatory gene expression) require 6–12 h for maximal effect [63–66].

The use of helium-oxygen mixtures may be beneficial in some children with croup. Helium-oxygen mixtures create conditions that favor laminar flow as opposed to turbulent flow. Recall that airway resistance is inversely proportional to the airway radius to the fifth power (r^5) under conditions of turbulent air flow (versus airway radius to the fourth power when laminar flow is present). Helium is a colorless, odorless gas with the lowest density of any gas except hydrogen. In addition, helium is more viscous than ambient air. As such, helium will reduce the Reynolds number and change a turbulent flow pattern to a laminar flow pattern, resulting in lower airway resistance and improved bulk flow [15, 16, 67]. Helium-oxygen gas (Heliox) mixtures have been shown to improve the work of breathing and gas exchange in children with croup [67–79]. Heliox has few side effects and is easy to administer by face mask, hood, high-flow nasal cannula, or via a tracheal tube in children on mechanical ventilatory support [74]. In order to minimize the risk of asphyxia secondary to administration of 100 % helium, helium-oxygen mixtures should only be administered from pre-mixed helium-oxygen cylinders. Currently, 80:20 helium-oxygen and 70:30 helium:oxygen mixtures are available. Therefore, children with a high oxygen requirement are unlikely to benefit (and may actually worsen) from heliox administration. The beneficial effects of helium are reduced with lower ratios of helium-to-oxygen, though it appears likely that helium will have at least some therapeutic value even at low concentrations [16, 68, 75].

Until the airway inflammation resolves, severe upper airway obstruction may develop and occasionally necessitate tracheal intubation. Prior to the introduction of corticosteroid therapy, tracheal intubation was required in approximately 2 % of children hospitalized with croup [8, 17–19]. Tracheal intubation is now commonly limited to those children who either have pre-existing airway abnormalities or who have been tracheally intubated in an outside facility prior to transfer. Generally, tracheal intubation with a tube smaller than what would be normally predicted for age and weight should be used in the minority of children requiring tracheal intubation and mechanical ventilatory support. Extubation can usually be accomplished within 2–3 days once an air leak has developed around the tracheal tube. Bronchoscopy is reserved for children who fail to develop an air leak after 7 days, or in children less than 6 months of age, who have a high likelihood of congenital malformations of the airway [8, 17–19]. Although the etiologies of many infections of upper respiratory tract are viral, bacterial superinfection may occur. However, uncomplicated croup is viral in origin and should not be treated with antibiotics. Antibiotic therapy may be considered in those children who fail to improve or who require tracheal intubation.

Supraglottis ("Epiglottitis")

Epiglottitis is a true emergency, though the term is somewhat misleading as the supraglottic structures are most severely affected. Supraglottitis is perhaps more appropriate for this reason and classically affects children between the age of 2 and 8 years [8, 17–19]. Historically, supraglottitis was most commonly caused by *Haemophilus influenzae* type B. *Streptococcus pneumoniae*, group A β-hemolytic *Streptococcus* (GABHS), and *Staphylococcus aureus* are reported more commonly in the post-Hib vaccination era [80–86]. Since the development and widespread use of the conjugated HIB vaccine, there has been a significant decrease in the incidence of supraglottitis. The incidence of supraglottitis in children <5 years of age has decreased from 41 cases per 100,000 in 1987 to 1.3 cases per 100,000 in 1997 [87]. The incidence of supraglottitis appears to have stabilized at around 1.3 cases per 100,000 children, primarily due to low or incomplete vaccination coverage in localized populations, as well as cases of supraglottitis caused by microorganisms other than *Haemophilus influenzae* type b [88].

Supraglottitis requires a high index of suspicion, especially now in the post-Hib vaccination era when many physicians have never seen a child with true supraglottitis. In addition, especially now in the post-Hib vaccination era, epiglottitis may present with atypical features, especially in children under 2 years of age [81, 89, 90]. Children classically present with rapidly progressive signs and symptoms, including high fever, irritability, drooling, and respiratory distress (the "4 D's" include drooling, dysphagia, dyspnea, and dysphonia). These children are toxic in appearance and prefer to rest in the tripod position. Stridor is relatively late and ominous. There is usually no viral prodrome. By the time that affected children present for medical attention, they are generally

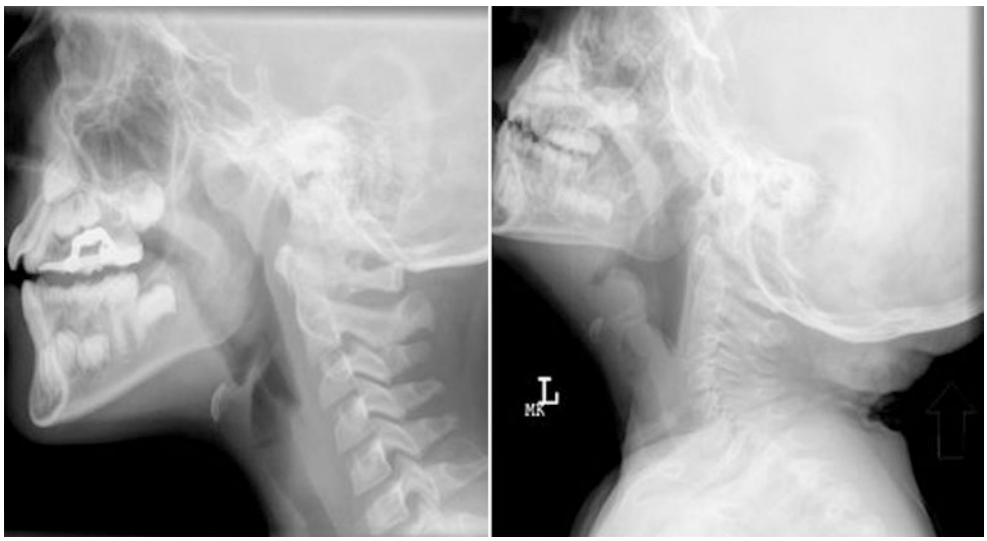


Fig. 2.8 Typical radiographic appearance of supraglottitis. (**a**) Normal lateral neck X-ray showing normal epiglottis**,** (**b**) Lateral neck X-ray showing the classic appearance of supraglottitis: (1) loss of cervical lordosis; (2) thick, rounded epiglottis ("thumb sign"); (3) loss of the vallecular air space; and thickening of the aryepiglottic folds

toxic and have inspiratory stridor [8, 17–19]. The voice tends to be muffled, rather than hoarse as in children with croup. Affected children assume a characteristic sniffing position in an attempt to maintain optimal airway patency. These children are usually anxious, which is a strong indication that their airway is significantly compromised.

When supraglottitis is suspected, intraoral examination and lateral neck radiograph should be deferred and only performed if equipment and personnel are available to secure the airway immediately. Excessive manipulation of the child and his airway should be avoided to minimize the risk of acute exacerbation of airway obstruction. The appearance on a lateral neck radiograph obtained with hyperextension of the neck is classic (Fig. 2.8), though diagnosis is usually confirmed by direct inspection of the airway in the operating room. When a diagnosis of supraglottitis is entertained based upon initial history and physical examination, the child should be accompanied by a physician skilled in airway management to the operating room. The child should be allowed to remain in his or her "position of comfort" and all anxiety-provoking procedures (e.g. phlebotomy, oral examination, etc) should be deferred. Direct laryngoscopy under anesthesia should be performed while maintaining spontaneous breathing [8, 17–19, 91–94]. Cultures of the supraglottic region should be obtained, and the trachea should be intubated. Treatment with broad-spectrum antibiotics effective against β-lactamase-producing microorganisms is initiated once cultures have been obtained (e.g. a second- or third-generation cephalosporin such as cefuroxime or ceftriaxone, or alternatively, ampicillin/sulbactam) [8, 17–19, 95, 96]. Antibiotic therapy should be tailored to the pathogenic organism, and the duration of antibiotic therapy is determined by the clinical response. Generally, symptomatic improvement and the development of an audible air leak around the tracheal tube occurs within 24–48 h [97]. Despite the virtual elimination of invasive HIB infection, it is important for pediatric intensivists to understand the management issues surrounding patients with supraglottitis to avoid disastrous outcomes.

Recent studies suggest that a less conservative approach than the one described above (i.e., direct visualization of the airway and tracheal intubation in the operative room setting) may be feasible in select patients [86, 98–101]. Whether this reflects a changing spectrum of disease is not known at this time. It should also be noted that most of the studies describing this less conservative approach to management are retrospective in nature and limited to the adult population. It is likely that the management of this once common malady of childhood will continue to evolve in the years to come.

Bacterial Tracheitis

Bacterial tracheitis, also known as pseudomembranous croup, is a relatively uncommon, but potentially life-threatening cause of infectious upper airway obstruction in children [8, 17–19]. It is characterized by thick, mucopurulent, membranous tracheal secretions that do not clear with cough, which have the potential to occlude the airway. Bacterial tracheitis is more insidious compared to supraglottitis and affects children between the ages of 6 months and 8 years with a peak incidence during fall and winter [8, 17–19, 102–104]. Children frequently present with a viral prodrome of several days duration, accompanied by low-grade fever, cough, and stridor (similar to croup). The viral prodrome is followed by rapid clinical deterioration characterized by a high fever and upper airway obstruction. Affected children are more toxic in appearance compared to children with croup. Radiographic examination often is indistinguishable from that of croup (*steeple sign*), and in fact, the noted similarities between these two disorders have led some authors to suggest

that bacterial tracheitis represents a bacterial superinfection of croup.

Historically, bacterial tracheitis is most commonly secondary to *Staphylococcus aureus*, though *Streptococcus pneumoniae*, GABHS, *Hemophilus influenzae, Moraxella catarrhalis*, anaerobic bacteria, and viruses have been implicated as well [102–112]. Infection with the parainfluenza virus has been implicated as the prodromal infection in many cases, further lending credence to the suggestion that bacterial tracheitis represents a bacterial superinfection of croup. Children with bacterial tracheitis are managed using the epiglottis management algorithm described above [107, 111]. Direct inspection of the airway under anesthesia should be performed in the operating room, and usually reveals subglottic edema with ulcerations, erythema, and pseudomembrane formation in the trachea. Removal of pseudomembranes and dead tissue from the airway at diagnosis, tracheal intubation, and administration of broad-spectrum antibiotics, directed against staphylococcal and streptococcal species are the cornerstone of treatment. Empiric therapy should be broadly directed against both gram-positive and gram-negative organisms until culture results are available. Staphylococcal coverage is of obvious importance. Anaerobic organisms may be treated with clindamycin. Extubation may be attempted following clinical improvement and the development of an air leak around the tracheal tube, usually within 3–5 days [8, 17–19, 107, 111].

Retropharyngeal Abscess

Retropharyngeal abscess has been called "the epiglottitis of the new millennium" [113]. The retropharyngeal space is comprised of a loose network of connective tissue and lymph nodes that drain the nasopharynx, paranasal sinuses, middle ear, teeth, and facial bones. Infection and abscess formation in this area generally result from lymphatic spread of infection or direct spread from the nasopharynx, paranasal sinuses, or middle ear. These lymph nodes atrophy during early childhood, thereby decreasing the risk of disease in older children and adolescents [8, 17–19, 114–116]. For this reason, trauma (e.g. from placing a pencil or stick in the mouth) and foreign body ingestion account for the majority of cases in older children and adolescents. Most cases of retropharyngeal abscess occur in children less than 5 years of age, so there is a significant overlap in the affected age range compared to supraglottitis and bacterial tracheitis [8, 17–19].

Children with retropharyngeal abscess present with a nonspecific constellation of symptoms that progress to high fever, sore throat, and neck stiffness. Fever, sore throat, dysphagia, drooling, muffled voice, and limited neck movement or torticollis are the most common presenting symptoms. Airway symptoms include stridor or stretor and difficulty in breathing. Symptoms often mimic those of supraglottitis. However, in contrast to supraglottitis, children with retropharyngeal abscess normally have a sore throat and cough for several days before showing symptoms of fever and respiratory distress. The neck stiffness may mimic that seen in children with meningitis, such that these children are often evaluated for meningitis. Physical examination may reveal the presence of a bulging unilateral neck mass. Additional physical findings commonly include diffuse erythema, tonsillar exudates, and swelling or bulging of the involved tonsillar region. Cervical adenopathy appears to be greatest on the side of the neck where deep infection is most involved [8, 17–19, 117–119].

The diagnosis of retropharyngeal abscess is confirmed by the presence of an abnormally increased pre-vertebral space on lateral neck radiographs (Fig. 2.9). Additional radiographic findings include the presence of gas or air fluid levels in the retropharyngeal space and the loss of the normal cervical lordosis. Computed tomography (CT) with contrast confirms the presence of abscess, determines its extent, and



Fig. 2.9 Typical radiographic appearance of a peritonsillar abscess. A retropharyngeal space measured from the most anterior aspect of C2 to the soft tissues of the posterior pharyngeal wall >7 mm (normal 3–6 mm) or a retrotracheal space >14 mm is suggestive of RTA. Normal prevertebral spaces are as follows: Anterior to C2: less than or equal to 7 mm; Anterior to C3–C4: less than 5 mm or less than 40 % of the AP diameter of the C3 and C4 vertebral bodies. A good *rule of thumb* to remember is that the upper pre-vertebral soft tissue should be no wider than one vertebral body width. NOTE: Adequate hyperextension of the head and neck is necessary in order to properly interpret the film. If the head and neck are not properly positioned, the pre-vertebral space will appear widened. In addition, crying can cause rapid changes in the size of the retropharyngeal space. If there is any doubt, repeat radiographic examination with either more hyperextension of the neck, fluoroscopy, or CT imaging is indicated

identifies its relationship to the airway [119–123]. While blood cultures are generally negative, culture of the abscess often yields anaerobic microorganisms such as *Prevotella, Porphyromonas, Fusobacterium* and *Peptostreptococcus* spp, as well as *Staphylococcus aureus*, GABHS, and *Haemophilus influenzae* [124, 125].

Treatment with broad spectrum antibiotics and close observation is highly effective, with drainage of the abscess recommended in children refractory to antibiotic therapy. Complications are rare with early recognition and appropriate treatment, though complications include spontaneous rupture into the pharynx leading to aspiration or spread of the infection laterally to the side of the neck or dissection into the posterior mediastinum through the facial planes and the prevertebral space. While rare, death can occur from aspiration, upper airway obstruction, erosion into major blood vessels, or extension to the mediastinum with mediastinitis. Tracheal intubation is often necessary to protect the patient from aspiration of the purulent content [8, 17–19, 119].

Peritonsillar Abscess ("Quinsy" Tonsillitis)

Peritonsillar abscess (PTA) rarely requires admission to the PICU, but can lead to significant airway obstruction and respiratory compromise if not recognized and left untreated [126]. PTA, also known as "quinsy" tonsillitis is the most common deep space head and neck infection in children and is thought to result from the direct contiguous spread of infection from the tonsils. Older children and adolescents appear to be most commonly affected, with no seasonal predilection. Children with PTA present with sore throat, neck pain, odynophagia or dysphagia, and fever. Physical examination typically reveals enlargement of the cervical lymph nodes, uvular deviation, and a muffled voice. Treatment options include broad spectrum antibiotics, needle aspiration of the abscess, incision and drainage, and tonsillectomy [127–129]. Complications include extension of the infection, acute upper airway obstruction (rare), and rupture of the abscess with aspiration of purulent material and subsequent pneumonia [127–129].

Recurrent Respiratory Papillomatosis

Recurrent respiratory papillomatosis (RRP) is the most common benign laryngeal neoplasm in children, and is usually caused by perinatal transmission of HPV-6 or HPV-11. RRP is characterized by the proliferation of squamous epithelial cells in the upper respiratory tract, which occasionally form lesions that cause severe to life-threatening airway obstruction. Affected children are usually between the ages of 2 and 5 years and typically present with stridor and voice changes. The classic triad consists of a first-born child delivered vaginally to an adolescent mother. The diagnosis of RRP is based upon endoscopic observation of characteristic lesions. Because any region of the upper aerodigestive tract is involved laryngoscopy, bronchoscopy, and careful inspection of oropharynx and nasopharynx should be performed [17–19, 130].

The primary goal of treatment is to prevent airway obstruction while the lesions are in the proliferative phase and minimize any complications of therapy. The mainstay of treatment for RRP is surgical debulking of the lesions in the operating room by one of several methods, including physical debridement with forceps and/or CO_2 laser vaporization, as often as weekly to assure a safe airway. Adjuvant medical therapies to control aggressive papillomatosis include topical chemotherapy, corticosteroids, podophyllin, tetracycline, autogenous vaccine, immune stimulators, acyclovir, isotretinoin, interferon, and cidofovir [131–133]. Tracheotomy should be avoided if at all possible, though tracheotomy is occasionally required due to acquired tracheal stenosis [17–19, 130–133].

Infectious Mononucleosis

Acute airway obstruction secondary to enlargement of the tonsils and adenoids is a well-recognized complication of infectious mononucleosis. Fortunately, this complication is exceedingly rare and appears to occur primarily in younger children. Parenteral corticosteroids are recommended, based primarily upon case reports and retrospective series [134–138]. Tracheal intubation may be required if airway obstruction is severe, and in such cases tonsillectomy is generally recommended [139, 140].

Non-infectious Disorders of the Pediatric Airway

Obesity

The prevalence of childhood obesity has increased dramatically in recent years. Obesity is associated with decreased upper airway patency, principally related to increased fat deposition in the lateral walls of the pharynx [141] and is a common cause of obstructive sleep apnea syndrome (OSAS) in children [142, 143]. Adenotonsillectomy is a commonly performed surgical procedure in this population, and children with OSAS secondary to obesity frequently develop complications that monitoring and care in the PICU [144–149].

Angioedema

Angioedema is an immunologically mediated, nonpitting edema that frequently results in acute airway obstruction. It

is caused by a kinin- and complement-mediated increase in capillary permeability that leads to edema, usually affecting the head and neck, face, lips, tongue, and larynx. Angioedema is most often due to ingestion (either food or medication), upper respiratory tract infection, and insect envenomation [18].

Angioedema represents a type 1 anaphylactic reaction and results from immunoglobulin E (IgE)-mediated activation of mast cells leading to the release of histamine and other mediators. Signs and symptoms typically occur approximately 15 min after exposure to an allergen and may lead to respiratory and circulatory collapse. Early symptoms include itching of the eyes, nose, and throat associated with facial flushing and a tightening sensation in the throat. Tachycardia, bronchospasm, urticaria and a "feeling of impending doom" are other features suggestive of an anaphylactic reaction. Respiratory distress is secondary to edema of the larynx, trachea, and even hypopharynx. The type 1 reaction may also lead to a "late" allergic response causing airway obstruction that appears several hours after exposure to the allergen, such as food or medications. Children with angioedema rapidly improve with intravenous corticosteroids, antihistamines, and subcutaneous epinephrine, which are the mainstay of treatment. The airway should be secured in any child demonstrating signs and symptoms of acute airway obstruction, such as stridor and respiratory distress [18].

Adenotonsillar Hypertrophy

Adenotonsillar hypertrophy is usually the result of infection. The majority of the children with adenotonsillar hypertrophy present with symptoms of chronic airway obstruction, especially at night time; however a small group will present suddenly during an acute viral upper respiratory tract infection that causes additional swelling. Infectious mononucleosis commonly causes enlargement of lymphoid tissue and may precipitate acute obstruction in rare situations (see preceding paragraphs). Children with underlying craniofacial abnormalities such as Down's syndrome [150, 151] and children with hypotonia are more susceptible to acute episodes of obstruction from adenotonsillar swelling. Careful questioning of caregivers will often elicit a history of preceding chronic airway obstruction, especially at night time with loud snoring, obstructed and irregular breathing, and even brief periods of apnea. During an acute infection, these symptoms become more severe. Severe, long-standing airway obstruction may progress to cor pulmonale and right heart failure. Therefore, failure to respond to medical therapy is usually an indication for tonsillectomy and adenoidectomy.

Acquired Subglottic Stenosis

A history of previous tracheal intubation dramatically increases the incidence of subglottic injury [152–155]. Subglottic stenosis may be congenital (see chapter on airway malformations) or acquired. Prior to 1965 and before the advent of neonatal intensive care, acquired subglottic stenosis more commonly affected older children and adults following either trauma or infection (particularly supraglottitis, diphtheria, and tuberculosis). Acquired subglottic stenosis in these cases was frequently observed as a complication following tracheotomy, and not prolonged tracheal intubation. Significant advances in pediatric critical care medicine, vaccination, and antimicrobial therapy has decreased the incidence of tracheotomy in this age group [152–155], and since 1965 the majority of cases of acquired subglottic stenosis involve children who develop subglottic stenosis following prolonged tracheal intubation due to preterm delivery. Early studies in this age group suggested that acquired subglottic stenosis occurs in 1.8 % of infants less than 1,500 g and one in 678 of infants greater than 1,500 g [153]. Given the significant advances in neonatal intensive care (especially with regards to the use of surfactant and non-invasive positive pressure ventilation), the incidence of acquired subglottic stenosis in this age group is likely lower. Regardless, even in the absence of newer data, acquired subglottic stenosis remains a significant complication following prolonged tracheal intubation.

Affected children generally present with feeding difficulty, changes in voice, stridor (usually biphasic), and respiratory distress. The feeding problems are so severe that failure to thrive is common. Occasionally affected children will present with recurrent croup or asthma which is refractory to medical therapy. The mainstay for diagnosis of subglottic stenosis is rigid bronchoscopy under general anesthesia. Flexible bronchoscopy may help to identify the level of airway collapse. CT or MRI scan may be necessary in order to rule out the possibility of extrinsic vascular compression. Finally, affected children should undergo a thorough evaluation for swallowing dysfunction, gastroesophageal reflux, and pulmonary function prior to surgical correction. Surgical options include an anterior cricoid spilt, tracheotomy, and laryngotracheoplasty [152, 156–161].

Laryngeal Neoplasms and Mediastinal Masses

With the exception of laryngeal papillomatosis, laryngeal tumors are rare in children. Some of the rapidly developing malignant mediastinal masses (e.g. lymphomas, certain type of acute leukemias) may impinge upon the intrathoracic trachea and lead to severe respiratory compromise. Aggressive medical therapy should be commenced immediately to decrease the size of tumor mass. Tracheal intubation

should only be considered for severe respiratory compromise as these masses may also impinge on the bronchial tree distal to the tip of the endotracheal tube and will not improve with positive-pressure ventilation. A stepwise and carefully planned, multi-disciplinary approach is clearly warranted here. In addition, less invasive diagnostic algorithms to avoid the need for general anesthesia, as well as the use of adjuncts such as non-invasive positive pressure ventilation and helium-oxygen mixtures should also be considered [162–170].

Airway Trauma

Damage to the upper airway can occur from multiple causes, including foreign body aspiration, thermal or chemical injury, and direct trauma to the airway itself, either blunt or penetrating.

Post-extubation Stridor

Tracheal intubation, although vital to facilitate mechanical ventilation in the intensive care and operating room setting, is associated with the potential development of glottic or subglottic edema (Fig. 2.10) resulting in stridor on extubation [171]. Post-extubation stridor is an inspiratory stridor that occurs within 24 h of extubation and is associated with tachypnea, increased work of breathing, and occasionally the need for re-intubation. Post-extubation stridor is relatively common problem and occurs in as may as 37 % of critically ill children [172]. Postextubation stridor may prolong length of stay in the intensive care unit, particularly if airway obstruction is severe and reintubation proves necessary. Reactive edema develops in the glottic or subglottic mucosa due to pressure necrosis and often worsens upon removal of the endotracheal tube [171–173].

Historically, cuffed tracheal tubes have not been generally recommended for children less than 8 years of age. Using an uncuffed tracheal tube, for example, does allow a tube of larger internal diameter to be used, minimizing resistance to airflow and the work of breathing in the spontaneously breathing child. A prolonged period of tracheal intubation and a poorly fitted tracheal tube are significant risk factors for damage to the tracheal mucosa regardless of whether the tracheal tube is cuffed or uncuffed. Cuffed tracheal tubes may have significant advantages over uncuffed tracheal tubes, including better control of air leakage and decreased risk of aspiration and infection in mechanically ventilated children. Therefore, cuffed tracheal tubes are being used with greater frequency in this age group [174, 175], especially when high inflation pressures are required to provide adequate oxygenation and ventilation in the setting of severe acute lung disease. The available data suggests that there is no difference in the incidence of post-extubation stridor in children who were tracheally intubated with cuffed tubes as compared to those who received uncuffed tubes [174–181].

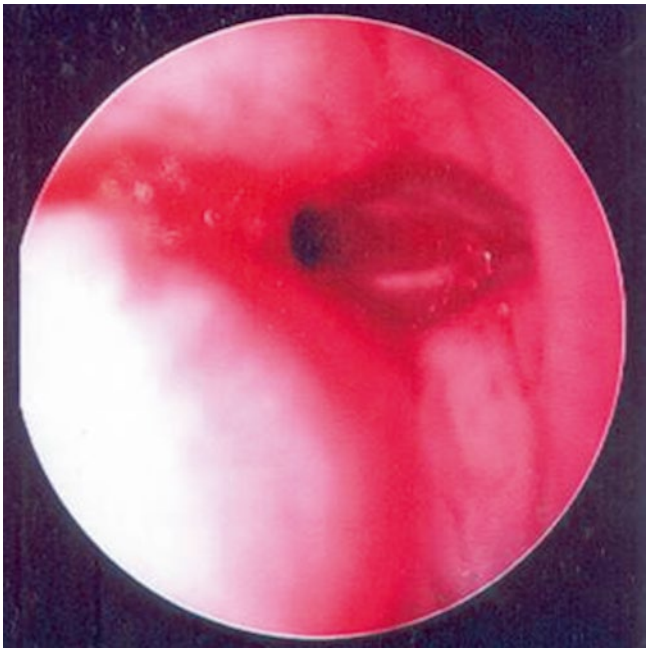


Fig. 2.10 Endoscopic appearance, subglottic edema from prolonged tracheal intubation

There are several factors associated with post-extubation stridor, including age, size of endotracheal tube, and type of injury [171–173, 182–184]. Patients suffering from burn and trauma appear to be at particularly significant risk. As discussed previously above, children with trisomy 21 are also at significant risk of developing post-extubation stridor. Children with trisomy 21 have smaller airways than other children due to an overall decrease in the diameter of the tracheal lumen. Tracheal intubation should therefore be performed with an endotracheal tube at least two sizes smaller than would be used in a child of the same age without trisomy 21 in order to avert potential trauma to the airway [183].

The *air-leak test* prior to extubation is a poor predictor of extubation success, though it may predict the presence of post-extubation stridor with some degree of accuracy [184–186]. Several treatment options for post-extubation stridor exist, though known have been shown to prevent subsequent re-intubation in severe cases. The vasoconstrictive properties of racemic epinephrine and its proven efficacy in the treatment of croup have led to its routine immediately following extubation in many neonatal and pediatric ICUs [42–47, 187, 188]. The use of corticosteroids in the prevention and/or treatment of post-extubation stridor are advocated by many pediatric intensivists, though

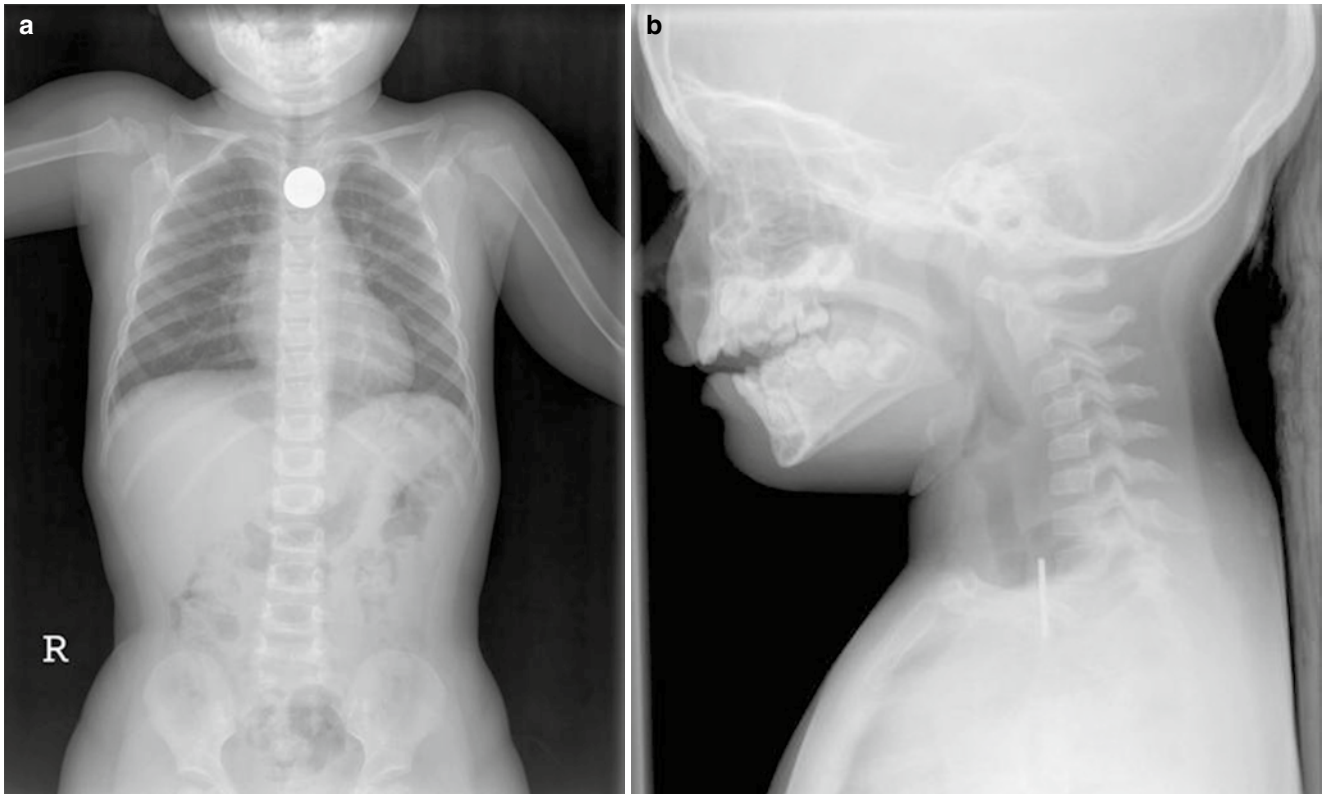


Fig. 2.11 Radiopaque foreign body (*coin*) in the esophagus. (**a**) AP Chest view, (**b**) Lateral Neck view

there is very little evidence to support the universal use of corticosteroids at this time. Dexamethasone at a dose of 1–1.5 mg/kg/day divided every 6–8 h (maximum daily dose 40 mg/day) has also been administered in an attempt to interrupt the progressive cycle of inflammation that results in edema of injured tissue following extubation. Again, the evidence that this therapy prevents re-intubation is limited [189–196], though one meta-analysis suggested a possible benefit [193]. Regardless, in a national survey of pediatric critical care fellowship program directors, 66 % of those surveyed continue to rely on the air leak test and use corticosteroids to prevent post-extubation stridor and extubation failure. Further, the majority stated that they would delay extubation and administer corticosteroids in the presence an air leak of ≥ 30 cm H_2O [194]. Finally, helium-oxygen mixtures (see preceding discussion) have also been used in several studies [195–201]. Heliox should be viewed only as a temporizing measure until either the aforementioned therapies become effective or the disease process naturally resolves. In the majority of cases, post-extubation stridor is self limited, though re-intubation is occasionally required. Unfortunately, re-intubation further exacerbates the reactive airway edema. Ideally, a smaller tracheal tube (generally one size smaller) than previously used should be placed with the hope of causing less airway injury. The new tracheal tube is generally left in place until air-leak is observed 24–48 h later. Anatomic airway problems like subglottic stenosis, tracheal compression, etc should be considered if post-extubation stridor persists following the second attempt at extubation.

Foreign Body Aspiration

Foreign body aspiration is an important cause of accidental death in infants and young children, compounded by the fact that infants seem to place almost any object in their mouths [202]. While most foreign bodies pass through the vocal cords and lodge in the lower airways, laryngeal foreign bodies are not uncommon and are immediately life-threatening. The clinical presentation depends upon the location of the foreign body as well as the degree of obstruction. Importantly, the actual aspiration event is not always identified and a high index of suspicion is required. Foreign bodies that are lodged in the glottic or subglottic airway (extrathoracic obstruction) often produce symptoms that mimic croup such as sudden onset of stridor and respiratory distress. In contrast, foreign bodies lodged in the distal trachea (intrathoracic obstruction) tend to produce coughing and wheezing, mimicking asthma or bronchiolitis.

The most commonly aspirated foreign bodies include vegetable matter like peanuts, grapes, and popcorn [202]. Large objects that are lodged in the proximal esophagus and apply

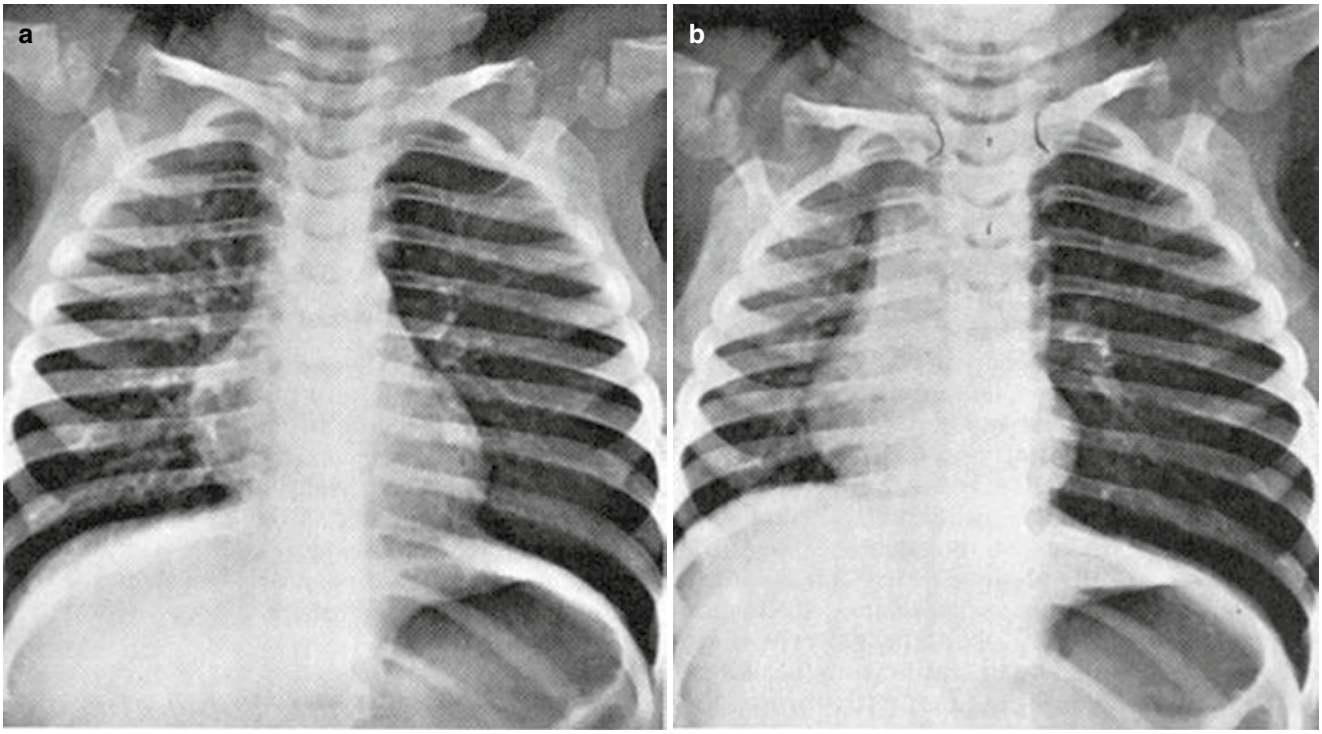


Fig. 2.12 Foreign body aspiration. Inspiratory and expiratory chest radiographs demonstrate hyperinflation due to a peanut fragment in the left mainstem bronchus. (**a**) The inspiratory film appears relatively normal except for a slight mediastinal shift to the right. (**b**) In expiration, the left lung remains overaerated (i.e., ball-valve mechanism), and the mediastinum moves far to the right

pressure to the posterior larynx may also produce stridor and signs of upper airway obstruction. Coins are the most common foreign bodies ingested (Fig. 2.11) [203, 204]. Coins are radio-opaque and usually easy to remove via rigid esophagoscopy. Children with a history of choking and respiratory distress should undergo immediate rigid bronchoscopy, which is both diagnostic and therapeutic. Radiographs may be helpful if the child is otherwise stable. Most distal tracheal or bronchial foreign objects can often be identified on inspiratory/expiratory films, lateral decubitus films, or chest fluoroscopy. Lateral neck radiographs are helpful if the foreign body is radio-opaque (Fig. 2.11). However, most aspirated foreign bodies are not radiopaque and lodge in the bronchi. The presence of atelectasis (i.e. distal to a bronchus that is completely occluded by a foreign body) or air trapping and hyperinflation (i.e. distal to a partially-obstructing foreign body), which are viewed best on expiratory films, are findings that are highly suggestive of foreign body aspiration (Fig. 2.12) [205, 206]. However, a recent study questioned the utility of this additional test [207]. Basic life support maneuvers should be initiated in the field, whenever possible. Rigid bronchoscopy is the *gold standard* for diagnosis of foreign body aspiration and is the treatment of choice [202]. Occasionally, tracheotomy is required. If bronchoscopic extraction is unsuccessful, pulmonary lobectomy may be necessary. Foreign bodies often elicit a local inflammatory response, which is generally self-limited. Racemic epinephrine and systemic corticosteroids may be beneficial in this scenario.

Inhalational Injury

Life-threatening airway obstruction may develop as a result of inhalational injury, laryngeal burns, or caustic ingestions. Any child with a scald injury to the face or neck should be evaluated for potential inhalational injury. Inhalational injury should also be suspected in children with any of the following signs or symptoms: evidence of soot in sputum or vomitus, burns of the face, singed nasal hairs, lip burns, wheezing, stridor, or the presence of severe burns. An aggressive approach with early endoscopic evaluation in the operating room suite and management of the airway with either tracheal intubation or tracheotomy is recommended.

Direct Trauma

Although direct trauma resulting in serious injury to the craniofacial skeleton and larynx is relatively uncommon, the types of injuries sustained are likely to be significant and potentially life threatening. The anatomic features of the pediatric airway (e.g. cephalad position of the larynx, etc) may explain the relative infrequency of airway injuries in children versus adults. However, while the pediatric larynx is soft, pliable, and less likely to fracture, the ligamentous and soft tissue support is less well-developed such that laryngotracheal separation is not uncommon [208–214].

Blunt trauma to the airway appears to be more common in children compared to penetrating trauma and is more common in the adolescent age group [208–214]. The most frequent causes of injury are motor vehicle accidents or direct blows to the larynx. Edema and hematoma formation frequently lead to acute upper airway obstruction. Although less common compared to adults, laryngeal fractures occasionally occur. Laryngotracheal separation, while relatively uncommon, is potentially life-threatening. The severity of airway obstruction dictates the extent of the initial evaluation and management. An unstable airway should be immediately secured using the flexible bronchoscope. Tracheal intubation without endoscopic evaluation is best avoided. If immediate surgical intervention is required, tracheotomy is preferable to cricothyrotomy. If the airway is stable, radiographic evaluation should include chest radiograph (to look for associated injuries, such as pneumothorax, pneumomediastinum, or subcutaneous emphysema), lateral neck radiograph (to evaluate the cervical spine), and CT. A barium swallow may be helpful to rule out the possibility of esophageal tear or laceration [208–214].

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Congenital Airway Anomalies

3

Michael J. Rutter and Matthew J. Provenzano

Abstract

Management of the pediatric airway in the pediatric intensive care unit (PICU) carries the inherent potential of becoming problematic. Practitioners must balance the immediate respiratory and ventilator needs of the patient with the potentially detrimental long-term sequelae of their management choices. The presence of congenital airway anomalies compounds this problem, making it more difficult to secure and maintain an adequate airway. Early identification of these anomalies can assist the practitioner in developing strategies to safely secure the airway, provide adequate ventilation, and mitigate complications. This chapter presents an overview of airway management in critically ill infants, with particular emphasis on infants and children with anatomic airway anomalies. The specific anomalies described include retrognathia, laryngomalacia, vocal cord paralysis, subglottic stenosis, posterior laryngeal cleft, vascular compression, and complete tracheal rings.

Keywords

Retrognathia • Laryngomalacia • Vocal cord paralysis • Subglottic stenosis • Posterior laryngeal cleft • Vascular compression • Complete tracheal rings

The Pediatric Airway in the PICU Setting: General Considerations

Prevention of Complications

Although prolonged tracheal intubation may be tolerated for weeks or even months in neonates, this tolerance decreases with age. The longer the period of tracheal intubation, the greater the relative risk of developing subglottic stenosis or posterior glottic stenosis. A variety of factors may act synergistically to increase the risk of laryngeal injury secondary to tracheal intubation. These factors include the composition of the endotracheal tube, the duration of tracheal intubation, patient agitation while tracheally intubated, and factors that predispose patients to mucosal damage, such as extraesophageal reflux and airway burns. However, the most potent predisposing factor to laryngeal damage is the size of the endotracheal tube itself. Ideally, the size of the tube selected should be *child appropriate* more so than *age appropriate*.

An ideal tube should be large enough to allow adequate ventilation but small enough to permit a leak of air through the subglottis at a subglottic pressure of less than 20 cm H_2O. Although the average 4 year old should accommodate a 5.0-mm endotracheal tube, a 4 year old with an asymptomatic, mild congenital subglottic stenosis may require a 3.0-mm endotracheal tube. In some children, the size of the endotracheal tube ideal for the larynx may not allow adequate pulmonary ventilation and toilet. In such cases, a larger endotracheal tube without a leak may be tolerated for a period of time – a calculated risk, as the true risk of developing subglottic stenosis is still small. To minimize the risk of developing subglottic stenosis in this situation, consideration should be given to early tracheotomy. A similar problem may occur with poor pulmonary compliance, whereby a leak

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pressure of less than 20 cm H_2O may not allow adequate ventilation. One possible solution is the use of a low-pressure cuffed endotracheal tube that permits higher pressure ventilation while still minimizing laryngeal trauma. For some children, the risks associated with tracheal intubation may be circumvented by the use of alternatives such as continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), high flow nasal cannula, or tracheotomy.

Difficult Intubation

Given the possibility of encountering unpredictable difficulties during attempts at tracheal intubation, it is prudent to have a cascade of options available to secure an airway. Maintaining spontaneous ventilation during attempts to intubate is recommended, as children who are not paralyzed may be able to at least partly maintain their own airway should problems be encountered during attempts at tracheal intubation.

Anatomic anomalies of the mandible present a predictable challenge, especially in the neonate. The retrognathic child, particularly infants with Pierre-Robin sequence, may be extraordinarily difficult to intubate irrespective of the degree of retrognathia or airway obstruction. Children with microsomia, temporomandibular fixation, macroglossia, and maxillofacial trauma may be similarly challenging to intubate.

Standard intubation techniques also may be challenging in children in whom neck extension should be avoided. The child with an unstable cervical spine is the best example of this. The risk may be known, such as in a child with Down syndrome or atlanto-occipital instability, or unknown, such as in an unconscious child with a head injury and possibly a cervical injury. If intubation is elective, flexion extension views of the cervical spine of children at risk of cervical instability are prudent. Children with Down syndrome, mucopolysaccharide storage disorders, and any major chromosomal anomalies are most at risk. In most cases, however, intubation without neck extension may still be safely performed.

It is usually possible to intubate in a standard fashion, with the largest possible anesthetic laryngoscope blade, a styleted endotracheal tube (with the tip of the stylet being angled anteriorly 30–45° in a retrognathic child), and with laryngeal pressure applied. If this is unsuccessful, intubation may be performed with flexible fiberoptic transnasal endoscopy, rigid ventilating bronchoscopy, an endotracheal tube threaded over a Hopkins rod telescope, or a laryngeal mask airway. Even in children who are difficult to intubate, a bag and mask with an oral airway may be sufficient to temporarily stabilize the airway until a more definitive solution can be arranged. For children in whom intubation is very difficult, either elective or emergent tracheotomy is generally required. Whenever possible, it is desirable to place a tracheotomy with the airway already secured with an endotracheal tube.

The Child with a Tracheotomy

In the PICU setting, a tracheotomy tube should be easily managed, as the child may be conveniently ventilated and usually does not require sedation. However, a tracheotomy is not without risk, and tube blockage or displacement may result in abrupt airway obstruction. Tracheotomy tube complications may be divided into those related to a fresh tracheotomy tract and those related to tube obstruction. A fresh tracheotomy carries the risk of tube displacement and subsequent difficulty with tube replacement. Precautions to prevent displacement include maturing the stoma (the skin is sewn directly to the tracheal cartilage) and placing stay sutures. These precautions are taken so that if the tracheotomy is displaced, traction on the stay sutures will open the tracheotomy and aid in replacement of the tube. Flexible bronchoscopy at the time of tracheotomy placement permits assessment of the tube position, assuring that it is not too close to the carina or down a bronchus.

Respiratory symptoms may occur from obstruction within the tube or distal to the tube. Regular suctioning to the tip of the tube, but not beyond, will usually prevent tube obstruction. Suctioning is the first intervention for suspected obstruction. Tube replacement should take place if difficulties persist. If symptoms continue, obstruction distal to the tube should be suspected. Ideally, flexible bronchoscopy down the tracheotomy tube will confirm the site of obstruction and a longer tube may be all that is required to bypass the obstruction (usually granulation tissue or tracheomalacia). Positive pressure will alleviate obstruction due to tracheomalacia or bronchomalacia. In an emergency situation, a longer tracheotomy tube or even an endotracheal tube placed through the stoma, will usually bypass the obstruction.

Single-Stage Airway Reconstruction

Airway surgery is frequently performed without retaining a tracheotomy tube, but rather relying on an endotracheal tube to act as a temporary stent and to maintain the airway; this is referred to as *single-stage reconstruction*. The endotracheal tube may be required for only a few hours or may be placed for up to 2 weeks. In general, the more complex the surgery, the longer the period of tracheal intubation required. A prerequisite for successful single-stage surgery is capable PICU staff who can manage a child who may be tracheally intubated for a prolonged period and minimize the risk of

accidental extubation, as reintubation may potentially compromise the reconstruction. Ideally, paralytic agents should be avoided, for should an accidental extubation occur, nonparalyzed children may be able to manage their own airway for a time that is sufficient to arrange reintubation under controlled conditions.

Many children requiring airway surgery have a history of prolonged intubation and sedation before tracheotomy placement. These children may be quite tolerant to a range of sedatives. Most children younger than 3 years of age require sedation, while most neurologically normal children older than age 3 do not. Despite tracheal intubation, neurologically normal children older than 3 years of age may be able to ambulate and even eat. For children who require sedation, the amount of sedation required may be remarkable, resulting in a need for ventilation and inotropic support. This may also present problems of oversedation upon extubation. As such, conversion to a rapidly metabolized agent such as propofol for 12 h before extubation is useful. The child should be as awake as possible before extubation.

A bronchoscopic evaluation of the airway the day prior to extubation is very useful to (1) assess whether it is prudent to attempt extubation, (2) remove excessive glottic granulation tissue, and (3) place a smaller endotracheal tube that allows resolution of some of the laryngeal edema. Once a child is extubated, glottic or subglottic edema is common, and stridor and retractions are to be expected. Laryngeal edema typically worsens for the first 24–36 h and then subsides. Every effort should be made to avoid re-intubation during this period. Useful adjunctive measures include the use of racemic epinephrine, heliox, CPAP, high-flow nasal cannula, corticosteroids (dexamethasone, 0.5 mg/kg daily), and chest physiotherapy. If a child requires reintubation, it is usually worth reattempting extubation after an additional 48 h. If a child has failed a trial of extubation on three occasions, tracheotomy should be considered.

There are no absolutes, and for some children single-stage surgery should be approached with caution. This includes children who are difficult to intubate, those who have a history of failed single-stage surgery, those who have severe or multilevel airway stenosis, and those who have a history of problems with sedation.

Congenital Anomalies of the Airway

Retrognathia/Glossoptosis

Retrognathia is seen with a variety of conditions, including Pierre Robin-sequence, Treacher-Collins syndrome, and Stickler syndrome. An associated cleft palate is common in severe cases. The degree of retrognathia is not always a reliable indicator of the degree of obstruction or of the potential problems with tracheal intubation. Although obstructing retrognathia is usually a problem encountered in the neonatal nursery, problems may be encountered years later. Such problems are often triggered by seemingly trivial surgical procedures or with the insidious onset of severe sleep apnea.

For neonates, the initial management includes prone positioning, the use of high-flow nasal cannula, and occasionally, the use of a nasal trumpet. CPAP is often not successful, as the mask tends to exacerbate the relative retrognathia. Because infants struggle with feeding, nasogastric tube placement is often required. If the airway remains compromised, tracheal intubation is desirable, but, as discussed previously, it may be challenging.

Surgical intervention is reserved for those patients with significant obstructive symptoms or feeding problems. Performing a tracheotomy is standard, and, in most children catch-up growth of the mandible will permit decannulation within 1–2 years. If catch-up growth is not apparent by 1 year of age, consideration can be given to mandibular distraction. In some cases, distraction may be an alternative to tracheotomy; however, this remains controversial [1, 2]. Even after tracheotomy, some children continue to have symptoms of obstruction, as there is an association with retrognathia and tracheobronchomalacia [3]. Performing flexible bronchoscopy through the tracheotomy tube is diagnostic, and management with CPAP, BiPAP, or positive pressure ventilation may be required. In cases of isolated tracheomalacia, replacing the tracheotomy tube with a longer tube that lies close to the carina may be sufficient.

Laryngomalacia

Laryngomalacia is the most frequent cause of stridor in the neonate, and most children are symptomatic at birth or within the first few days of life. Stridor is generally mild, but is exacerbated by feeding, crying, and lying in a supine position. In 50 % of cases, symptoms worsen during the first 6 months of life, and, in virtually all children with laryngomalacia, symptoms resolve by 1 year of age. In less than 5 % of cases, severity mandates surgical intervention. In severe cases, symptoms may include apnea, cyanosis, severe retractions, and failure to thrive. In severe cases, cor pulmonale is seen. There also are some children in whom apnea and cyanosis are not marked but who are clearly obstructed, thus causing family stress and concern. In a subset of these children, intervention also is warranted.

Diagnosis is confirmed by flexible transnasal fiberoptic laryngoscopy. Characteristic findings include short aryepiglottic folds, with prolapse of the cuneiform cartilages. In some cases, a tightly curled (Ω shaped) epiglottis is also observed. Because of the Bernoulli effect, characteristic collapse of the supraglottic structures is seen on inspiration.

Also, inflammation suggestive of reflux laryngitis is frequently seen. The need for intervention is determined not by the endoscopic appearance of the larynx, but rather by the symptoms of the infant.

Children with laryngomalacia rarely present with acute airway compromise. In the 5 % of children who require operative management, this may be arranged in a semi-elective fashion within 1–2 weeks of presentation. Preoperative management of gastroesophageal reflux (GER) is prudent. Supraglottoplasty (also termed epiglottoplasty) has replaced tracheotomy as the preferred intervention. This is a rapid and effective endoscopic procedure, directed at the infant's specific laryngeal pathology. Both aryepiglottic folds usually are divided. In addition, one or both cuneiform cartilages may be removed. If the aryepiglottic folds alone are divided, postoperative intubation is generally not required; however, overnight intubation should be considered if more extensive surgery has been performed.

Following supraglottoplasty, overnight observation in the PICU is desirable, as laryngeal edema may compromise the airway, necessitating reintubation. Extubation is usually possible within 24 h of the surgery. In some children, obstruction persists postoperatively [4]. Bedside fiberoptic laryngoscopy can differentiate between laryngeal edema or persistent laryngomalacia. Reflux management helps mitigate laryngeal edema. Occasionally, the postoperative appearance of the larynx is adequate, but the infant is still struggling. In such cases, there is sometimes an underlying neurologic component to the laryngomalacia. Although the neurologic problems may be extremely subtle initially, they may become much more evident with time [5]. This group of children is far more likely to require tracheotomy placement.

Vocal Cord Paralysis

Vocal cord paralysis is the second most common cause of neonatal stridor. This condition may be either congenital or acquired and may be either unilateral or bilateral. Bilateral vocal cord paralysis is usually congenital, whereas unilateral paralysis is an acquired problem caused by damage to the recurrent laryngeal nerve. Given the length and circuitous course of the left recurrent laryngeal nerve compared to the right, most children with acquired vocal cord paralysis have unilateral left-sided paralysis.

Congenital cord paralysis is usually idiopathic, but may also be seen with central nervous system pathology, including hydrocephalus and Chiari malformation of the brainstem [6]. Up to 90 % of infants with bilateral vocal cord paralysis ultimately require tracheotomy. By contrast, children with unilateral vocal cord paralysis usually have an acceptable airway, but a breathy voice, and are at a slightly higher risk of aspiration.

As with laryngomalacia, the diagnosis is established with awake flexible transnasal fiberoptic laryngoscopy. The risk factors for acquired paralysis are patent ductus arteriosus repair, the Norwood cardiac repair, and esophageal surgery, especially tracheoesophageal fistula repair. For older children, thyroid surgery is an additional risk factor.

For an infant with stridor and retractions due to bilateral vocal cord paralysis, tracheotomy is indicated. Stabilization may be achieved with intubation, CPAP, or high-flow nasal cannula as an alternative temporizing measure. In up to 50 % of children with congenital idiopathic bilateral vocal cord paralysis, the paralysis spontaneously resolves by 1 year of age. Surgical intervention to achieve decannulation is thus usually delayed until after 1 year. Similarly, children with acquired bilateral vocal cord paralysis may have spontaneous recovery several months after recurrent laryngeal nerve injury if the nerve is only stretched or crushed but is otherwise intact. However, spontaneous resolution is less commonly seen in children with acquired vocal cord paralysis than in those with idiopathic congenital paralysis.

Most children with unilateral vocal cord paralysis do not require surgical intervention. For those with bilateral paralysis, there are several surgical options and no single option offers a perfect result. The aim of surgery is to achieve an adequate decannulated airway while maintaining voice and not exacerbating aspiration. Surgical options include laser cordotomy, partial or complete arytenoidectomy (endoscopic or open), vocal process lateralization (open or endoscopically guided), and posterior cricoid cartilage grafting [7]. In a child with a tracheotomy, it is often desirable to maintain the tracheotomy to ensure an adequate airway before decannulation. In a child without a tracheotomy, a single-stage procedure can be performed.

Acquired bilateral vocal cord paralysis is usually more recalcitrant to treatment than idiopathic cord paralysis, and more than one procedure may be required to achieve decannulation. For patients who have undergone any such procedures, postextubation stridor may respond to CPAP or high-flow nasal cannula. A child's postoperative risk of aspiration should be assessed by a video swallow study prior to resuming a normal diet. During the initial weeks following surgery, there is sometimes an increased risk of aspiration with certain textures, particularly thin fluids.

Subglottic Stenosis

Subglottic stenosis (SGS) can be either congenital or acquired. Congenital SGS is comparatively rare; in the neonate, it is defined as a lumen 4.0 mm in diameter or less at the level of the cricoid. Acquired SGS is much more frequently seen and is normally a sequelae of prolonged intubation of the neonate. The cause of congenital SGS is thought

to be a failure of the laryngeal lumen to recanalize. This condition is one of a continuum of embryologic failures that include laryngeal atresia, stenosis, and webs. In its mildest form, congenital SGS appears as a normal cricoid with a smaller than average diameter, usually elliptical in shape. Mild SGS may manifest in recurrent upper respiratory infections (often diagnosed as croup) in which minimal subglottic swelling precipitates airway obstruction. In a young child, the greatest obstruction is usually 2–3 mm below the true vocal cords. More severe cases may present with acute airway compromise at delivery. If endotracheal intubation is successful, the patient may require intervention before extubation. When intubation cannot be achieved, tracheotomy placement at the time of delivery may be lifesaving. Important to note, infants typically have surprisingly few symptoms. Even those with grade III SGS may not be symptomatic for weeks or months.

Congenital SGS is often associated with other congenital head and neck lesions and syndromes (e.g., a small larynx in a patient with Down syndrome). After initial management of SGS, the larynx will grow with the patient and may not require further surgical intervention. However, if initial management requires tracheal intubation, the risk of developing an acquired SGS in addition to the underlying congenital SGS is considerable.

Radiologic evaluation of an airway that is not intubated may give the clinician clues about the site and length of the stenosis. Useful imaging modalities include (1) inspiratory and expiratory lateral soft-tissue neck films, (2) fluoroscopy to demonstrate the dynamics of the trachea and larynx, and (3) a chest x-ray. The single most important investigation, however, is high-kilovoltage airway films. These films can identify the classic *steepling* observed in patients with SGS as well as possible tracheal stenosis. The latter condition is generally caused by complete tracheal rings, which may predispose the patient to a life-threatening situation during rigid endoscopy.

Evaluation of SGS, whether congenital, acquired, or a combination of both, requires endoscopic assessment. Endoscopy is necessary for the diagnosis of laryngeal stenosis. Flexible fiberoptic endoscopy provides information on dynamic vocal cord function. Rigid endoscopy with Hopkins telescopes provides the best possible examination. Precise evaluation of the endolarynx should be carried out, including grading of the SGS. SGS caused by scarring, granulation tissue, submucosal thickening, or a congenitally abnormal cricoid can be differentiated from SGS with a normal cricoid, but endoscopic measurement with endotracheal tubes or bronchoscopes is required for an accurate evaluation.

The greatest risk factor for developing acquired SGS is prolonged intubation with an inappropriately large endotracheal tube. The appropriate endotracheal tube size is not the largest that will fit but rather the smallest that allows for adequate ventilation. Ideally, the tube should leak air around it, with subglottic pressures below 25–30 cm H_2O. Other cofactors for the development of acquired SGS include GER and eosinophilic esophagitis (EE).

Children with mild acquired SGS may be asymptomatic or minimally symptomatic. Observation rather than intervention may thus be appropriate. This is often the case for children with grades I or II SGS. Those with more severe SGS (grades III and IV), however, are symptomatic, with either tracheal dependency or stridor and exercise intolerance. Unlike congenital SGS, acquired SGS is unlikely to resolve spontaneously and thus requires intervention.

For children with mild symptoms and a minor degree of SGS, endoscopic intervention may be effective. Endoscopic options include radial laser incisions through the stenosis and laryngeal dilatation [8]. More severe forms of SGS are better managed with open airway reconstruction. Laryngotracheal reconstruction using costal cartilage grafts placed through the split lamina of the cricoid cartilage is reliable and has withstood the test of time [9, 10]. Costal cartilage grafts may be placed through the anterior lamina of the cricoid cartilage, the posterior lamina of the cricoid cartilage, or both. These procedures may be performed as a two-stage procedure, maintaining the tracheal tube and temporarily placing a suprastomal laryngeal stent above the tracheal tube. Alternatively, in selective cases, a single-stage procedure may be performed, with removal of the tracheal tube on the day of surgery and with the child requiring intubation for 1–14 days [11]. Better results are currently being achieved with cricotracheal resection than with laryngotracheal reconstruction for the management of severe SGS; [12] however, this is a technically demanding procedure that carries a significant risk of complications. Reconstruction of the subglottic airway is a challenging procedure and the patient should be optimized before undergoing surgery. Preoperative evaluation includes assessment and management of GER, EE, and low-grade tracheal infection, particularly oxacillin-resistant *Staphylococcus aureus* (ORSA) and *Pseudomonas.*

Posterior Laryngeal Clefts

Posterior laryngeal clefts result from a failure of the laryngeal groove to fuse during embryogenesis. Although these clefts are generally not obstructive in nature, infants with laryngeal clefts sometimes present with significant obstruction. Aspiration is the hallmark clinical feature of this disorder. While gross aspiration may occur with associated apnea, cyanosis, and even pneumonia, often the symptoms are those of microaspiration, with choking episodes, transient cyanosis, and recurrent chest infections. As such, the diagnosis may initially be elusive.

Patients commonly have associated anomalies that affect the airway or other organ systems. Associated airway anomalies include tracheomalacia (>80 %) and tracheoesophageal fistula (TEF) formation (20 %). Non-airway associations include anogenital anomalies and GER. The most common syndrome associated with posterior laryngeal clefting is Opitz-Frias syndrome, characterized by hypertelorism, anogenital anomalies, and posterior laryngeal clefting.

Diagnosis is challenging. Although contrast swallow studies may suggest the risk of aspiration, definitive diagnosis requires rigid laryngoscopy and bronchoscopy, with the interarytenoid area being specifically probed to determine if a posterior laryngeal cleft is present. Figure 3.1 shows a modification of the Benjamin and Inglis classification system, illustrating cleft types I to V.

Management involves maintaining an appropriate airway while minimizing the risk of aspiration. Initial management decisions should consider whether the infant requires tracheotomy placement, gastrostomy tube placement, or Nissen fundoplication. Although none of these is essential, each increases the likelihood of successful cleft repair. Protection against aspiration is also crucial, and nasojejunal feeding may be a useful way of stabilizing an infant. Surgical repair may be performed endoscopically for most type I and some type II clefts; however, longer clefts that extend into the cervical or thoracic trachea require open repair. The transtracheal approach provides unparalleled exposure of the cleft while protecting the recurrent laryngeal nerves. A two-layer closure is recommended, with the option of performing an interposition graft if warranted; a useful interposition graft is a free transfer of clavicular or tibial periosteum. The most challenging cleft to repair is the type V cleft, which extends to the carina or beyond. Performing such surgery is anesthetically daunting. Type V clefts are prone to anastomotic breakdown and the infant often has multiple congenital anomalies [13].

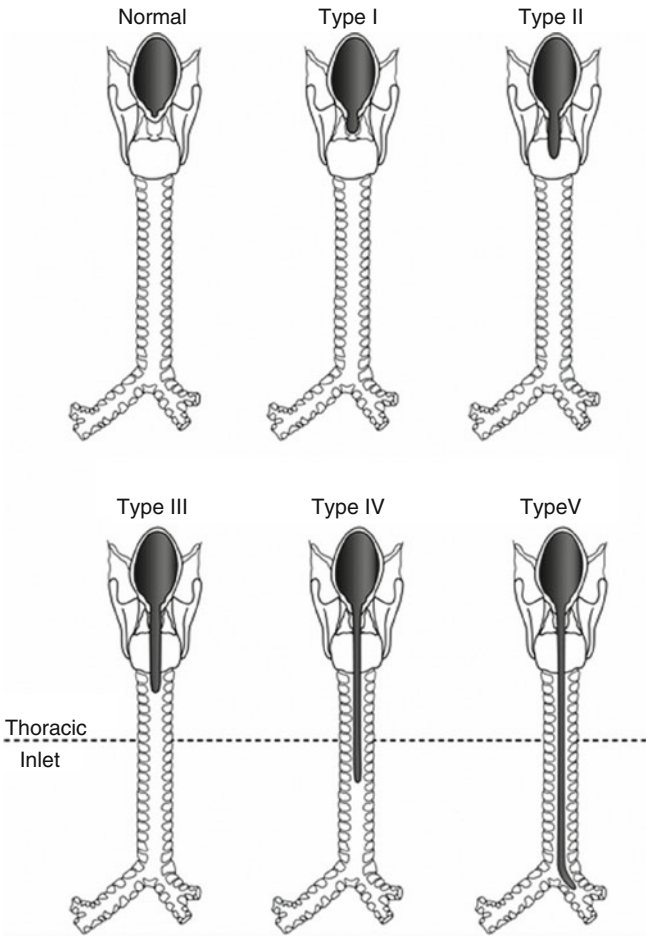


Fig. 3.1 Classification of posterior laryngeal clefts (a modification of the Benjamin and Inglis classification). The larynx and trachea are viewed from the posterior aspect. Type I: Cleft to but not below the true vocal cords. Type II: Cleft into the cricoid cartilage but not into the cervical trachea. Type III: Cleft through the cricoid into the cervical trachea. Type IV: Cleft into the thoracic trachea. Type V: Cleft to or beyond the carina

Vascular Compression

Vascular compression of the airway, particularly innominate artery compression, is not uncommon; however, it is usually asymptomatic or minimally symptomatic. Symptomatic vascular compression of the trachea or bronchi is rare but associated with marked symptoms, including biphasic stridor, retractions, a honking cough, and *dying spells*. Symptoms tend to substantially worsen when the child is upset. Forms of vascular compression affecting the trachea include innominate artery compression, double aortic arch, and pulmonary artery sling. Vascular rings resulting from a retroesophageal subclavian artery and a ligamentum arteriosum are less likely to be associated with airway obstruction. Bronchial compression by the pulmonary arteries or aorta may be significant but are more commonly a unilateral problem unless associated with major cardiac anomalies.

The diagnosis of airway compression is best established with rigid bronchoscopy. Thoracic imaging then assists in establishing the relevant vascular anatomy. Imaging modalities include high resolution computer tomography (CT) imaging with contrast enhancement and three-dimensional reconstruction, magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA), and echocardiography. Less commonly, formal angiography is required. Although the primarily role of imaging is to evaluate the intrathoracic vasculature, excellent images of the airway and the thymus gland may also be obtained.

In a child with an airway compromised by vascular compression, CPAP may provide a limited degree of temporary

improvement, as there is often segmental tracheomalacia in the region of the vascular compression. Otherwise, tracheal intubation may be required. Because of the proximity of a vascular structure, prolonged intubation is avoided due to the risk of forming an arterial fistula. Similarly, although tracheotomy will establish an unobstructed airway, there is also an increased risk of a vascular fistula into the airway.

The surgical management of symptomatic vascular compression addresses the specific pathology involved. Innominate artery compression responds well to thymectomy and aortopexy, but if little thymus is present, an alternative is reimplantation of the innominate artery more proximately on the aortic arch [14]. A double aortic arch requires ligation of the smaller of the two arches, which is usually the left. A pulmonary artery sling is transected at its origin, dissected free, and reimplanted into the pulmonary trunk anterior to the trachea. There is a high incidence of complete tracheal rings in children with a pulmonary artery sling, and these should also be repaired at the time of vascular repair.

Alleviating vascular compression will improve the airway; however, it may take months for it to completely normalize. This is a consequence of long-standing vascular compression having adversely affected the normal cartilaginous development of the compressed segment of trachea, with resultant cartilaginous malacia or stenosis. Until the airway normalizes, persistently symptomatic children may require airway stabilization with a tracheotomy or a trachelopexy [15]. Tracheal stabilization with stenting is not recommended, as it is associated with a high incidence of complications. Temporary tracheotomy is generally a more desirable alternative.

Complete Tracheal Rings

Although complete tracheal rings are rare, they are life threatening. They present with insidious worsening of respiratory function over the first few months of life, stridor, retractions, and marked exacerbation of symptoms during intercurrent upper respiratory tract infections. Children with distal tracheal stenosis usually have a characteristic biphasic wet-sounding breathing pattern that transiently clears with coughing; this pattern is referred to as *washing machine breathing*. The risk of respiratory failure increases with age. Although the diagnosis is made with rigid bronchoscopy, an initial high-kilovolt airway film may warn of tracheal narrowing. Bronchoscopy should be performed with great caution. The smallest possible telescopes should be used, as any airway edema in the region of the stenosis may turn a narrow airway into an extremely critical airway. The location, extent, and degree of stenosis are all relevant; however, if the airway is exceptionally narrow, it may be more prudent to establish the diagnosis rather than to risk causing post-traumatic edema by forcing a telescope through a stenosis.

Because 50 % of children have a tracheal inner diameter of approximately 2 mm at the time of diagnosis, the standard interventions for managing a compromised airway are not applicable. More specifically, the smallest tracheal tube has an outer diameter of 2.9 mm, and the smallest tracheotomy tube has an outer diameter of 3.9 mm; hence, the stenotic segment cannot be intubated. This may leave extracorporeal membrane oxygenation (ECMO) as the only viable alternative for stabilizing the child [16]. This situation is best avoided by performing bronchoscopy with the highest level of care.

Over 80 % of children with complete tracheal rings have other congenital anomalies, which are generally cardiovascular in origin. As such, investigation should include a high-resolution contrast-enhanced CT scan of the chest and an echocardiogram. Specifically, a pulmonary artery sling should be excluded, as this is a common association. If present, it should be repaired concurrent with the tracheal repair. Most children with complete tracheal rings require tracheal reconstruction [17]. The recommended surgical technique is the slide tracheoplasty [18]. This approach yields significantly better results than any other form of tracheal reconstruction and is applicable to all anatomic variants of complete tracheal rings.

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Status Asthmaticus

4

Derek S. Wheeler and Riad Lutfi

Abstract

Status asthmaticus is one of the most common admission diagnoses in the PICU. While studies suggest that the overall prevalence of asthma in children has leveled off in recent years, these same studies suggest that the severity of asthma is getting worse. Given the increasing prevalence of obesity and its association with asthma severity, the number of patients admitted to the PICU with status asthmaticus is likely to increase. A stepwise, but aggressive approach to management of these patients is recommended.

Keywords

Asthma • Status asthmaticus • Acute respiratory failure • Lower airway obstruction • Obstructive lung disease • Acute exacerbation • Dynamic hyperinflation • Auto-PEEP

Introduction

Asthma is the most common pediatric respiratory disease and remains one of the most common reasons children require hospitalization in the United States. Current statistics suggest that nearly 27 million Americans suffer from this disease (approximately 8 % of the U.S. population), including 7.1 million children in 2009 [1–5]. Asthma poses a significant economic burden to the healthcare system, accounting for approximately 10.5 million missed days of school, 7.5 million outpatient visits, 2.1 million emergency department (ED) visits, 500,000 hospitalizations, and an estimated $18 billion in total health care expenditures (including direct and indirect costs) every year [1, 2, 4–14]. The World Health Organization (WHO) estimates that over 300 million people around the world suffer from asthma, with over 250,000 asthma-related deaths every year [15]. Status asthmaticus, defined as a condition of progressively worsening bronchospasm unresponsive to standard therapy [16, 17], accounts for a significant number of admissions to the pediatric intensive care unit (PICU) each year (Wheeler, *unpublished data*), though by comparison, only a small percentage of all children admitted to the hospital with an acute asthma exacerbation require treatment in the PICU [18–27]. While recent trends suggest that the incidence of childhood asthma may be leveling off, the overall disease burden, as the statistics above suggest, remains quite high. Racial disparities and access to care continue to plague our health care system, resulting in potentially avoidable adverse outcomes in children with asthma [3, 5]. Moreover, there is significant variation in the management of critically ill children with status asthmaticus [28–31]. Given all of these factors, there continues to be great interest in the identification and development of treatment strategies that can effectively manage and improve the outcome of critically ill children diagnosed with status asthmaticus.

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Epidemiology

According to National Consensus Guidelines [32], asthma is defined as a recurrent and chronic inflammation of the airways, resulting in airway hyperresponsiveness, increased mucous production, and airflow obstruction. The severity of asthma is classified according to the frequency of symptoms, pulmonary function tests, and the degree in which the signs and symptoms impair activities of daily living (Fig. 4.1). In addition, children who have at least one acute exacerbation requiring oral systemic corticosteroids per year are classified as intermittent asthma, while those children who have ≥2 exacerbations in 6 months requiring oral systemic corticosteroids or ≥4 wheezing episodes per year lasting >1 day are classified as persistent asthma [32]. The overwhelming preponderance of evidence suggests that the worldwide incidence of asthma is increasing [33–35]. Since 1980, in fact, the frequency of asthma has approximately doubled [36]. Certainly some of the increases in disease prevalence may be attributed to increased awareness and better reporting, though studies utilizing similar case definitions continue to show an epidemic increase in the incidence of asthma, especially in westernized countries such as the United Kingdom, Australia, and New Zealand. Far lower prevalence rates have been observed in India, China, Africa, and other countries in Asia and Eastern Europe [35], though several studies demonstrate increasing prevalence rates of asthma in countries as they become more westernized [37, 38].

Similar trends have been observed in the United States. For example, the National Center for Health Statistics (NCHS) reported results from the National Health Interview Survey (NHIS) showing that the self-reported prevalence of asthma increased by nearly 75 % across all age groups between 1980 and 1994. The greatest increases occurred among preschool children (<5 years), in which the prevalence rate rose by nearly 150 % [11]. The prevalence rates are highest among African Americans and children from lower socioeconomic backgrounds [8, 11, 39, 40]. The overall trend of increasing asthma prevalence has leveled off slightly in recent years [1–5, 11], though the disease remains a significant problem, especially in certain segments of the population.

Germane to the present discussion, the morbidity and mortality from asthma appears to be steadily rising in certain high-risk groups of the population [1, 8–12, 41–43]. Some investigators have suggested that this apparent increase can be attributed to complications associated with the increased usage of β–agonist therapy, though this probably reflects a greater severity of illness and subsequent need for therapy rather than an actual cause-and-effect association [44–50]. Rather, the wealth of evidence suggests that undermedication, particularly with regards to the inadequate use of

		Persistent		
	Intermittent	Mild	Moderate	Severe
Symptoms	≤ 2 days/week	> 2 days/week	Daily	Throughout the Day
Nighttime awakenings	0-4 years of age: 0 5-11 years of age: ≤ 2x/month	0-4 years of age: 1-2x/month 5-11 years of age: 3-4x/month	0-4 years of age: 3-4x/month 5-11 years of age: > 1x/week	0-4 years of age: > 1x/week 5-11 years of age: Often 7x/week
Short-term $Beta_2$-agonist use for symptom control	< 2 days/week	> 2 days/week	Daily	Several times per Day
Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
Lung Function (Age 5-11 years only)	Normal FEV_1 between exacerbations FEV_1 = >80% predicted FEV_1/FVC > 85%	FEV_1 = >80% predicted FEV_1/FVC > 80%	FEV_1 60-80% predicted FEV_1/FVC 75-80%	FEV_1 < 60% predicted FEV,/IFVC < 75%

Fig. 4.1 Classification of asthma in children

corticosteroids, and lack of recognition of the severity of an asthma attack by both the patient or parent (causing a delay in seeking medical care), as well as the healthcare provider are more important factors [51–58].

There appear to be two clinical subsets of children who die from status asthmaticus [59]. For example, some children with fatal asthma usually have a long history of poorly controlled, severe asthma, often with a previous history of respiratory failure (type I, or *slow onset-late arrival*). This pattern of fatal asthma, which is responsible for the majority of asthma-related deaths is generally considered preventable, with death occurring secondary to acute respiratory failure and asphyxia or from complications associated with mechanical ventilation [60–65]. Pathologic examination in these cases demonstrates extensive bronchial mucus plugging, edema, and eosinophilic infiltration of the airways. Alternatively, some children present with only a mild history of asthma, or oftentimes even without a prior history of asthma, experience the sudden onset of bronchospasm, and rapidly progress to cardiac arrest and death (type II, or *fast-onset*) [66–69]. If recognized and managed early, these children respond faster to β-agonists and mechanical ventilatory support compared to children with type I fatal asthma [70]. Pathologic examination in these cases shows *empty* airways devoid of mucus plugging with a greater proportion of neutrophils than eosinophils [71].

Robertson et al. [72] reviewed 51 pediatric deaths from asthma between 1986 and 1989 and found that nearly one-third of these children were judged to have mild asthma with no prior hospitalizations for asthma. Sixty-three percent of these children experienced a sudden collapse within minutes of the onset of symptoms, while 75 % died before reaching the hospital. Only 25 % of these children had an acute progression of chronic, poorly controlled asthma that resulted in eventual death. The authors of this study concluded that only 39 % of these deaths were preventable by earlier recognition and intervention. Over a 6-year period at the Hospital for Sick Children in Toronto, 89 children were admitted to the PICU for status asthmaticus. Three children died in the PICU from hypoxic-ischemic encephalopathy following out-of-hospital cardiac arrest [18]. Kravis and Kolski [73] reported a case series of 13 deaths secondary to asthma. Only one child died following admission to the hospital. Similarly, nearly 50 % of asthmatic children in another study died before reaching the hospital, with the time from the onset of symptoms to death less than 1 h in 21 % and less than 2 h in 50 % of these cases, respectively [74, 75]. These series further underscore the need for early recognition for children at risk for type II fast-onset, sudden asphyxial asthma. Accordingly, several authors have attempted to define characteristics or *risk factors* of children who die of asthma (Table 4.1) [16, 44, 51–53, 55, 66, 67, 72, 74, 76–88].

Pathophysiology

Severe airway obstruction resulting from inflammation, bronchoconstriction, and excessive mucus production is at the heart of the gas exchange abnormalities and symptomatology in children with status asthmaticus. The marked increase in airway resistance leads to a dramatic increase in the work of breathing and may be characterized by marked reductions in FEV_1, FEV_1/FVC, and $FVC_{25–75}$ [89–91]. As the degree of airway obstruction worsens, expiration becomes active rather than passive. Inspiration often occurs prior to termination of the previous expiration, resulting in air-trapping and lung hyperinflation [92, 93]. Residual volume (RV) and functional residual capacity (FRC) are increased, with the increase in RV exceeding that of the increase in FRC [92, 94–96]. Total lung capacity (TLC) is also increased to a variable extent [92, 95]. The increase in lung volumes during an acute asthma exacerbation may increase the caliber of the airways and temporarily improve the resistive work of breathing [97, 98], though at a significant mechanical disadvantage [99, 100].

Air-trapping and lung hyperinflation lead to a phenomenon called *dynamic hyperinflation* in spontaneously breathing patients, as well as intrinsic positive end-expiratory pressure ($PEEP_i$) or *auto-PEEP* in patients on mechanical ventilator support [101]. Dynamic hyperinflation has several adverse effects on the cardiovascular and respiratory systems. For example, the increased lung volumes shift tidal breathing to a less compliant portion of the pressure-volume curve. In addition, flattening of the diaphragm produces an additional mechanical disadvantage. Dynamic hyperinflation also eventually results in premature closure of the airways, which produces a further increase in airways resistance, thereby worsening gas exchange. These factors collectively increase the work of breathing and increase the physiologic dead-space. The gas exchange abnormalities produced by dynamic hyperinflation result in ventilation-perfusion mismatch. As

Table 4.1 Risk factors for potentially fatal asthma

1. History of previous attack with:
Severe, rapid progression of symptoms
Respiratory failure requiring tracheal intubation or ventilatory support
Seizures or loss of consciousness
PICU Admission
2. Attacks precipitated by food allergy
3. Denial or failure to perceive the severity of illness
4. Poor compliance
5. Lack of social support network
6. Associated psychiatric disorder (e.g. Depression)
7. Non-white children
8. Obesity

dynamic hyperinflation progressively worsens, patients are at risk for pneumothorax ("alveolar rupture").

The effects of dynamic hyperinflation and auto-PEEP on cardiorespiratory interactions are quite complex, and the reader is referred to the chapter on cardiorespiratory interactions in this textbook for additional information. Suffice it to say that right ventricular afterload is increased by a combination of factors including lung hyperinflation (increased pulmonary vascular resistance), hypoxic pulmonary vasoconstriction (ventilation-perfusion mismatch), and acidosis. During expiration, the increase in intrathoracic pressure secondary to dynamic hyperinflation impedes systemic venous return, thereby worsening left ventricular preload. During inspiration, the large negative intrathoracic pressures required to overcome airways resistance markedly increase left ventricular afterload [59, 102]. These changes are detected clinically as an increase in the pulsus paradoxus (see below).

Clinical Manifestations

The initial clinical assessment of the child presenting with status asthmaticus should focus on the major organ systems and will provide important clues to the potential for progression to respiratory failure. A quick assessment of the child's neurologic status may demonstrate early signs of hypoxia, which can include restlessness, irritability, confusion, anxiety, and an inability to recognize parents. Conversely, the child who is awake, alert, and cooperative is less likely to deteriorate acutely. Further, the child with impending respiratory failure often prefers a sitting or tripod position in an unconscious effort to maximize diaphragmatic excursion [103]. While tachypnea is the usual compensatory response to hypoxia, bradypnea in the context of status asthmaticus is an ominous finding. Grunting, nasal flaring, retractions, and use of the accessory muscles of breathing are often present. The presence of dyscoordinate, *seesaw* breathing, which if severe will manifest as paradoxical movement of the thoracic cage during breathing (i.e. the chest moves inward during inspiration), is often a harbinger of impending respiratory failure. The older child may be able to communicate the complaints of dyspnea and *air hunger*, though if airway obstruction is severe the child will often speak only in short phrases or even single words.

Tachycardia is the usual physiologic response in status asthmaticus, which may result from a combination of factors, including anxiety, acidosis, fever (if present), and hypoxia. The presence of a pulsus paradoxus (over a 10 mmHg change in systolic blood pressure between inspiration and expiration) is often present in severe airway obstruction and represents a useful prognostic measure of respiratory compromise [104]. Recent advances in the technology of monitoring devices have resulted in dramatic improvements in the precision and accuracy of determining the pulsus paradoxus and may further strengthen its utility as an objective, effort-independent sign in children with status asthmaticus [105–108].

Pulse oximetry provides for a rapid determination of the arterial oxygen saturation. The SaO_2 may be useful to differentiate patients who are likely to improve with therapy versus those patients who are likely to progress to respiratory failure. For example, an increase in oxygen saturation following albuterol nebulization predicts patients who are likely to improve [109], and respiratory failure rarely occurs in patients with an oxygen saturation >92 % on initial presentation [110]. The degree of hypoxemia significantly correlates with the degree of airway obstruction, as determined by the forced expiratory volume in 1 s (FEV_1) [111–113]. Furthermore, hypoxemia appears, at least in some studies, to be an independent risk factor for both hospitalization and increased length of stay [109, 114–119].

Hypoxemia is multifactorial in origin, resulting from a combination of factors including ventilation-perfusion mismatch, alveolar hypoventilation, and hypercarbia (though by the alveolar gas equation, clinically significant hypoxemia, i.e. $PaO_2 < 60$ mmHg, does not occur under normal conditions, breathing ambient air at sea level until a $PaCO_2 > 72$ mmHg is attained) [120]. Significant hypoxemia, however, is relatively uncommon in children with status asthmaticus [102, 121–123]. For example, one study documented a significant correlation between SaO_2 and FEV_1 ($r^2 = 0.59$), though the range of SaO_2 for any given FEV_1 was quite variable, and some children had significant airways obstruction despite normal SaO_2 [112]. The mean SaO_2 of 150 children presenting to the ED with status asthmaticus who subsequently required hospitalization was approximately 93 % [115]. A large, multicenter trial involving over 1,000 children presenting to the ED with status asthmaticus documented a mean SaO_2 of 95 ± 4 %. In this particular study, the mean SaO_2 for the 241 children who subsequently required hospitalization was 93 ± 5 % ($p < .001$ compared to children not requiring hospitalization) [119, 124]. Therefore, the presence of significant hypoxemia should alert the physician to search for some additional underlying cause, such as diffuse atelectasis secondary to mucus plugging, pneumonia, or pneumothorax [125].

The degree of airway obstruction is rapidly determined by assessment of pulmonary function using the FEV_1 and the peak expiratory flow rate (PEFR). The PEFR is defined as the greatest flow that can be attained during a forced expiration starting from total lung capacity (i.e. complete lung inflation) and is often utilized as a measure for monitoring the severity of illness upon initial presentation and in response to therapy. PEFR are easily obtained using a handheld spirometer and are endorsed by the National Asthma

Education Program [32]. The test is effort-dependent, so the accuracy and reliability of the results rely heavily on close supervision. Interpretation of test results should only be made after correction for age and sex. Generally, however, PEFR is 70–90 % of baseline or predicted normal in mild exacerbations, 50–70 % of baseline or predicted normal in moderate exacerbations, and < 50 % of baseline or predicted normal in severe exacerbations. It should be noted that adequate PEFR measurements are often difficult to obtain in children during an acute asthma attack, especially those with an exacerbation severe enough to warrant admission to the PICU [126]. For this reason, PEFR assessment should not delay therapy in a critically ill child and attempts at PEFR assessment should be discontinued if the child's clinical condition deteriorates during testing.

Based on a rapid assessment, the physician caring for the child with status asthmaticus should be able to have a reasonable impression of the severity of airway obstruction (Table 4.2). The modified Becker Clinical Asthma Score (Table 4.3) is a clinical asthma score which was originally developed by Becker et al. [127] and later modified by DiGiulio et al. [128]. This widely-used score assesses the severity of an acute asthma exacerbation based upon the acuity of physical signs for four clinical characteristics (respiratory rate, wheezing, I/E ratio, and accessory muscle use) and assigns a score for each variable ranging from 0 to 12

Table 4.2 Assessment of the severity of acute asthma

Mild	Moderate	Severe
History		
Intermittent wheezing	Frequent hospitalizations (no intensive care unit admissions)	Previous PICU admission
Few hospitalizations	Chronic medications ≤ 2 treatments	Chronic medications ≥ 2 treatments
No chronic medications		
Physical examination		
CNS		
Absence of CNS signs	Anxious, restless, irritable	Coma, seizures
		Inability to recognize parents
Respiratory system		
No cyanosis in room air	Cyanosis on < 1.0 F_IO_2	Cyanosis on 1.0 F_IO_2
Good air entry with wheezes	Decreased air entry with wheezes	Silent chest
Speaks in full sentences	Speaks in phrases or partial sentences	Speaks only in single words or short phrases
Cardiovascular system		
Tachycardia	Tachycardia	HR greatly increased or slightly decreased
No pulsus paradoxus	Pulsus paradoxus 10–20 mmHg	Pulsus paradoxus > 20 mmHg
Pulmonary function tests		
PEFR		
70–90 % predicted or baseline	50–70 % predicted or baseline	< 50 % predicted or baseline
FEV_1/FVC		
85 %	75 %	45 %
Laboratory data		
Pulse oximetry		
> 95 %	90–95 %	< 90 %
Blood gases		
$PaO_2 > 80$	PaO_2 60–80	$PaO_2 < 60$
$PaCO_2 < 35$	$PaCO_2 < 50$	$PaCO_2 > 50$

Table 4.3 The modified Becker score for assessing asthma severity

Score	Respiratory rate	Wheezing	I/E ratio	Accessory muscle use
0	<30	None	1:1.5	None
1	30–40	Terminal expiration	1:2.0	One site[a]
2	41–50	Entire expiration	1:3.0	Two sites
3	>50	Inspiration and entire expiration	>1:3	Three sites or neck strap use

I/E Inspiration/Expiration

[a]Site refers to chest wall musculature, such as intercostals and subcostal muscles

(0 indicating minimal disease severity). There are other clinical asthma scores that are currently used [129–131].

While arterial blood gas (ABG) analysis is not predictive of outcome, it may be useful in the initial evaluation and triage of children with status asthmaticus to the PICU. Typical ABG results during an acute asthma exacerbation show normal PaO_2 and respiratory alkalosis, though hypoxemia with PaO_2 approaching 60 mmHg may be observed in moderate to severe exacerbations [132]. However, serial ABG analyses are more useful in following response to treatment compared to a single measurement. While the initial $PaCO_2$ may be slightly below normal, a progressive increase in $PaCO_2$ is considered an early warning sign of severe airway obstruction and impending respiratory failure.

Metabolic acidosis is well-described in both adults and children with status asthmaticus [133–141]. The majority of studies suggest that the metabolic acidosis reported in these patients is secondary to accumulation of lactic acid, presumably from the prolonged and markedly increased work of breathing (with coincident respiratory muscle fatigue) associated with status asthmaticus. Additional factors include tissue hypoxia secondary to (i) oxygen supply/demand imbalance in respiratory muscles (i.e., insufficient oxygen delivery to meet excessive oxygen demands), (ii) dehydration accompanying status asthmaticus, both from poor oral intake and increased insensible losses through the respiratory tract, (iii) ventilation-perfusion mismatching (rarely sufficient to produce tissue hypoxia, however), and (iv) decreased cardiac output associated with hyperinflation. Alternatively, stimulation of β-adrenergic receptors by endogenous catecholamines and β-agonists results in increased glycolysis and lipolysis, potentially leading to excess lactic acidemia through excess substrate utilization [136, 140, 141]. Okrent et al. [142] noted the presence of metabolic acidosis in 10/22 adults with status asthmaticus, all of which had a non-anion gap acidosis with normal whole blood lactate levels. They suggested that the non-anion gap metabolic acidosis in these patients was due to the excessive renal bicarbonate excretion which occurred as a renal compensatory response to a preceding period of hyperventilation and subsequent respiratory alkalosis.

Hypokalemia is the most common electrolyte abnormality in children with status asthmaticus and is a well-recognized complication of β-agonist administration [136, 143–153]. In addition, the glucocorticosteroids used in the management of asthma can possess unwanted mineralocorticoid effects, leading to hypokalemia [149, 153]. Children with status asthmaticus are often dehydrated due to increased insensible fluid losses from the respiratory tract, coupled with poor oral intake of fluids. Dehydration may produce thicker, more tenacious bronchial secretions, leading to worsening bronchial mucus plugging. While the majority of children require intravenous fluid re-hydration, overzealous fluid administration may lead to fluid retention and pulmonary edema. Children with status asthmaticus have elevated plasma antidiuretic hormone (ADH) levels and are at risk for hyponatremia and fluid overload if given large volumes of hypotonic fluid [154, 155]. In addition, the high negative transpulmonary pressures associated with status asthmaticus may promote fluid accumulation around the respiratory bronchioles [156], leading to pulmonary edema and worsening respiratory status.

Chest radiographs are generally not helpful in the diagnosis and management of children with mild and uncomplicated asthma [125, 157–167]. The majority of chest radiographs in children with asthma show atelectasis or hyperinflation/hyperaeration. For example, in a study by Brooks et al. [157], only 7 out of 128 children with acute asthma had a clinically significant X-ray finding, three of which were suspected on clinical assessment alone. Further, Tsai et al. [125] prospectively reviewed 445 children presenting to the ED with acute asthma and found no significant correlation between radiographic findings on chest X-ray and duration of hypoxemia, hospital length of stay, or admission to the PICU, even in those children who were hypoxemic. Most of the aforementioned studies, however, excluded children who were admitted to the PICU. While objective data are lacking, we believe that chest radiographs should be obtained in every child with status asthmaticus requiring admission to the PICU to examine for evidence of infection or air-leak syndromes secondary to hyperinflation. In addition, chest radiographs should be obtained in children with suspected foreign body aspiration, fever, or in those not responding appropriately to treatment. Hypoinflation on chest radiograph is highly correlated with disease severity [168] and may warrant more intensive monitoring and treatment.

Management

Several studies have shown that a protocolized, systematic approach to the treatment of children who are admitted to the hospital with status asthmaticus will result in improved outcomes and lower hospital costs [169–173]. While asthma management protocols are being used in many PICUs, further studies are necessary to show that these improve outcomes and decrease costs [174]. Importantly, experience has shown that implementation of a clinical pathway requires a real commitment of resources, training, and education by all healthcare providers involved, and the benefits may not be realized initially [175].

Oxygen

The administration of supplemental oxygen is considered standard therapy for children with status asthmaticus [176]. As discussed above, hypoxemia, when present, is

multifactorial in origin, resulting from a combination of factors including ventilation-perfusion mismatch, alveolar hypoventilation, and hypercarbia [120], though again, significant hypoxemia is relatively uncommon in children with status asthmaticus [102, 121–123]. When present, hypoxemia may produce pulmonary hypertension (via hypoxic pulmonary vasoconstriction), worsen bronchoconstriction, and decrease oxygen delivery to the muscles of respiration in the face of tremendous metabolic demand. It should also be mentioned that some bronchodilators, particularly the β–agonists, reduce hypoxic pulmonary vasoconstriction and thus worsen hypoxemia, at least initially [177–179]. Therefore, these medications should be administered concurrently with supplemental oxygen rather than air [124, 178, 180].

Systemic Corticosteroids

The use of corticosteroids in the treatment of acute asthma is well-established, and numerous clinical trials both in children and adults demonstrate the benefits of corticosteroids in improving PEFR, decreasing need for β-agonists, and reducing the rate of hospital admission [181–189]. A meta-analysis by Rowe et al. [187] reviewed 30 randomized, controlled trials that evaluated the administration of corticosteroids in children and adults with status asthmaticus. Early administration of corticosteroids reduced hospital admission and improved pulmonary function in both children and adults. A Cochrane Database review of 7 randomized, controlled clinical trials involving a total of 426 children (274 with oral prednisone vs. placebo, 106 with intravenous steroids vs placebo and 46 with nebulized budesonide vs prednisolone) concluded that administration of systemic corticosteroids produce some improvements for children admitted to the hospital with acute asthma. In this review, a significant number of children treated with corticosteroids were discharged early after admission (>4 h). The length of stay was shorter in the steroid groups, though there were no significant differences between groups in pulmonary function or oxygen saturation measurements. In addition, children treated with steroids in the hospital were less likely to relapse within 1–3 months following discharge. Based on the wealth of available evidence, expert opinion and published guidelines [176, 190, 191] recommend the administration of corticosteroids in the routine management of status asthmaticus within the initial 48 h of treatment.

The standard recommended dosage of corticosteroid (methylprednisolone 2–4 mg/kg/day divided every 6 h intravenously) will maintain a minimal plasma steroid concentration of 100–150 μg cortisol/100 mL [192]. However, the optimal dosing of systemic corticosteroids in children with status asthmaticus remains an unresolved issue [193]. Several studies in both children [182, 194] and adults [195–198] suggest that *high-dose* corticosteroid therapy offers few advantages over *low-dose* corticosteroids in the treatment of status asthmaticus. Oral administration of corticosteroids appears to be equally efficacious to intravenous or intramuscular administration [199–201]. However, oral corticosteroids are generally not recommended in children with severe status asthmaticus and impending respiratory failure.

The peak anti-inflammatory effects of corticosteroids usually become evident between 6 and 12 h after administration of the first dose [202]. Early administration of corticosteroids in the ED should therefore be associated with more rapid improvement in pulmonary function and reduce the need for hospitalization. A Cochrane Database review of 12 randomized, controlled studies involving 863 patients, including both children and adults, suggested that administration of corticosteroids within 1 h of presentation to the ED significantly reduced admission rates. These benefits appeared greatest in patients with more severe exacerbations [203]. Since the publication of this systematic review, additional studies have shown that early administration of systemic corticosteroids in children presenting to the ED with acute asthma exacerbations is beneficial [204–206]. Despite the lack of studies specifically addressing the administration of corticosteroids in children with status asthmaticus and impending respiratory failure, the available evidence would suggest that timely administration of corticosteroids in this population would provide early benefits.

Although corticosteroids are widely used in the treatment of asthma, the molecular mechanisms responsible for their anti-inflammatory effects remain under active investigation. Corticosteroids are believed to inhibit pro-inflammatory gene expression, at least partially through a mechanism involving the transcription factor, nuclear factor (NF)-κB [207–210]. This would appear to account for at least some of the delayed onset of action for corticosteroids in acute asthma discussed above, as the anti-inflammatory effects require inhibition of gene expression (so-called *genomic effects* of corticosteroids). Additional studies have suggested that corticosteroids upregulate β-adrenergic receptor gene expression and enhance β-adrenergic signaling pathways in airway smooth muscle cells [211, 212]. Consistent with these mechanisms that depend upon new gene expression, the available clinical evidence suggests that systemic corticosteroids require between 6 and 24 h in order to produce a maximal anti-inflammatory therapeutic effect [202, 203, 213]. However, so-called *non-genomic* effects (i.e. effects that do not require new gene expression) have also been reported, possibly through membrane-stabilizing effects or effects on ion channels [214–217]. These non-genomic effects are more or less immediate and may account for at least some of the beneficial effects associated with early administration of corticosteroids in the ED.

Inhaled Corticosteroids

A Cochrane Database review of over 20 randomized, controlled trials (13 of which were exclusively pediatric trials) suggested that inhaled corticosteroids reduced hospital admission in patients presenting to the ED, even when they were not treated with oral or intravenous corticosteroids, though the data supporting any synergistic role when co-administered with systemic corticosteroids was less clear [218]. Few studies have been performed in critically illy children in the PICU [88], and there are no prospective, randomized, controlled studies on which to base recommendations for the use of inhaled corticosteroids in this population. The currently available evidence does not support the use of inhaled corticosteroids in lieu of systemic corticosteroids (administered I.V., P.O., or I.M.) in the PICU, and the possible synergistic effects versus adverse effects with combined administration of inhaled corticosteroids and systemic corticosteroids in this population are not known.

Beta-Adrenergic Agonists (Table 4.4)

Epinephrine

Subcutaneous epinephrine has been used for decades for the treatment of status asthmaticus and was once considered the standard treatment of choice [219–221]. However, subcutaneous epinephrine has fallen out of favor in recent years, largely due to the widespread availability, ease of administration (painless aerosol vs. painful IM injection), and efficacy of relatively newer β-adrenergic agonists such as albuterol [222–226]. However, many experts still believe that subcutaneous (now administered IM instead of subcutaneously) epinephrine continues to have a role in the treatment of critically ill children with impending respiratory failure secondary to status asthmaticus [170, 227–231]. Intramuscular (IM) administration of epinephrine (0.01 mg/kg, or 0.01 mL/kg of 1:1,000 concentration or 1 mg/mL, maximum dose 0.3–0.5 mL) may be considered in children who are rapidly decompensating despite inhaled β-adrenergic agonists (see below) and in children who are unable to cooperate with inhalational therapy secondary to anxiety, altered mental status, or apnea. IM epinephrine may be administered every 20 min for three doses. Severe airflow obstruction may be relieved by IM epinephrine to a

Table 4.4 Bronchodilators currently used in the management of status asthmaticus

Agent	Parenteral	Aerosol
Epinephrine hydrochloride	*Intramuscular* 1:1,000, 1 mg/mL 0.01 mL/kg/dose every 15–20 min; may be repeated three times if clinically indicated	No current indications
Albuterol (salbutamol)	*Intravenous* 5–15 μg/kg/dose intermittent dose -or- 1 μg/kg loading dose followed by continuous infusion at 0.2 μg/kg/min; dose may be increased by 0.1 μg/kg/min increments to clinical improvement or greater than 20 % increase in heart rate)	*Intermittent* 0.5 % solution, 5 mg/mL 2.5 mg in 2.5 mL 0.9 % saline 0.5 % solution, 5 mg/mL 0.1–0.3 mg/kg in 2.5 mL 0.9 % saline *Continuous*
Terbutaline sulfate	*Subcutaneous* 1:1,000 or 1 mg/mL 0.01 mL/kg (0.01 mg/kg), maximum dose 0.3–0.5 mL every 15–20 min; may be repeated three times if clinically indicated *Intravenous* 1 mg/mL 2–10 μg/kg loading dose followed by continuous infusion at 0.5 μg/kg/min; dose may be increased by 0.1–0.2 μg/kg/min increments as clinically indicated every 15–30 min; doses as high as 10 μg/kg/min have been reported	*Intermittent* 1 mg/mL 0.01–0.03 mL/kg every 4–6 h (minimum dose 0.1 mL, maximum dose 2.5 mL)
Ipratropium bromide	Not available in parenteral form	Infants and children: 250 μg every 20 min for three doses then every 2–4 h Adolescents: 500 μg every 20 min for three doses then every 2–4 h
Magnesium sulfate	*Intravenous* 50–75 mg/kg (maximum dose 2 g) every 4–6 h -or- 50–75 mg/kg loading dose followed by continuous infusion at 10–20 mg/kg/h Titrated to keep serum magnesium 4 mg/dL–5.5 mg/dL	*Intermittent* Magnesium used as a vehicle for albuterol in lieu of 0.9 % saline (dose varies among several studies)
Ketamine	*Intravenous* 2 mg/kg loading dose followed by continuous infusion at 1–2 mg/kg/h	Not available

degree sufficient to allow adequate delivery of aerosolized β-adrenergic agonists to the distal airways, thereby allowing these agents to take effect.

Albuterol (Salbutamol)

Based on a wealth of available evidence, frequent albuterol nebulization is considered standard therapy for children presenting with status asthmaticus [32]. Several studies have compared the efficacy of small-volume nebulizers versus metered dose inhalers (MDI) with spacers for the treatment of acute asthma exacerbations in children [232]. While nebulizers allow the concurrent administration of supplemental oxygen, some studies have suggested that close to 90 % of the drug is lost to the atmosphere [233]. Drug delivery is maximized with the use of a mouthpiece versus a facemask, flow rates of 6–8 L/min, and total solution volumes of 3–4 mL [234, 235]. The available evidence suggests that there are no differences between MDI's with spacers compared to nebulizers, regardless of the severity of the acute asthma exacerbation [232, 236], and either option appears reasonable in at least the ED setting. We remain convinced, however, that continuous albuterol nebulization remains the most appropriate choice for the management of critically ill children with status asthmaticus (see below).

Continuous albuterol nebulization has been shown to be safe and effective in children with status asthmaticus and impending respiratory failure [173, 237–243]. Continuous nebulization provides sustained stimulation of the beta-adrenergic receptors in the airways, thereby preventing the rebound bronchospasm that can occur with intermittent nebulization. In addition, continuous nebulization of albuterol may improve promote progressive bronchodilation, thereby improving drug delivery in the distal airways. Systemic absorption of albuterol resulting from continuous nebulization may account for a portion of its bronchodilatory effects [244–246].

While continuous nebulization of albuterol appears to be safe, side effects such as muscle cramps, hypokalemia, and hyperglycemia commonly occur. Katz et al. [239] documented elevated serum CPK-MB concentrations in two of 19 patients receiving continuous nebulized albuterol. Seven patients developed nonspecific T-wave changes on ECG, though no patients developed sings of myocardial ischemia or cardiac arrhythmias other than sinus tachycardia. Craig et al. [242] documented elevated serum CPK concentrations in three of 17 patients receiving continuous nebulized albuterol. Only one of these three patients had elevated serum CPK-MB concentrations, and none of these patients developed signs of myocardial ischemia or cardiac arrhythmias. The significance of these findings is unclear at present. Several investigators have documented elevated serum CPK-MB concentrations in healthy volunteers following vigorous exercise [247–249], and Choi [250] suggested that the excess work of breathing associated with severe airway obstruction is similar to vigorous exercise. Therefore, the elevated CPK concentrations in these patients may not be indicative of myocardial injury. For these reasons, prudence recommends that continuous nebulized albuterol should be administered only in a closely monitored setting.

Albuterol in reality exists as a 50:50 mixture of two mirror-image enantiomers – the active R-albuterol and S-albuterol. In contrast, levalbuterol (Xopenex®) is pure R-albuterol and is currently available as a solution for nebulization. Emerging data suggests that S-albuterol may have deleterious effects – in fact, S-albuterol is thought to promote bronchoconstriction [236] – so that administration of only the R-enantiomer appears to be an appropriate treatment rationale. However, the majority of studies in children with acute exacerbations of asthma suggest that there is no clinical benefit to the use of levalbuterol versus racemic albuterol [251–253]. Carl et al. [254] noted that children treated with levalbuterol had a lower hospitalization rate compared to children treated with albuterol in a randomized trial involving over 500 children. However, this study has several methodologic flaws which could have potentially biased the results, especially when considered in the context of more recent trials suggesting no clinical benefits to using levalbuterol versus racemic albuterol. In addition, two recent studies comparing continuous levalbuterol to racemic albuterol failed to show any difference in outcome or safety [255, 256]. Given these data, unless more conclusive evidence becomes available, racemic albuterol should be preferentially used in the treatment of children with status asthmaticus.

Intravenous albuterol is not currently available for clinical use in the United States. However, following a similar rationale to the use of either IM epinephrine or intravenous terbutaline (see below), intravenous administration of albuterol via either bolus (5–15 μg/kg) or continuous infusion (1 μg/kg loading dose followed by 0.2 μg/kg/min increased by 0.1 μg/kg/min to clinical improvement or greater than 20 % increase in heart rate) is widely used outside of the United States and has been studied in both children and adults with status asthmaticus [257–262]. However, one study suggested that there was no clinical differences between intravenous albuterol compared to intravenous aminophylline in 44 children presenting to the ED with status asthmaticus [261]. Intravenous albuterol may also be associated with an increased incidence of side effects, including tremors, nausea/vomiting, hypoxemia, and tachyarrhythmias [263].

Terbutaline

Terbutaline is a selective β_2-receptor adrenergic agonist that has been administered to children with status asthmaticus via the subcutaneous [223, 264], nebulized [265–267], and parenteral routes [266, 268–272]. In certain cases, critically ill children with status asthmaticus may fail to respond to con-

tinuous, nebulized albuterol, in part due to the inability of the albuterol to reach its site of action within the lung secondary to severe bronchospasm and mucus plugging [273]. In this situation, an intravenous (or intramuscular) agent, such as terbutaline may be beneficial. However, several adult trials have failed to show any difference between continuous, nebulized terbutaline and intravenously administered terbutaline [274–276]. There are a few studies on intravenous terbutaline that have been performed in critically ill children with status asthmaticus, most of which suggest that terbutaline has limited benefit over other agents [174, 277, 278]. While terbutaline appears to be relatively safe [270, 279], there is a potential for cardiac toxicity (similar mechanism to isoproterenol – see below), and serial cardiac troponins should be measured [279, 280].

Isoproterenol

Isoproterenol is a non-selective β-agonist that is no longer clinically used for the treatment of status asthmaticus, though it is mentioned here for historical interest. Isoproterenol is a potent bronchodilator when administered either by aerosol (0.5 % solution, 5 mg/mL; 0.01–0.03 mL/kg diluted with 1.5 mL saline every 2–6 h) or continuous intravenous infusion (0.02 % solution, 0.2 mg/mL; 0.05–0.1 μg/kg/min, increase by 0.05–0.1 μg/kg/min every 15–20 min until clinical response or greater than 20 % increase in heart rate) [281–289]. However, isoproterenol was associated with tachyarrhythmias and myocardial ischemia and was removed from clinical use when albuterol became widely available [73, 290–293].

Ipratropium Bromide

The autonomic nervous system is intimately involved in the regulation of airway smooth muscle tone and mucous secretion. The parasympathetic nerve fibers, which are largely confined to the larger, central airways, stimulate bronchoconstriction and increased mucous secretion (mediated through the neurotransmitter, acetylcholine). In contrast, the sympathetic nerve fibers are distributed more peripherally in the smaller airways and stimulate bronchodilation [294]. This dual-innervation suggests that a therapeutic strategy aimed at both the cholinergic and adrenergic pathways would be beneficial in the treatment of status asthmaticus. There are at least three subtypes of muscarinic receptors in the human airways – M_1, M_2, and M_3 [295, 296]. The M_1 subtype is localized to the parasympathetic ganglion and mediates cholinergic transmission. The prejunctional M_2 receptors inhibit the release of acetylcholine and serve as a negative feedback mechanism, thereby limiting bronchoconstriction. Conversely, stimulation of the M_3 receptors, which are localized to airway smooth muscle and submucosal glands, results in bronchoconstriction and increased mucous production. The M_2 receptors are thought to be dysfunctional in patients with asthma, especially following viral infection, resulting in unopposed M_1 and M_3 activity, producing excessive bronchoconstriction [297].

The nonselective, muscarinic antagonist, ipratropium bromide is a quaternary ammonium atropine derivative that has been used successfully in the treatment of chronic obstructive pulmonary disease (COPD) and chronic asthma. Increasing evidence suggests that a synergistic reduction in airflow obstruction in both children and adults when treated with both ipratropium bromide and albuterol [294, 298, 299]. For example, three studies showed that the addition of ipratropium bromide to albuterol aerosols in children presenting to the ED with status asthmaticus significantly reduced the rate of hospital admission [300–302]. However, two studies in children hospitalized with acute asthma suggested that the addition of ipratropium to standard therapy offered no additional benefit [303, 304]. A Cochrane Database review suggested that ipratropium bromide should not be used in lieu of albuterol, as multiple studies have shown that it is less effective than albuterol when used as a single-agent [305]. However, there are no studies of ipratropium bromide combined with standard therapy in critically ill children who are admitted to the PICU with status asthmaticus. Given the low risk of adverse effects and until more definitive evidence is available, the addition of ipratropium bromide to standard therapy appears to be a reasonable strategy in this population.

Magnesium

Rosello and Pla [306] first reported the use of magnesium for the treatment of acute asthma in 1936. Since that time, magnesium has been shown to be a direct bronchodilator [307–310], and numerous case reports [311–313] have noted clinical efficacy in patients with respiratory failure complicating status asthmaticus. The mechanism of action by which magnesium produces bronchodilation in asthma is not entirely clear. Magnesium administration may serve to replace an underlying magnesium deficiency. Several studies have shown that patients with status asthmaticus have an underlying hypomagnesemia [314–318], and frequent β-agonist therapy has been demonstrated to result in decreased magnesium levels [319]. Alternatively, magnesium may act as a pharmacologic agent via one or more of several potential mechanisms. Regardless of the exact mechanism, it is clear that magnesium acts principally as a calcium antagonist, directly inhibiting calcium uptake in smooth muscle cells, thereby resulting in smooth muscle relaxation [320–326].

A Cochrane Database review showed that nebulized magnesium was not as effective as albuterol, nor did nebulized

magnesium offer any additional benefits when used concomitantly with albuterol [327]. The available data with intravenous magnesium sulfate therapy appears to be more promising. Pabon et al. [328] presented their experience with the use of intravenous magnesium sulfate in four children with status asthmaticus admitted to the PICU. All four patients responded favorably to magnesium without any adverse effects. Five small, prospective, randomized, controlled trials comparing intravenous magnesium and placebo in children presenting to the ED with status asthmaticus have been conducted since that time [329–333]. Four of these trials [329–331, 333] demonstrated significant improvements in respiratory function and a decreased number of hospital admissions in children who were randomized to the magnesium groups. Scarfone et al. [332], on the other hand, failed to demonstrate any significant differences in these parameters between the magnesium and placebo groups. Two subsequent meta-analysis of these five studies concluded that magnesium sulfate provides additional benefit to children with status asthmaticus when added to a regimen of frequent, nebulized beta-adrenergic agonists and corticosteroids [334, 335].

The correct dose and frequency of administration has not been adequately defined. However, there is increasing evidence to suggest that increasing the serum magnesium level > 4 mg/dL is necessary to produce effective bronchodilation [307, 309]. Onset of action is quite rapid (within minutes), and the effects last for approximately 2 h [307, 309, 336]. Given the short duration of action, some physicians advocate the use of a continuous infusion of magnesium sulfate [337, 338]. Side effects appear to depend upon the serum magnesium concentration. Mild effects include nausea, vomiting, facial flushing, and dry mouth. In our experience, hypotension is a frequent side effect. At serum magnesium levels > 12 mg/dL, loss of deep tendon reflexes, muscle weakness, and respiratory depression, as well as cardiac conduction defects may be seen [307, 309, 339].

Theophylline (Table 4.5)

Theophylline has been used as a bronchodilator for the treatment of reversible obstructive airway disease for many years and was once considered the bronchodilator of choice for the management of acute asthma. However, the current role of theophylline in the available armamentarium for management of status asthmaticus is less clear. Several studies in hospitalized children diagnosed with mild to moderate status asthmaticus failed to demonstrate any added benefit when theophylline or aminophylline was added to a standard regimen of frequently nebulized beta-agonists and intravenously administered corticosteroids [128, 340–345]. In addition, a published meta-analysis of these trials concluded that any benefits associated with the use of theophylline in treating children with mild to moderate status asthmaticus were slight, and that the available evidence suggested a detrimental effect with theophylline treatment as measured by an increased number of albuterol treatments and hospital length of stay [346]. The aforementioned studies, however, excluded children from participation if they were diagnosed with impending respiratory failure or if they required admission to the PICU.

Table 4.5 Dosing guidelines for intravenous theophylline

Loading dose (in patients not currently receiving aminophylline or theophylline):
6 mg/kg (based on aminophylline) administered over 20–30 min
Continuous infusion:
6 weeks to 6 months: 0.5 mg/kg/h
6 months to 1 year: 0.6–0.7 mg/kg/h
1–9 years: 1–1.2 mg/kg/h
9–12 years and young adult smokers: 0.9 mg/kg/h
12–16 years: 0.7 mg/kg/h
Adults (healthy, nonsmoking): 0.7 mg/kg/h
Older patients and patients with cor pulmonale, patients with CHF or liver failure: 0.25 mg/kg/h

Note: Serum theophylline levels should be obtained 3 h after the initial loading dose and every 12–24 h thereafter. The dose should be adjusted to maintain serum theophylline concentrations between 12 and 20 μg/mL

If the serum theophylline concentration <12 μg/mL, a repeat bolus of theophylline (based on the assumption that 1 mg/kg will increase the serum theophylline concentration approximately 2 μg/mL) should be administered and the continuous infusion should be increased by 10 %

If the serum theophylline concentration is between 12 and 16 μg/mL, no changes are made

If the serum theophylline concentration is >16 μg/mL, the continuous infusion is decreased by 10 %

If the serum theophylline concentration is > 22 μg/mL, the continuous infusion should be discontinued until the concentration falls below 20 μg/mL

Theophylline may offer several potential advantages for the treatment of status asthmaticus in the PICU population. For example, theophylline produces bronchodilation and improves airflow without adversely affecting ventilation-perfusion matching [347]. As discussed above, the use of intravenous beta-agonists, like terbutaline or albuterol, can worsen pulmonary gas exchange, despite improved airflow, because the beneficial effect of hypoxic pulmonary vasoconstriction [348, 349]. Theophylline's diuretic effects may also reduce excess alveolar fluid and microvascular permeability [347, 350]. Finally, theophylline increases respiratory drive, improves mucociliary clearance, reduces pulmonary vascular resistance, and improves contractility of the diaphragm, all of which may benefit the tenuous child with impending respiratory failure secondary to status asthmaticus [347].

Three trials have examined the effects of theophylline when added to the standard treatment regimen of beta-agonists, corticosteroids, and oxygen in critically ill children who were admitted to the PICU with status asthmaticus

Table 4.6 Theophylline toxicity

Theophylline serum concentration (μg/mL)[a]	Adverse reactions
15–25	GI upset, GE reflux, diarrhea, nausea, vomiting, abdominal pain, nervousness, headache, insomnia, agitation, dizziness, muscle cramp, tremor
25–35	Tachycardia, occasional PVC
>35	Ventricular tachycardia, frequent PVC, seizure

[a]Note: Adverse effects do not necessarily occur according to serum levels. Arrhythmia and seizure can occur without seeing the other adverse effects

Table 4.7 Medications affecting theophylline clearance resulting in either increased or decreased serum levels

Decreased theophylline level	Increased theophylline level
Aminoglutethimide	Alcohol
Carbamazepine	Allopurinol (>600 mg/day)
Isoproterenol (I.V.)	Beta–blockers
Isoniazid[a]	Calcium channel blockers
Ketoconazole	Cimetidine
Loop diuretics[a]	Ciprofloxacin
Nevirapine	Clarithromycin
Phenobarbital	Corticosteroids
Phenytoin	Disulfiram
Rifampin	Ephedrine
Ritonavir	Erythromycin
Sulfinpyrazone	Esmolol
Sympathomimetics	Influenza virus vaccine
	Interferon, human recombinant alpha 2-a and 2-b
	Isoniazid[a]
	Loop diuretics[a]
	Methotrexate
	Mexiletine
	Oral contraceptives
	Propafenone
	Propranolol
	Tacrine
	Thiabendazole
	Thyroid hormones
	Troleandomycin (TAO®)
	Verapamil
	Zileuton

[a]Note: Both increased and decreased theophylline levels have been reported

[277, 351, 352]. Notably, two of these trials included children who developed respiratory failure and required mechanical ventilation [351, 352]. These studies suggest that theophylline continues to have a role in the management of severe acute exacerbations of asthma in children; however other therapies with a lower risk of adverse effects (Table 4.6) should be utilized first. In addition, serum theophylline concentrations should be followed closely, as several medications (Table 4.7) affect theophylline clearance. Importantly, a single-center retrospective series suggested that aminophylline was independently associated with increased length of stay in the PICU [353]. Perhaps the largest drawback to theophylline in the current era is the relative lack of experience with its use, especially given its narrow therapeutic index.

Helium-Oxygen

According to Hagen-Poiseuille's law, the change in air flow resulting from a reduction in airway diameter is directly proportional to the airway radius elevated to the fourth power. While airway resistance is inversely proportional to the radius of the airway to the *fourth power* when there is laminar flow, resistance is inversely proportional to the *fifth power* when there is turbulent flow. The therapeutic use of helium-oxygen mixtures in children with asthma therefore appears reasonable based upon the physical properties of helium. Helium-oxygen gas mixtures reduce the Reynolds number (because it is less dense and more viscous compared to air) and renders turbulent flow less likely to occur in the small airways [354, 355]. Several small series and anecdotal reports suggest that helium-oxygen decrease the work of breathing and improved respiratory mechanics in both tracheally intubated and nonintubated children with status asthmaticus [356–362]. A Cochrane Database review, however concluded that the available evidence does not currently support a role for the administration of helium-oxygen mixtures to ED patients with moderate to severe acute asthma [363]. Two additional trials (one performed in the ED, one performed in the PICU) were not included in the aforementioned Cochrane Database review. One trial suggested that continuous albuterol nebulized with helium-oxygen mixtures resulted in a greater clinical improvement compared to continuous albuterol nebulized with 100 % oxygen [364]. However, the second trial suggested that helium-oxygen mixtures offered no additional benefits [365]. The utility of helium-oxygen in children for the treatment of status asthmaticus and impending respiratory failure therefore remains unproven.

Ketamine

Ketamine is a dissociative anesthetic agent that causes bronchodilation secondary to a combination of factors, including the drug-induced release of endogenous catecholamines,

inhibition of vagal tone, and direct muscle relaxation [366, 367]. For these reasons, it is the induction agent of choice for the tracheal intubation of children with asthma. While ketamine has been used successfully for the treatment of refractory bronchospasm in intubated patients [368–374], there is controversy surrounding its use in nonintubated patients due to its propensity to increase pulmonary secretions, cause occasional laryngospasm, and induce hallucinations. Numerous case reports and anecdotes [368, 375–377], as well as a prospective study in children [378], however, suggest that ketamine may be a safe and efficacious adjunct to standard therapy in the treatment of children with status asthmaticus and impending respiratory failure. Ketamine should only be used in a monitored setting, however, and additional prospective, randomized, controlled trials demonstrating its efficacy and safety in this setting are justified [379].

Leukotriene Modifying Agents

Leukotriene modifying agents (LMAs) are a newer class of asthma medications which are approved for use in the chronic treatment of moderate-to-severe asthma. The leukotrienes (LTs) are biologically active fatty acids generated from arachidonic acid (AA) by the enzyme 5-lipoxygenase. 5-lipoxygenase generates leukotriene A_4 (LTA_4) from AA. LTA_4 is metabolized to LTC_4, LTD_4, and LTE_4 (the so-called *slow-reacting substances of anaphylaxis*). The LTs produce bronchoconstriction, stimulate mucus secretion, decrease mucociliary clearance, increase vascular permeability, and recruit eosinophils and basophils into the airway, thereby perpetuating the airway inflammation that is the hallmark of asthma [380]. Activation of LT pathways during acute asthma exacerbations, as determined by urinary LTE_4 levels, appears to strongly correlate with the degree of airway obstruction [381]. A Cochrane Database review of the available clinical trials in both adults and children suggested that LMAs offer no significant benefits for the management of acute asthma exacerbation [382].

Mechanical Ventilation

Status asthmaticus leading to respiratory failure is an important cause of morbidity and mortality due to the potential risks of barotrauma and cardiovascular instability associated with the use of mechanical ventilation in these children [16, 22, 383–387]. Given these risks, many experts feel that mechanical ventilation should be avoided at all costs [16, 383], frequently viewing this modality as *a last ditch effort* or the *therapy of last resort*. While the decision to tracheally intubate a child with status asthmaticus should not be taken lightly, the potential benefits of ventilatory support, especially when used carefully and judiciously with appropriate goals in mind, appear to be outweigh the potential adverse effects. Non-invasive positive pressure ventilation is an attractive modality that may obviate the need for tracheal intubation [388, 389].

There are few absolute indications for tracheal intubation in children with status asthmaticus (e.g., coma, cardiac arrest), though failure to maintain adequate oxygen saturations, a worsening metabolic acidosis, and decreasing mental status are all signs that respiratory arrest is imminent. The decision to tracheally intubate should be based upon the clinical examination and not the results of an arterial blood gas. Interestingly, children who present to a community hospital ED (as opposed to a pediatric ED) are more likely to be tracheally intubated, though they are also more likely to have a shorter duration of tracheal intubation as well. These results suggest that children with status asthmaticus receive less aggressive treatment up front, compared to those who present to a pediatric ED [30]. Similar results have been found for critically ill children who are intubated before admission to the PICU versus those who are intubated after admission to the PICU [26].

Critically ill children with acute respiratory failure secondary to status asthmaticus are quite ill, and a rapid-sequence intubation technique should be performed by the most experienced physician available. Ketamine (2 mg/kg IV) is an excellent choice for an induction agent due to its bronchodilatory properties (discussed above), though propofol (2 mg/kg IV) may be an effective alternative. Neuromuscular blockade with either succinylcholine (if there are no contraindications to its use) or rocuronium produce acceptable conditions for laryngoscopy and tracheal intubation within 1–3 min. These children will require high inspiratory pressures and the use of a cuffed tracheal tube is justifiably preferable in this scenario [16, 67, 386]. More than half of the complications in patients requiring mechanical ventilation for status asthmaticus occur at or around the time of tracheal intubation [16] and include hypoxemia, hypotension, and cardiac arrest. Hyperventilation should be avoided, and hypotension should improve with volume resuscitation and slowing the respiratory rate to avoid further air-trapping and dynamic hyperinflation. A tension pneumothorax should be considered if these measures fail to relieve hypotension and hypoxemia – in these cases, needle thoracentesis is life-saving.

The goals of mechanical ventilation are to maintain acceptable oxygenation, avoid complications, and *buy time* to allow the corticosteroids and bronchodilators to break the cycle of bronchospasm and airway inflammation. Mechanical ventilation should NOT be targeted towards the results of an arterial blood gas! A landmark article by Darioli and Perett in 1984 introduced the concept of *permissive hypercapnia*, in which low tidal volumes and respiratory rates were used in

adult asthmatics, dramatically reducing the frequency of barotraumas and death compared to historical controls [390]. Similarly, strategies that emphasize the use of *low* tidal volumes (6–10 mL/kg), short inspiratory times (0.75–1.5 s) and correspondingly longer expiratory times to allow adequate time for emptying, and lower-than-normal respiratory rates in children with status asthmaticus result in improved survival [385–387]. The degree of hypercapnia that can be safely tolerated is not known – several case reports of severe acute hypercapnia in children with reported $PaCO_2$ as high as 269 mmHg, usually associated with near-fatal status asthmaticus, have been reported in the literature [391]. Sodium bicarbonate can be administered to maintain a relatively physiologic pH [383, 392] and in some cases may even reduce $PaCO_2$ [393].

The most appropriate mode of mechanical ventilatory support may differ between individual patients, and even in any one patient and their stage of illness [394]. Pressure control [395], volume control [385, 386, 396], and pressure support [397] ventilation have all been used in children with status asthmaticus. Each mode of ventilation has its advantages and disadvantages. It must be emphasized that there is not likely to be one "best mode" for supporting critically ill children with acute respiratory failure secondary to status asthmaticus. We generally prefer a pressure-regulated volume-control mode (PRVC) due to the advantage of delivering a constant tidal volume, even in the face of changing lung compliance and airways resistance, as well as the fact that this mode uses a decelerating flow pattern that minimizes peak inspiratory pressures.

The use of positive end-expiratory pressure (PEEP) in this population remains controversial, and many experts continue to recommend against using PEEP due to the concerns for more air trapping and auto-PEEP [398]. However, low-level PEEP may minimize dynamic airway collapse and decrease trigger work in spontaneously breathing patients [16, 102, 399–401]. Some physicians have advocated setting the PEEP based upon the amount of intrinsic or auto-PEEP, which is measured using an end-expiratory hold maneuver [402–404]. Importantly, however, auto-PEEP may grossly underestimate end-expiratory alveolar pressure in critically ill patients with severe airway obstruction, due to widespread airway closure [398]. We generally set external PEEP just below auto-PEEP [405], though there have not been any studies on setting PEEP in critically ill children with status asthmaticus.

Additional, potentially lifesaving techniques of invasive support have been reported in the literature but have not been adequately studied. For example, tracheal gas insufflation is a method that may reduce the physiologic deadspace and improve ventilation [406, 407]. The use of high frequency oscillatory ventilation in children with acute respiratory failure secondary to status asthmaticus has also been described [408]. Finally, extracorporeal life support (ECLS) may be potentially lifesaving in children with refractory status asthmaticus [26, 31, 357, 409–414].

Volatile Anesthetics

Inhalational anesthetics were used for the treatment of status asthmaticus and acute respiratory failure as early as 1939 [415]. The bronchodilatory properties of these agents are well known, and proposed mechanisms include direct stimulation of the β-adrenergic receptor, direct relaxation of bronchial smooth muscle, inhibition of the release and action of bronchoactive mediators (e.g., histamine, acetylcholine), and depression of vagally mediated airway reflexes [416]. In addition, preliminary studies in certain animal models suggest that inhalational anesthetics may mediate bronchodilation via an epithelial-dependent mechanism involving either nitric oxide or a prostanoid [417, 418]. Halothane appears to be particularly effective [419–421], though concerns regarding its potential toxicity, including direct myocardial depression, hypotension, and arrhythmias, have limited its use in this setting. These adverse effects may be further potentiated in children with status asthmaticus who will have some degree of hypoxia, hypercapnia, and acidosis and who are frequently managed with the concomitant administration of β-adrenergic agents and/or theophylline [422]. Inhalational anesthetics may also precipitate malignant hyperthermia and require special, expensive equipment to administer, monitor, and scavenge gases.

The use of isoflurane in status asthmaticus and acute respiratory failure offers several advantages over halothane. Isoflurane has a low blood-gas solubility coefficient, such that the depth of anesthesia can be rapidly titrated and recovery from anesthesia is relatively short. Isoflurane produces less myocardial depression and is less arrhythmogenic compared with other inhalational anesthetics such as halothane. Given its role as a general anesthetic, concomitant administration of sedation/analgesia and neuromuscular blockade is not necessary. Finally, while isoflurane produces dose-dependent hypotension via direct vasodilation, there is a compensatory increase in heart rate so that cardiac output is relatively preserved [396, 423, 424]. In addition, the hypotension is usually responsive to volume resuscitation.

Isoflurane has been used with some success in both children and adults with status asthmaticus refractory to conventional therapy [396, 425–431]. Based on these data and the theoretical advantages discussed above, we currently favor isoflurane over other inhalational anesthetics like halothane. Isoflurane should only be administered in consultation with an anesthesiologist using either an anesthesia machine or vaporizer custom-fitted to a standard PICU ventilator [396, 431, 432]. An inline volatile gas analyzer is necessary for

monitoring the inspiratory and expiratory concentration of isoflurane. Finally, a system to scavenge exhaled gases is necessary. We generally start therapy with 1–2 % isoflurane and increase the dose by 0.1 % every 15 min until a therapeutic effect is achieved (decrease in PIP ≤35 cm H_2O with tidal volumes 8–10 mL/kg with improving air entry on clinical examination). Sedation, analgesia, and neuromuscular blockade are discontinued, as this dose of isoflurane provides adequate anesthesia. Other therapeutic agents, e.g. albuterol, corticosteroids, magnesium, terbutaline, etc. are continued. Isoflurane undergoes minimal metabolism, though prolonged isoflurane has been associated with an increase in plasma fluoride concentration due to the release of fluoride ions [423]. Fluoride concentrations > 50 μmol/L are nephrotoxic [433], though subclinical nephrotoxicity may occur at lower levels with prolonged exposure [434, 435]. Renal function should therefore be monitored closely. Interestingly, a multicenter database review from 40 participating children's hospitals suggested that there is no mortality benefit to the use of volatile anesthetics in status asthmaticus, though there was a significant association with increased LOS and hospital costs [436]. Unfortunately, the experience with this treatment is rare enough that a prospective, randomized clinical trial will likely be never performed.

Conclusion

Status asthmaticus is one of the most common admission diagnoses in the PICU. While studies suggest that the overall prevalence of asthma in children has leveled off in recent years, these same studies suggest that the severity of asthma is getting worse. Given the increasing prevalence of obesity and its association with asthma severity, the number of patients admitted to the PICU with status asthmaticus is likely to increase. A stepwise, but aggressive approach to management of these patients is recommended.

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Bronchiolitis

5

Kentigern Thorburn and Paul Stephen McNamara

Abstract

Bronchiolitis produces significant morbidity and mortality worldwide every year. Approximately 3–10 % of all infants hospitalized with bronchiolitis develop acute respiratory failure and require admission to a pediatric intensive care unit. The vast majority of cases are caused by Respiratory Syncytial Virus (RSV), though other viruses (human metapneumovirus, parainfluenza, influenza, adenovirus, rhinovirus, coronavirus and bocavirus) may also cause bronchiolitis. Bronchiolitis is not merely a single organ disease (i.e. lung), but impacts on extrapulmonary organ systems. Basic supportive management remains the cornerstone. There is a paucity of established therapeutic options, with supplementary oxygen, continuous positive airway pressure (CPAP), humidified high-flow nasal oxygen, mechanical ventilation being the mainstay of respiratory support.

Keywords

Bronchiolitis • Respiratory syncytial virus (RSV) • Co-morbidity

Introduction

Bronchiolitis is a common acute, potentially life-threatening, viral respiratory illness that affects predominantly infants and young children around the world, usually as a seasonal epidemic. Although "bronchiolitis" is actually a pathological description, bronchiolitis is used as a clinical diagnosis for a disease characterized by coryza, cough, fever, increased respiratory effort, hyperinflation of the chest, wheezing, widespread fine crackles on auscultation, and poor feeding. Around 2–3 % of all infants in resource-rich countries are admitted to the hospital with bronchiolitis. Annually, bronchiolitis is estimated to account for two million children under 5 years of age requiring medical attention and 60,000–90,000 hospitalizations in the USA alone [1]. Approximately 3–10 % of infants hospitalized with bronchiolitis develop respiratory failure and require admission to a pediatric intensive care unit (PICU) [2, 3]. This chapter will concentrate on severe bronchiolitis that requires critical care, and especially respiratory, support.

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Pathogens, Pathogenesis and Pathophysiology

Respiratory syncytial virus (RSV) accounts for 50–70 % of the cases of bronchiolitis, with less common viral pathogens being parainfluenza, influenza, adenovirus, human metapneumovirus, rhinovirus, coronavirus, and bocavirus. Even though outbreaks of pyrexial respiratory illnesses have been

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described for many centuries, probably the first description of an outbreak of RSV was reported in 1941 [4]. Adams described an outbreak of nosocomial chest infections in 32 infants in a neonatal unit that resulted in 9 deaths, with cytoplasmic inclusions identified in the lungs at autopsy. RSV was first identified in 1956 from a colony of chimpanzees with coryza and designated "chimpanzee coryzal agent". Subsequently a year later in 1957 it was isolated from children with lung disease in Baltimore, USA [5]. Since then RSV has been recognized as the single most important virus causing acute respiratory tract infections in infants and young children throughout the world [1, 6, 7]. Although primarily a respiratory pathogen of infants and young children, RSV infects and re-infects adults, and causes significant disease in the elderly and in those patients with chronic lung disease or immunocompromise [6].

RSV is classified in the order *Mononegavirales*, family *Paramyxoviridae* (Greek *para* for "beside" or "beyond" + *myxa* for "mucus") and subfamily *Pneumovirinae*, with the closely-related human metapneumovirus. Other family members include the *Paramyxivirinae*: parainfluenza virus types 1, 2, 3; mumps and the morbillivirus measles. In the same order *Mononegavirales*, the fellow RNA viruses influenza A and influenza B reside in the family *Orthomyxoviridae* (Greek *orthos* for "straight" + *myxa* for "mucus"). RSV is a pleomorphic (spherical or filamentous form) enveloped RNA virus 120–300 nm in size that contains a non-segmented single-strand negative-sense RNA genome. Two large surface glycoproteins, fusion protein (F) and attachment protein (G), are the major antigenic determinants and induce antibody production. There are two major groups of RSV strains, A and B, that are distinguished by antigenic characteristics, mainly in variations in the G (attachment) protein, as there are few differences in the F (fusion) protein between the strains [6, 8, 9].

RSV infects respiratory epithelial cells by attaching itself to the cell surface by means of a capsular glycoprotein, the G (attachment) protein. A second capsular glycoprotein, the F (fusion) protein, mediates fusion with the epithelial cell membrane along with adjacent cells, resulting in the formation of giant multinucleated cells – syncytia – for which the virus is named [10]. It is suggested that another structural capsular/envelope protein, the SH (small hydrophobic) protein, plays a role in both syncytial formation and blocking of cell death/apoptosis. RSV virion assembly occurs at the plasma membrane of infected cells and are released by budding, taking a lipid bilayer membrane derived from the infected host cell with them. Infectious RSV is probably in the filamentous form [10].

RSV (and other paramyxoviruses) transmission is by direct inoculation of contagious secretions from hands and self-inoculation of eyes and nose. Transmission requires close or direct contact with large droplets residing on fomites like skin, cloth or clinical surfaces. Transmission through aerosolization is more a feature of the influenza viruses, adenovirus, rhinovirus and coronavirus. RSV's incubation period can be 2–8 days, usually 2–5 days [6]. The virus replicates in nasopharyngeal epithelium and then spreads to lower respiratory tract 1–3 days later.

Respiratory viruses causing bronchiolitis (especially RSV) have a direct cytopathic effect on respiratory epithelial cells. The characteristic infective and inflammatory process of bronchiolitis leads to loss of cilial motility, submucosal edema, increased mucus secretion, infiltration by leukocytes, necrosis and sloughing of the respiratory epithelial cells of the small airways, all of which obstructs airflow through the small/distal airways [10]. During expiration this enhances dynamic small/distal airways narrowing, producing disproportionate turbulence and decreased airflow causing air-trapping. Further air-trapping can be caused by a ball-valve mechanism of airway obstruction due to intraluminal plugging by mucus and cellular debris. Clinically the inflammatory process in the small/distal airways (i.e. bronchiolitis) can result in both pulmonary hyperinflation and areas of atelectasis, along with wheezing due to small/distal airways obstruction.

The extent to which structural/anatomical factors impact on the degree of distal airways obstruction is governed by vector properties (for example Pouiseille's Law dictating that the turbulence in the airflow in a cylinder increases to the power of 4 with each decrease in radius), and the physical size/absolute diameter of the distal airway. Inherent variations in the infected individual's inflammatory and apoptotic response also influence the degree of submucosal edema, increased mucus secretion, and sloughing of epithelial cells. The former factors probably account for the high incidence of respiratory disease in younger smaller individuals with their smaller distal airways (e.g. premature infants) [3, 10]. The latter, individualistic inflammatory response, continues to fuel much research worldwide.

Clinically, air-trapping and atelectasis increase work of breathing due to increased end expiratory lung volume and decreased lung compliance. Respiratory failure is usually the result of worsening lung compliance and respiratory muscle fatigue. Apnea, which is common in infants with bronchiolitis, can be secondary to severe lung disease or central in origin.

The respiratory epithelial cells usually recover within 2–4 days, but histologically the ciliated epithelial cells take 2 weeks to regenerate [6]. Both laboratory and human studies have demonstrated that immune competent hosts clear the virus following natural RSV infection within 3 weeks, whereas immunocompromised hosts with deficiencies of cellular immunity tend to suffer more severe disease and have prolonged viral shedding [6].

Immune Response to RSV Infection

Protection against upper (URTI) and lower respiratory tract infections (LRTI) requires a balance between humoral and cellular immunity. Local secretory IgA is the prominent humoral mediator of resistance in the upper respiratory tract, whereas serum IgG provides additional protection in the lower respiratory tract. The F and G surface glycoproteins are the only RSV proteins to induce protective neutralizing antibodies (mainly of the IgG1 subclass) in children [6]. In neonates and infants, high levels of maternally-derived neutralizing antibodies confer some protection [6, 7].

Cellular immunity plays the predominant role in combating and recovering from RSV infection, with T-lymphocytic stimulation and response playing an integral function. The antiviral and cell-mediated immune reaction to RSV infection is primarily orchestrated by RSV-infected respiratory epithelial cells and by alveolar macrophages. T helper 1-type cytokines – interferon γ (IFNγ), interleukin type 2 (IL-2), IL-12; T helper 2-type cytokines – IL-4, IL-5, IL-6, IL-10; antiviral interferons – IFNα, IFNβ; and chemokines – C, CC, CXC and CX_3C subgroups, attract and activate leukocytes, especially alveolar macrophages, to the RSV-infected respiratory tract. These cytokines and chemokines may enter the systemic circulation and impact on outlying cells in extrapulmonary sites [8, 11, 12] (Fig. 5.1).

Much of our understanding of the immune response to RSV infection comes from animal models or studies in children with severe disease (i.e. intubated and mechanically ventilated children from whom respiratory samples can be obtained) [11, 12]. Therefore the immunopathogenesis of RSV disease in the great majority of children who develop mild respiratory symptoms, and may not see a doctor or attend hospital, is largely inferred [8, 11, 12]. A misdirected immune cascade, characterised by an overexuberant release of inflammatory mediators ("cytokine storm") and infiltration of a range of monocytes and polymorphonuclear cells may predispose to more severe bronchiolitis, which is further manipulated by host genetic and acquired factors. Contrary to prevailing inflammatory avalanche theories, a study in Chilean children (where mechanical ventilation was not available) dying from RSV or influenza bronchiolitis and

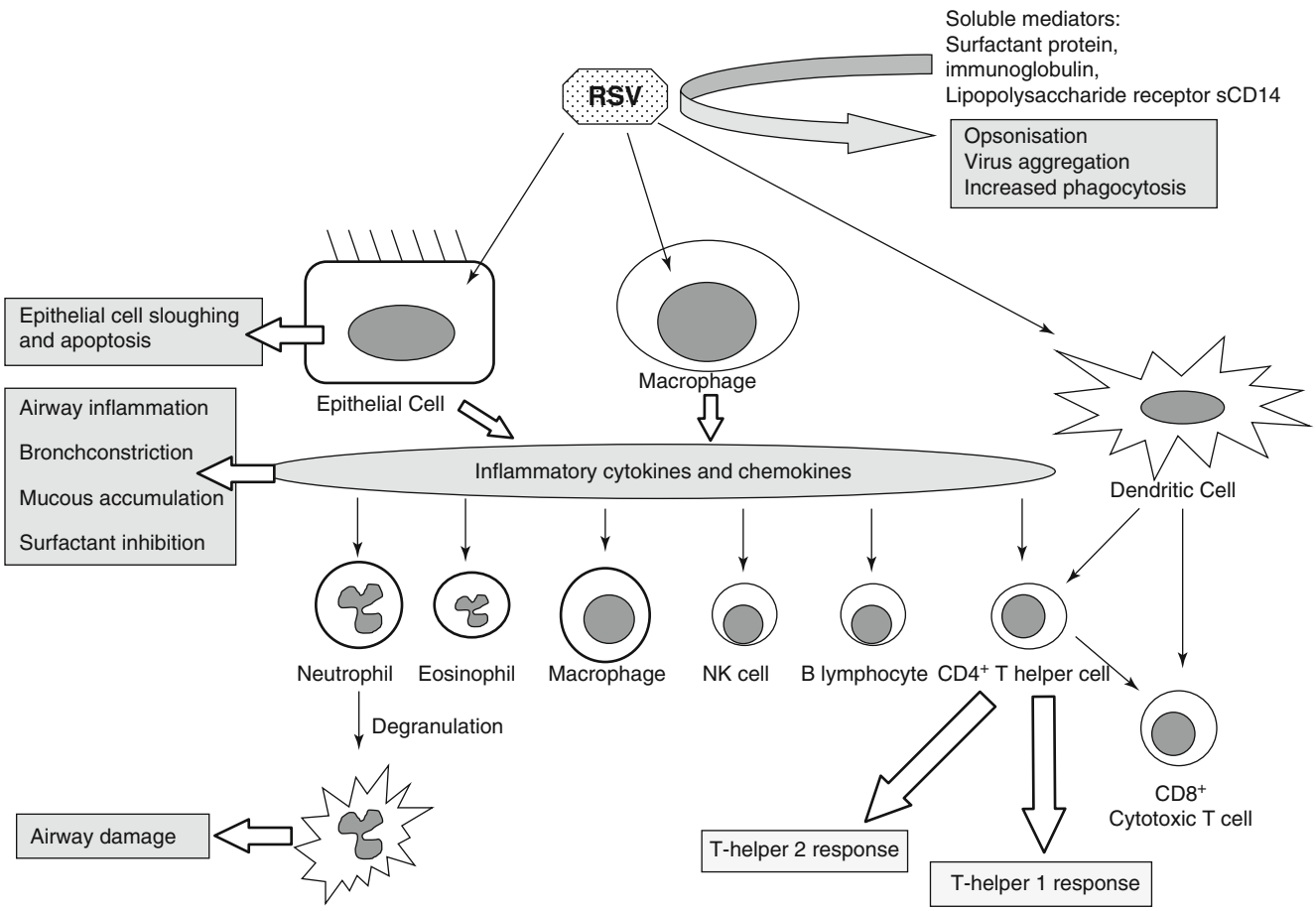


Fig. 5.1 Diagram of the inflammatory pathways and resultant clinical impact triggered by infection with respiratory syncytial virus (RSV)

North American infants surviving RSV or influenza bronchiolitis found a blunted adaptive cell-mediated immune response with a relative absence of cytotoxic T-cells [10]. In the fatal cases, especially with RSV infection, there was excessive viral antigen and overwhelming apoptotic sloughing of infected respiratory epithelial cells [10].

In a trial of a formalin-inactivated vaccine in the late 1960s, immunized children suffered more severe disease than controls when they subsequently contracted natural RSV (re) infection (80 % required hospitalization compared to 5 % of controls). Vaccinated children lacked specific mucosal antibodies; their serum antibodies were deficient in fusion-inhibiting and neutralizing activity; some had increased lymphocytic and/or eosinophilic proliferation [6]. These findings suggested that protection against RSV infection necessitates a balance between humoral and cellular immunity. However, the relative contributions of the humoral and cellular immune components in RSV infection and immunity to subsequent RSV infection is still debated [6, 8, 10]. Effective and appropriately-restrained protection from RSV bronchiolitis most probably requires a viral neutralizing response (humoral/antibody + cellular) without an excessive RSV-specific cytotoxic T-lymphocyte response [8, 11].

Primary infection with RSV does not lead to acquired immunity against future infections. Although naturally acquired immunity is neither durable nor complete, it does appear to provide some protection as subsequent infections are less severe [6, 9]. Despite extensive study of the major surface glycoprotein (G), the fusion protein (F), and even the transcription antiterminator matrix protein, the reasons for this lack of acquired immunity remain unclear [9].

Epidemiology

RSV affects about 60–70 % of infants by the age of 1 year and 90 % of children by the age of 2 years, most commonly as a respiratory tract infection. Peak infection rates occur in infants 6 weeks to 6 months of age. Re-infection occurs frequently (throughout life), but illness tends to be milder [6]. Virtually all children have developed antibodies to RSV by 3 years of age [3].

RSV infection can occur throughout the year, but RSV epidemics occur at predictable annual intervals during the winter months in moderate climates, and during hot and rainy season in tropical climates [13, 14]. In the northern hemisphere the annual 'RSV season' is usually between November and March, with the typical peak period being December through to February. During their first RSV infection, between 25 % and 40 % of infants have bronchiolitic (or pneumonic) signs and symptoms, and up to 3 % require hospitalization (in developed/resource-rich nations) [1, 15]. In the USA, RSV bronchiolitis accounts for up to 90,000 hospitalizations annually, 20,000 in the UK, and 3,000 in the Netherlands [1, 15]. Generally the reported hospital admission rates for children under 1 year of age in the USA and Europe is around 25–30 per 1,000 infants [3]. Incidence and hospitalization rates for bronchiolitis in resource-limited areas are lacking owing to the paucity of epidemiological studies and cost-saving restrictions in laboratory confirmation of viral infection [4, 7, 16]. Both A and B strains circulate concurrently within a RSV season. There are distinct genotypes within the strains which vary in dominance within a community from year to year [17]. This may account for the frequency of re-infection as any immunity to previous genotypes is evaded [17]. Approximately 3–10 % of infants hospitalized with RSV infection (and about 1 % of all those with bronchiolitis) develop respiratory failure and require admission to PICU [2, 3]. Amongst the children from resource-rich countries admitted to PICU with bronchiolitis, the reported incidence of those requiring mechanical or non-invasive ventilation varies from 50 % to 100 % depending more on the country, than the region or unit [2, 18, 19].

Mortality

The mortality rate for those hospitalized with bronchiolitis is low at 1–3 %, but increases in children with severe bronchiolitis requiring intensive care management [2, 20, 21]. Mortality is higher in those with co-morbidity (especially underlying congenital heart disease, chronic lung disease, immunocompromise, neuromuscular disease), with nosocomial infection [21], and in developing/resource-limited nations. RSV is the most common viral cause of death in children below 5 years of age and especially in infants less than 1 year old [8, 20]. It has been estimated that annually in the USA up to 2,700 deaths are caused by RSV [15, 20], and that world-wide 199 000 deaths in children less than 5 years of age were attributable to RSV-associated lower respiratory tract infection in 2005 [7].

Clinical Diagnosis

The diagnosis of bronchiolitis for the vast majority of children around the world is made on clinical grounds – coryza, cough, fever, increased respiratory effort, hyperinflation of the chest, wheezing, fine crackles on auscultation, poor feeding and dehydration; which may be backed up by non-specific chest radiographic findings of hyperinflation and patchy atelectasis, and/or below normal oxygen saturations on pulse oximetry [3, 22–24]. Chest radiography does not differentiate the different viral causes of bronchiolitis or even viral bronchiolitis from bacterial LRTI [24, 25]. Additionally, clinical severity and chest radiography changes

do not correlate well [25]. Although oxygen saturation measurements may influence clinicians in admitting infants with bronchiolitis, the benefits of pulse oximetry in this group have not been proven [3, 22, 24]. Some authors have suggested that certain clinical features like cyanosis and crackles relate to disease severity in bronchiolitis, but others have questioned the validity and reliability of auscultatory findings due to variations in inter-observer agreement [26].

Laboratory Confirmation of Bronchiolitis

Diagnostic methods for confirming and identifying the viral pathogen in resource-rich countries include viral isolation and culture; direct immunofluorescence and enzyme-linked immunosorbent assays (ELISA) that detect antigen; reverse-transcriptase polymerase chain reaction (RT-PCR) that detect nucleic acid. Serological testing (acute and convalescent antibody viral titres) is usually clinically unhelpful as seroconversion may take weeks and have a poor response. RSV rapid antigen detection tests (immunofluorescence and enzyme-linked immunoassays) generally have overall sensitivity and specificity of 80–90 % (range 60–95 %) [23]. RT-PCR is reported to offer greater sensitivity and multiplex PCR kits that detect several viruses simultaneously are readily available [13]. Most commonly nasopharyngeal aspirates are tested, but in intubated patients an endotracheal aspirate or broncho-alveolar lavage can be utilized. The quality of the sample, largely dependent on the sampler's technique and expertise, govern the accuracy of diagnostic testing rather than the site sampled [23].

Clinical Phenotype

Bronchiolitis is the most common lower respiratory tract manifestation of viral disease and typically results in air-trapping leading to increased end expiratory lung volume and decreased lung compliance, compatible with an obstructive lung disease pattern [3, 6]. However, bronchiolitis is a heterogeneous disease with some patients having a significant degree of lung consolidation and more restrictive, than obstructive, lung disease [27]. Some authors have discriminated restrictive from obstructive RSV lung disease on pulmonary function tests (decrease respiratory compliance) [28] or ventilatory indices (oxygen index, alveolar-arterial oxygen gradient, mean airways pressure) [29], in addition to four-quadrant alveolar consolidation on chest radiograph in mechanically ventilated children. In everyday pediatric practice clinicians cannot strictly dichotomise this heterogeneous lung disease into restrictive and obstructive forms, especially when each potentially occurs within different parts of the same lung [16, 27]. In the USA and some European countries "RSV bronchiolitis" and "RSV pneumonia" are differentiated clinically by the presence of localized crackles and consolidation on chest radiograph [3]. Informed clinicians generally appreciate the pneumonic aspects of severe bronchiolitis whether labelled "RSV bronchiolitis", "RSV pneumonia" or "RSV pneumonitis".

Severity of Disease and Risk Factors

The vast majority of children with bronchiolitis will be treated in the community, with only up to 3 % requiring admission to hospital [15, 24, 30] – most studies therefore define severe disease by the need for hospitalization [3, 15, 30]. Approximately 3–10 % of infants hospitalized with bronchiolitis require admission to PICU [2, 3] – most pediatric intensivists would regard PICU admission as representing severe disease. Although a number of clinical scoring systems have been proposed (and frequently utilized in bronchiolitis studies), none have proved better than clinical judgement [30–32]. Even national guidelines on indications for hospital referral, for example those produced by the American Academy of Pediatrics or the Scottish Intercollegiate Guidelines Network, still rely on clinical judgement in interpreting clinical features and recognition of risk factors that predispose to severe disease [24, 30, 33].

Risk factors that are associated with increased severity of disease can be divided into host and environmental risk factors. Host factors include chronological age less than 6 weeks, prematurity, chronic lung disease, congenital heart disease, neurological disease, and immunodeficiency [1, 3, 6, 14, 15, 21]. Additionally there are some indicators to suggest a host genetic predisposition (for example surfactant protein D gene polymorphism) to severe RSV infection [4, 34]. Dual respiratory infections (RSV in addition to other respiratory viruses or concomitant bacteria) have also been shown to increase disease severity as indicated by the need for PICU admission and mechanical ventilation [1, 19, 35, 36]. Environmental factors include poverty, overcrowding, malnutrition, and exposure to postnatal tobacco smoke, older siblings, nursery attendance [1, 3].

The viral strain (A or B) appears not to be an important factor as studies have failed to show significant differences in virulence and severity of disease between A and B strains [6]. The viral load and/or uncontrolled viral replication may well influence disease severity. Higher viral loads in tracheal aspirates of ventilated infants with "severe RSV LRTI" compared to "mild disease" (differentiated on mean airways pressure and oxygenation indices) have been found [37]. A higher nasal viral load in ventilated compared to non-ventilated bronchiolitic children was demonstrated in an initial study, however, a subsequent larger study (from the same research team) failed to find a significant difference [38].

Viral load and/or uncontrolled viral replication being a factor is supported by the finding of excessive viral antigen and overwhelming apoptotic sloughing of infected respiratory epithelial cells in the fatal cases of Chilean children dying from RSV (especially) or influenza bronchiolitis [10]. However, viral strain and viral load alone cannot fully account for variations in disease severity, so it remains likely that variations in pre-existing structural elements of the distal respiratory tree and the inherent immune response also play key roles [10, 14].

Extrapulmonary Manifestations/Effects

Clinical consequences peripheral to the lung parenchyma are well described in RSV infection [39], despite most RSV research having concentrated on the lungs and the mechanics of pulmonary immunopathology. Extrapulmonary effects beg the question as to whether these are direct RSV effects (i.e. RSV infection of that tissue) or indirect, being secondary to parenchymal lung disease and its causative respiratory compromise or consequential of prowling inflammatory mediators?

RSV, like the other *Paramyxiviridae*, can infect non-epithelial cells if it can gain access to the receptors on their surface, as demonstrated by the use of monkey kidney cells for RSV culture in vitro. However the transit of RSV to distant organs would have to be hematogenous. RSV-RNA has been detected by RT-PCR in whole blood, but not plasma of infants and neonates, but this alone merely indicates cell-associated RSV genome. RSV-RNA is not necessarily viable RSV and is more likely to be virus phagocytosed by neutrophils or monocytes. To escape their white cell captors, RSV would need to replicate and break out, which has not yet been demonstrated. Viable RSV floating freely in plasma would hold the potential for distant RSV infection.

Evidence of deposition in distant organs comes from detection of the virus in the myocardium, liver, and cerebrospinal fluid [39]. However, strong convincing evidence of RSV-related inflammation or infection at these sites is less forthcoming. Elevated cardiac troponin levels in infants with severe RSV infection are well described. Unfortunately this is not necessarily indicative of RSV-directed myocardial injury, but more likely the result of (right) heart strain secondary to severe lung parenchymal disease [40, 41]. Likewise, it is highly suggestive that raised hepatic transaminases in this patient group are consequential to hepatic congestion or ischemia due to right heart failure, itself secondary to parenchymal lung disease and/or pulmonary hypertension [41, 42]. Proof of a RSV hepatitis would take histological verification (i.e. liver biopsy), which for ethical reasons is only ever going to occur postmortem. Apneas and seizures undoubtedly occur in RSV infection, but presently there is more support for RSV encephalopathy than RSV encephalitis [39]. The reported frequency of bronchiolitis-induced apnea varies from 1 % to 24 % of those children admitted to hospital, and up to 20 % of those admitted to PICU [43, 44]. Unfortunately many of the reports fail to adequately adjust for the confounding consequence that hypoxic episodes and hypercapnea may have on the patient's neurological status. When not related to hypoxic or electrolyte imbalance triggers, RSV's central influence/effect is probably related to released neurotoxic inflammatory chemokines and cytokines [12, 13]. Endocrine impact/consequences appear to be the sequelae of severe RSV pulmonary disease and/or its treatment. It is likely that occurrences of hyponatremia and hyponatremic seizures are largely related to the use of hypotonic/electrolyte-poor intravenous solutions [39]. Further research is required to scrutinize whether the reported neuroendocrine stress response in RSV bronchiolitis is no more than an epiphenomenon reflecting severity of RSV disease. Extrapulmonary effects are not uncommon and are more likely to be the end result of release of inflammatory mediators than direct effects.

Therapeutic Options in PICU

> Oxygen is vitally important in bronchiolitis and there is little evidence that any other treatment is useful – Reynolds and Cook 1963 [45].

It is 50 years since this statement by Reynolds and Cook and the clinical situation essentially remains the same. Maintaining adequate oxygenation and hydration is the mainstay of largely supportive treatment in bronchiolitis [23, 33, 46].

Oxygen

There are no randomized controlled trials or systematic reviews investigating the use of oxygen in LRTI, let alone bronchiolitis. Evidence for the use of oxygen supplementation is extrapolated from case–control studies that show hypoxemia as a risk factor for near-fatal asthma. It is generally recommended that oxygen saturation levels are maintained above 90 % (USA) and above 92 % (UK) [24, 30, 33].

Bronchodilators

Bronchodilators, generally $ß_2$ agonists (or the anticholinergic, ipratropium bromide), are commonly prescribed in children with bronchiolitis in North America and Europe [32]. Heterogenicity in study design and the bronchodilator used complicate comparisons between studies. On systematic

review, no improvement in oxygenation, hospital admission rate or duration of hospitalization has been demonstrated [47]. There are few studies investigating the benefit of bronchodilators in children with bronchiolitis requiring mechanical ventilation [48]. Any transient improvement in measured lung functions did not translate to significant and sustained clinical benefit or decrease in length of ventilation [16]. Their routine use in ventilated patients, as with non-ventilated patients, remains unsupported [16, 24, 47].

Adrenergics: Epinephrine (Adrenaline)

Nebulized epinephrine with its ß-adrenergic bronchodilator effect, along with the α-adrenergic effect of pulmonary vasoconstriction and reduction in edema, has been considered useful and used in the treatment of bronchiolitis. Although studies on nebulized epinephrine in bronchiolitis show it to have a good safety profile, short-term improvement in clinical scores when compared to both placebo and salbutamol failed to translate into clinically significant improvement in oxygenation or hospital admission rates as confirmed by a Cochrane review [49]. Routine use is generally not recommended [24, 30]. More recently, combination therapy with dexamethasone has shown promise in decreasing hospital admission [50].

Corticosteroids

The rationale for the use of corticosteroids (inhaled, oral or intravenous) comes from their acknowledged benefit in other obstructive airways disease, such as asthma, and their ability to inhibit the immune response which contributes to the pathogenesis of bronchiolitis [8, 37]. Heterogenicity in study design and the corticosteroid administered make comparisons between studies difficult. Systematic reviews have failed to demonstrate benefit in outcome (requirement for hospital (re)admission, requirement for respiratory support, or length of stay in hospital) from systemic corticosteroids or from inhaled corticosteroids [51]. Recently a prematurely-terminated international multicenter randomized controlled trial (the Steroid Treatment in Artificially ventilated children with RSV infection [STAR] trial) investigating the potential benefit of dexamethasone in ventilated children with RSV bronchiolitis failed to demonstrate a difference (duration of ventilation or supplemental oxygen; length of PICU or hospital stay) between the dexamethasone and placebo groups in both the mild and severe oxygen abnormalities subgroups [52]. Likewise a previous meta-analysis combining three trials investigated the role of corticosteroids in ventilated children with RSV bronchiolitis showed no overall effect on duration of mechanical ventilation or hospitalisation [53].

Methylxanthines

Data from uncontrolled trials suggest that there may be some benefit in using methylxanthines, such as theophylline and caffeine, in infants with bronchiolitis-associated apneas [54]. A randomized, double blind, placebo controlled trial to determine whether treatment with caffeine citrate reduces length of PICU stay (primary measure) and frequency of apneic episodes (secondary measure) in infants with viral bronchiolitis associated with apnea is in progress in Qatar (proposed completion date April 2013) [55]. At present there is no convincing evidence base.

Chest Physiotherapy, Nebulised Hypertonic Saline

Three trials have failed to demonstrate compelling evidence of the benefit of chest physiotherapy in bronchiolitis, as borne out by a systematic review [56]. Hypertonic saline by improving mucus viscosity and elasticity, enhancing mucus transport, and decreasing epithelial edema may counter some of the bronchiolitis pathophysiological complications [57]. A meta-analysis of four trials investigating the effect of nebulization with hypertonic 3 % saline solutions vs. 0.9 % saline solutions suggested that nebulized 3 % saline solutions may hold some benefit – reduced length of hospital stay and a decreased clinical severity score. However, none of the studies included mechanically ventilated children [58].

Ribavirin

Ribavirin is a purine nucleoside analogue that is believed to interfere with viral nucleic acid function. Ribavirin has activity against RSV and influenza. Ribavirin is expensive, difficult to deliver as the nebulized droplets adhere to the ventilatory circuit, and teratogenic (therefore potentially toxic to both the patient and the treating team). Systematic reviews have failed to show any convincing effect in the acute [59] or ventilated setting [53]. Because of high cost, safety concerns, challenges in delivery, and weakness with trial data, ribavirin is usually only considered in immunocompromised children in the PICU setting in Europe [33], and the American Association of Pediatrics recommends against its routine use [24].

Antibiotics

Because bronchiolitis has a viral etiology and the reported incidence of extrapulmonary concurrent or secondary bacterial infections is low, many advocate against the routine use

of antibiotics in bronchiolitis [3, 6, 24, 30]. However, in the critical care environment this approach is challenged as bacterial co-infection/concomitant bacterial pneumonia can be found in up to 40 % children requiring mechanical ventilation for severe RSV bronchiolitis [19, 60, 61]. Co-morbidity does not seem to convey additional risk for concomitant bacterial pneumonia [19, 60]. Pediatric intensivists should consider tracheobronchial sampling on intubation or PICU admission, empirical antibiotic cover, and antibiotic review/rationalization with subsequent microbiological results.

Exogenous Surfactant

Endogenous surfactant lowers the surface tension within the alveoli at the alveolar-capillary membrane level. The rationale for exogenous surfactant comes from the findings of low levels of surfactant phospholipids and proteins, along with reduced surfactant function, in children with severe bronchiolitis [18, 62]. Due to its endotracheal route of administration exogenous surfactant can only be considered in intubated children. A systematic review of the three published randomized controlled trials (79 patients) highlighted the inadequacy of available data – variations in surfactant used, study designs, and between-study lengths of ventilation of the control groups confound effective interpretation [62]. Any future large randomized controlled trial will be hampered by the need for multiple centers to obtain adequate numbers and the expense of exogenous surfactant.

Helium – Oxygen (Heliox) Mixture

The pathophysiological rationale for heliox is that with a density one-seventh that of air it would result in decreased resistance to airflow. A number of randomized controlled (some even double-blind) studies using inhaled heliox have been performed in infants with bronchiolitis. None have demonstrated significant beneficial effect in real clinical terms (i.e. need for intubation, duration of ventilation or of PICU stay) [63].

Inhaled Nitric Oxide (iNO)

Inhaled nitric oxide (iNO) by nature of its route of administration produces vasodilation in the bronchial tree, thereby enhancing the blood flow and the ventilation-perfusion quotient. There is a single study examining the effect of inhaled nitric oxide on respiratory mechanics in 12 ventilated infants with RSV bronchiolitis [64]. It concluded that iNO had no apparent bronchodilator effect in the majority of acutely ill infants with bronchiolitis and did not appear to provide any additional benefit over the use of salbutamol. A Cochrane review of randomized controlled trials (535 ventilated children and adults) analysed the effect of iNO in acute hypoxemic respiratory failure [65]. It found that iNO did not demonstrate any statistically significant effect on mortality or ventilator-free days, and only transiently improved oxygenation in patients with hypoxemic respiratory failure.

Recombinant Human DNAse (rhDNAse)

Intraluminal mucus plugs in the distal airways are an important pathophysiologic feature in RSV bronchiolitis. DNA released by degenerating leukocytes is present in these mucus plugs and contributes to their increased viscosity and adhesiveness [66]. By cleaving this released DNA, rhDNAse can help liquefy the mucus. Anecdotal data suggested that rhDNAse was effective in infants with severe RSV bronchiolitis [66]. A multicenter, randomized, double-blind placebo-controlled study in 224 infants with RSV bronchiolitis found that administration of rhDNAse did not reduce the length of hospital stay, duration of supplemental oxygen, and number requiring intensive care or mechanical ventilation [67].

Respiratory Support

If despite oxygen supplementation children develop respiratory failure artificial respiratory support (non-invasive or mechanical ventilation) may become necessary. The application of continuous positive airway pressure (CPAP) keeps the airways open and thereby facilitates expiratory flow, improves compliance, reduces work of breathing and enhances gas exchange. There is supportive evidence that delivery of CPAP via a mask or nasal prongs may reverse impending respiratory failure and avoid intubation [68–70]. On this front, humidified high-flow nasal oxygen is demonstrating great promise in providing effective respiratory support – preventing progression of respiratory failure to needing mechanical ventilation and shortening admissions [71]. Intubation and mechanical ventilation (positive pressure ventilatory support) is the mainstay of supportive therapy for children with viral bronchiolitis-induced respiratory failure due to worsening lung compliance, imminent respiratory collapse secondary to exhaustion, or apnoea and respiratory arrest. Already in the 1980s, retrospective studies confirmed the effectiveness of mechanical ventilation in bronchiolitis-associated respiratory failure [72]. Unfortunately there are no randomized controlled trials on the level of positive end-expiratory pressure (PEEP) or ventilatory strategies (for example, volume-controlled versus pressure controlled, or high frequency versus conventional ventilation) for ventilated children with bronchiolitis-induced respiratory failure [18]. Perhaps this is because bronchiolitis is a heterogeneous lung disease with varying obstructive and restrictive

elements, rather than a homogenous clinical entity [18, 27]. When maximum conventional mechanical ventilation or high frequency oscillatory ventilation (HFOV) fail to stabilize or reverse deteriorating oxygenation (and ventilation), extracorporeal life support (ECLS)/extracorporeal membrane oxygenation (ECMO) is the last port of call for these refractory cases. Survival rates of ECLS/ECMO for RSV bronchiolitis are better than other indications for ECLS/ECMO and range from 71 % [73] to as high as 96 % [74], with a low reported rate of neurological sequelae [75].

Preventive Therapies and Treatments

RSV Immunotherapy

Hyperimmune RSV immunoglobulin (RSVIG) and monoclonal RSV immunoglobulin augment neutralizing antibodies and are used for immunoprophylaxis in high risk patients [3, 6, 24]. They have been shown to reduce hospital admissions from RSV bronchiolitis [76, 77]. Both are expensive, offer partial protection, and require monthly intravenous (RSVIG) or intramuscular (monoclonal RSV immunoglobulin) injections [77]. Their prohibitive expense has lead to many cost-effectiveness analyses and the restriction of use to targeted high risk groups [24, 77, 78]. The use of hyperimmune RSV (polyclonal) immunoglobulin has fallen out of favour due to its intravenous route, the intravenous volume required, an increased risk of adverse outcomes in infants with cyanotic heart disease, and possible inactivation of live vaccines (for example measles-mumps-rubella) [78]. RSVIG is not licensed for treatment in the UK.

Palivizumab, the first humanized monoclonal antibody against the surface F glycoprotein in RSV, is the immunoprophylactic agent generally favored and has been studied extensively [77]. Palivizumab has been shown to reduce RSV-related hospital admission by 55 % in preterm infants born at less than 32 weeks gestation [76] and by 45 % in infants born with significant congenital heart disease [79]. Despite this reduction in hospital admission for serious RSV disease, the cost-benefit balance for infants born at more than 32 weeks gestation or with congenital heart disease is still debated intensely [24, 77]. Although the RSV-IMpact trial examining the efficacy of palivizumab in preterm infants demonstrated an overall reduction in hospitalization of 55 % compared to controls, it did not impact on the number requiring PICU admission (1.3 % vs. 3 %) or the number requiring mechanical ventilation (0.2 % vs. 0.7 %) [76]. Similarly, despite an overall reduction in hospitalization of 45 % compared to controls in the trial examining the efficacy of palivizumab in children with congenital heart disease, the number requiring PICU admission (2 % vs. 3.7 %) or the number requiring mechanical ventilation (1.3 % vs. 2.2 %) was not significantly different [79]. Post palivizumab licensure studies comparing the number of children requiring PICU admission and mechanical ventilation in the RSV seasons prior to palivizumab to those in the RSV seasons following its prophylactic use have found no significant reductions following the introduction of palivizumab [80]. Currently a second generation recombinant humanized monoclonal IgG1 antibody, motavizumab, with enhanced anti-RSV neutralizing activity is being tested.

Internationally guideline recommendations for RSV immunoprophylaxis with palivizumab generally reflect widely accepted high risk subgroups [30, 33, 78]:

1. Children under 2 years of age with chronic lung disease (oxygen dependency for at least 28 days from birth) on home oxygen or who have had prolonged use of oxygen, or receiving medical therapies for chronic lung disease
2. Children under 2 years of age (USA) or infants less than 6 months of age (UK) who have hemodynamically significant congenital heart disease (cyanotic or acyanotic) and/or pulmonary hypertension
3. Children under 2 years of age with severe congenital immuno-deficiency (UK)
4. Children under 2 years of age with "significant congenital abnormalities of the airway or a neuromuscular condition that compromises handling of respiratory tract secretions" (USA).

Vaccination

The first RSV vaccine produced in the 1960s was a formalin-inactivated vaccine. Even though it produced high serum antibody levels it resulted in worse bronchiolitis following RSV infection in the vaccinated group than the control non-vaccinated children [3, 6, 15]. Development of an effective RSV vaccine is being actively explored and is a high research priority [3, 6]. A RSV vaccine needs to offer better protection than that from natural infection and be effective in the first weeks of life when maternally-acquired anti-RSV antibodies are still present. Live attenuated vaccines have the potential advantages of being delivered intranasally and inducing both a local mucosal and a systemic immune response. However, they tend to be unstable, too virulent and revert back to wild-type virus [3, 6, 15]. Vaccines produced from purified viruses, recombinant vectors, and plasmids containing complementary DNA of the viral genome that generally target the F (fusion) and G (attachment) transmembrane glycoproteins are being trialled [3, 6, 32].

New Anti-RSV Agents

Novel small molecule antivirals (for example, small inhibitory RNAs) are currently being developed that inhibit RSV replication by interfering with specific mRNA causing

mRNA degradation and targeted down-regulation [81]. They may hold the potential for a direct and directed anti-RSV therapy.

Conclusion

Bronchiolitis produces significant morbidity and mortality worldwide every year. Not all children are equal when it comes to bronchiolitis – those with underlying chronic conditions/comorbidity carry an additional risk of severe disease and death. Although a basic supportive management approach remains the cornerstone, our understanding of bronchiolitis, its pathogenesis and pathophysiology, its impact on multiple organ systems and its treatment options, has progressed over time.

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Pneumonia

6

Carrie I. Morgan and Samir S. Shah

Abstract

Respiratory diagnoses continue to make up a large number of admissions to the pediatric intensive care unit (PICU), most notably lower respiratory infections including pneumonia. This chapter will focus on pediatric community-acquired pneumonia (CAP), immunocompromised pneumonia, and aspiration pneumonia.

The pathogenesis for developing pneumonia varies; it can occur by direct inhalation of infectious particles in the air or aspiration, direct extension from the upper airways, and hematogenous spread. There are multiple levels of defense against pathogen invasion including anatomic barriers, as well as innate and adaptive immunity, which may be compromised in PICU patients.

The etiologies of pediatric pneumonia vary depending on age, host condition, and environmental factors like time of year and location. Viruses remain the most common form of lower respiratory tract infection in children, especially in neonates. Community-acquired bacterial pneumonia continues to be most prevalent in younger children as well, most often affecting children less than 5 years of age who are otherwise healthy. Despite immunizations and public health initiatives, the most common bacterial causes of CAP have remained largely unchanged over the last several decades and include: *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae* (including non-typable strains) and *Moraxella catarrhalis*. Pulmonary infection in an immunocompromised host provides a much broader differential and must be aggressively treated without delay.

This chapter will also address various imaging modalities and typical findings with pediatric pneumonia. Methods for pathogen identification are broad and range from non-specific markers of illness to invasive techniques for culture. The mainstay of therapy continues to be antibiotics tailored to the patient and presumed etiology; more novel therapies may include corticosteroids or macrolide antibiotics for immune modulation. In those patients with pneumonia with effusion or empyema, drainage therapies with thoracostomy tubes or a VATS procedure may be indicated.

Keywords

Pediatric • Pneumonia • Critical care • Antibiotics • Effusion • Empyema

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Introduction

Respiratory diagnoses continue to make up a large number of admissions to the pediatric intensive care unit (PICU) [1]. Lower respiratory tract infections are considered to be any infection beneath the anatomic level of the vocal cords, including bronchitis, bronchiolitis, tracheitis, and pneumonia [2]. Pneumonia remains an important cause of pediatric morbidity and mortality. There are nearly two million pneumonia-related deaths worldwide each year among children 5 years of age and younger [3, 4]. In the U.S., pneumonia causes over three million outpatient visits and more than 150,000 hospitalizations each year [5, 6]. In the developed world, early recognition and availability of antimicrobial therapies and respiratory support have lessened the mortality of pneumonia, but its morbidities remain. While widespread use of the heptavalent pneumococcal conjugate vaccine in 2000 was associated with fewer pneumonia-associated complications in infants <1 year of age, complications remained unchanged or increased in school-age children and adolescents [5]. Thus, despite our best efforts at prevention through vaccination, morbidities continue to plague our patients and pneumonia remains a common cause of pediatric hospital admission.

This chapter will focus on pediatric community-acquired pneumonia (CAP), immunocompromised pneumonia, and aspiration pneumonia. Hospital acquired pneumonia is an important type of lower respiratory infection found in the PICU, but it is discussed extensively in the chapter on Hospital-acquired Infections elsewhere in this textbook. The definition of pneumonia is generally accepted to be a lower respiratory illness with fever, respiratory symptoms including tachypnea, and often, radiologic evidence of parenchymal infiltrates [7]. The World Health Organization (WHO) has defined pneumonia solely based on clinical findings due to the lack of radiologic studies in many parts of the world [8].

Definition of Pneumonia and Guidelines for Admission to the Pediatric Intensive Care Unit

Determining the type of pneumonia can help guide clinical management. Previously healthy children presenting with the signs and symptoms of a lower respiratory tract infection are generally considered to have CAP. Aspiration involves inhaling foreign material beyond the vocal cords, often causing aspiration pneumonitis (chemical pneumonitis) or pneumonia (an infectious process secondary to the aspiration) [9, 10]. Commonly aspirated materials in children include oropharyngeal secretions, gastric contents, water, hydrocarbon, lipid, and foreign bodies [11]. Guidelines for admission to the ICU are available for both young children and adults, and are summarized in Table 6.1 [12, 13].

Table 6.1 Guidelines for ICU admission for children >3 months of age and adults from the Infectious Diseases Society of America and the American Thoracic Society

1a. Children >3 months of age
Need for invasive ventilation
Need for noninvasive positive pressure ventilation
Impending respiratory failure
Persistent tachycardia, hypotension, or need for pharmacologic hemodynamic support
SpO_2<92 % on FiO_2 ≥0.5
Altered mental status, whether due to hypercarbia or hypoxemia
Severity of illness scores, taken in context of clinical findings
1b. Adults
Need for invasive ventilation
Need for noninvasive positive pressure ventilation
Septic shock necessitating vasopressor support
Minor criteria (3 or >):
Respiratory rate >30 breaths/min
PaO_2/FiO_2 ratio <250
Multilobar infiltrates
Confusion/disorientation
Uremia (BUN > 20 mg/dL)
Leukopenia (WBC < 14,000 cells/mm^3)
Hypothermia <36°
Hypotension requiring aggressive fluid resuscitation

Adapted from Refs. [12, 13]

Pathogenesis

Pneumonia can occur by direct inhalation of infectious particles in the air or aspiration, direct extension from the upper airways, and hematogenous spread. Anatomic and cellular protection serves as the first line of defense against potential pathogens. Airway mucus traps inhaled toxins and microbes and helps to transport them up and out of the respiratory tract via ciliary beating and cough, a mechanism referred to clinically as mucociliary clearance [14]. When the microbe burden or virulence of the organism surpasses the abilities of these simple mechanical protections, the innate immune response is activated. The innate immunity is responsible for immediate recognition and control of microbial invasion. In mammals, conserved receptors enable rapid recognition of pathogens to begin elimination of the infection as well as initiate the adaptive immune response. Activating the innate immune receptors in the airway epithelium leads to mobilization and activation of dendritic cells, T cells, and B cells that amplify antigen recognition, antibody production, and further cellular recruitment and inflammation [15]. The specifics of these interactions and signaling cascades are beyond the scope of this chapter, but are further discussed in other chapters within this text.

The lower respiratory tract remains generally clear of pathogens [2]. The mechanisms by which microbes are able

to overwhelm defensive measures and result in pneumonia vary and depend on host conditions. The most common mechanism of pathogen entry is via inhalation of infectious particles, particularly in the case of specific organisms that spread via respiratory droplets such as *Mycobacterium tuberculosis*. Many viruses that cause lower respiratory tract infections are also spread utilizing aerosolized modes of transmission, including respiratory syncytial virus (RSV), influenza, and rhinoviruses. Due to their smaller size compared with bacteria, viruses consolidate more efficiently on smaller particles [16, 17]. Hematogenous spread results in pneumonia when bacteria in the bloodstream directly deposit in lung tissue.

Pulmonary aspiration can occur as a result of swallowing dysfunction, gastroesophageal reflux, anatomic anomalies such as tracheoesophageal fistulas, or an inability to protect the airway from oropharyngeal secretions. In the PICU, many patients have neurologic diseases that coexist with one, if not several, of these aforementioned mechanisms. Furthermore, impaired consciousness, as may occur with head injury, intoxication, sedation, and tracheal intubation, can also impair the ability to protect the airway, diminish the cough reflex, and exploit the patency of the anatomical connection between the larynx and trachea [9, 10, 18]. Direct aspiration of a large inoculum of infectious organisms can result when there is impairment of the host's anatomic defense, usually the gag and cough reflex. This most commonly occurs in children with profound neurologic impairment or during tracheal intubation [19, 20].

Etiologies

Community-Acquired Pneumonia

Viruses still remain the most common cause of lower respiratory tract infection, especially in infants [21]. The occurrence of primary viral infections and co-infections with bacterial pneumonia are receiving more attention in recent years due to advances in detection methods to improve the reliability and sensitivity in diagnosis [22]. Viruses have been found in approximately 50 % of sampled patients with a range of 43–67 %, although this prevalence is difficult to compare across studies that utilize different identification techniques [22–28]. The most commonly noted infectious viruses were rhinovirus, human bocavirus, human metapneumovirus (hMPV), and respiratory syncytial virus (RSV). Human metapneumovirus causes significant respiratory infection, accounting for 5–8 % of viral pneumonia cases [29, 30]. Human bocavirus, first described in 2005, is detected in up to 10 % of children with respiratory infections [31]. However, co-infection with another virus occurs in more than half of human bocavirus infected children, making its role as a predominant respiratory pathogen unclear. One possible explanation for the high prevalence of viral co-infection with human bocavirus is that this virus is shed in respiratory tract secretions for a longer period of time than other viruses [32–34]. Other important respiratory tract pathogens include adenovirus, parainfluenza viruses, and influenza A or B, all of which vary in prevalence based on season and epidemic periods.

The most common complication of viral pneumonia is a secondary bacterial infection. Bacterial co-infection occurs in about 15–33 % of pediatric patients hospitalized with a lower respiratory tract infection [23]. The most often occurring combination was rhinovirus and *Streptococcus pneumoniae*, though it remains difficult to interpret the causal role of rhinovirus in lower respiratory tract infections [23, 25]. RSV remains an important cause of bronchiolitis in infants and can often progress to pneumonia. A recent study noted that 40 % of children admitted to the PICU with RSV bronchiolitis had bacterial co-infection [35].

Community-acquired bacterial pneumonia continues to be most prevalent in younger children as well, most often affecting children less than 5 years of age who are otherwise healthy. Despite immunizations and public health initiatives, the most common bacterial causes of CAP have remained largely unchanged over the last several decades and include: *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae* (including non-typable strains) and *Moraxella catarrhalis* [7, 8, 21, 23]. In developing countries, other bacterial and viral etiologies must be considered, including *Mycobacterium tuberculosis, H. influenzae* type b (in unvaccinated areas of the world), and the measles virus [8].

In infants under 3–4 weeks of life, the most common etiologic agents include Group B *Streptococcus, Listeria monocytogenes,* and Gram-negative enteric bacteria. *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* (formerly *Chlamydia pneumoniae*), once considered to occur primarily among adolescents and young adults, are increasing being recognized as a cause of CAP in younger children, including those less than 5 years of age [21].

Immunocompromised Pneumonia

There are many causes of immunodeficiency in pediatrics including congenital, acquired (HIV/AIDS), or iatrogenic (during chemotherapy or after solid organ or stem cell transplant). These states can result in deficiencies in humoral immunity, cellular immunity, and neutrophil availability or function, making the host susceptible to not only typical pneumonia etiologies, but many opportunistic agents. Thus, the approach to an immunocompromised patient must be altered to consider the type and severity of immunodeficiency, as well as the temporal pattern after chemotherapy or

transplant. Other considerations that are important in immunocompromised patients include neutropenia, where a low white blood cell count can hinder the patient's ability to exhibit CXR findings and the lack of inflammation can alter the clinical presentation, and environmental factors and exposures that can cause geographic and temporal clustering of pathogens [11].

The causes of pneumonia following solid organ and stem cell transplant may follow a predictable temporal relationship. In the early post-transplant period (<1 month), infections from nosocomial or iatrogenic sources are most common. In the middle post-transplant period (1–6 months), donor-associated and opportunistic infections, including reactivation of latent infections, predominate; specific causes include *Cytomegalovirus* (CMV), Epstein-Barr virus (EBV) or Human Herpes Virus 6 (HHV6). Late post-transplant period (>6 months) etiologies include community-acquired infections as well as infections associated with profound immunosuppression [36, 37]. In an effort to diminish the risk associated with post-transplant immunosuppression, immunosuppressive agents (e.g., calcineurin inhibitors, high-dose corticosteroids) are used sparingly when possible and most protocols include anti-viral (especially CMV), anti-fungal, and *Pneumocystis jiroveci* (PCP) prophylaxis [36]. Still, many common infections continue to pose a great risk. For example, viral infections (e.g., RSV, influenza, adenovirus) cause greater virulence following solid organ or stem cell transplantation immediately after transplant when cellular immunity is profoundly low. Later in the course of transplantation, fungi such as *Aspergillus* spp. and *Candida* spp. become more prevalent causes of pneumonia with long-term steroid therapy [11, 37]. Thus, when a pulmonary process is suspected, aggressive treatment with broad-spectrum antibiotics, antifungals, and antivirals must be employed. Immunocompromised patients with pulmonary infiltrates may rapidly progress to respiratory failure and, thus, often require ICU care. Infection must be aggressively treated without delay, but other conditions must also be sought including pulmonary hemorrhage, malignancy, idiopathic pneumonitis, or cardiac disease [11, 38].

Aspiration Pneumonia

The clinical presentation of aspiration pneumonitis or pneumonia can vary and like other pneumonia etiologies, aspiration can result in acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) manifested by severe pulmonary inflammation and alveolar-capillary permeability injury. It is estimated that approximately one-third of patients with aspiration pneumonitis develop ALI/ARDS [39]. Etiologies of aspiration pneumonia depend if the aspiration is community acquired or hospital acquired. Bacteriologic studies in aspiration patients have shown that community acquired aspiration pneumonias are generally the same bacterium as CAP, including *H. influenzae*, *S. pneumoniae*, *S. aureus*, and enterobacteriaceae species. In those patients who aspirated in a hospital setting, the most common organisms cultured were gram-negative enteric bacteria including *Pseudomonas aeruginosa*. These recent studies failed to grow any anaerobic organisms, refuting the prior studies that endorsed anaerobes as common etiologies [10].

Diagnostic Approach

Imaging

The role for imaging in pediatric pneumonia is to detect the presence of pneumonia, determine the location and extent, and identify complications such as effusion or empyema. Modalities include chest radiographs (CXR), ultrasound (US), and computed tomography (CT) [11]. The presence of an infiltrate on CXR, combined with clinical and other laboratory findings can aid in the diagnosis of pneumonia. However, these modalities are not sufficiently sensitive or specific to reliably differentiate between viral, bacterial, and atypical bacterial causes [40]. The main use for US is to identify and characterize a parapneumonic effusion or empyema and provide image guidance for chest tube placement. This modality is limited by availability of equipment and operators. Chest CT is helpful to further evaluate difficult cases, particularly immunocompromised children with ill-defined infiltrates on CXR, complex empyema or effusion, or recurrent or chronic pneumonia [11]. Imaging findings in pneumonia can be non-specific, but when combined with other factors such as patient age, immune status, and historical information, they may help to narrow the differential diagnosis.

In viral pneumonia, the most common findings are bilateral symmetrical parahilar and bronchial opacities with or without atelectasis and air trapping; pleural effusions are rare (Fig. 6.1). This is in contrast to bronchopneumonia, a form of bacterial pneumonia that begins as peribronchiolar inflammation and spreads to the lung parenchyma. Bacterial pneumonia is characterized by consolidation and filling of the alveolar air spaces with exudate, inflammation, and fibrin. Bronchopneumonia is typical of many bacteria including *S. pneumoniae*, *H. influenzae*, *S. aureus*, and Gram-negative enteric bacteria. The CXR often reveals fluffy lobar consolidation or diffuse bilateral opacities extending peripherally, with or without associated pleural effusion. In aspiration pneumonia, the CXR may reveal ground-glass or consolidative opacities predominantly involving the middle and lower (dependent) lobes [41]. Finally, atypical pneumonia etiologies include *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae* and, less commonly, *Legionella* species. The CXR findings for these atypical causes are varied. Diffuse

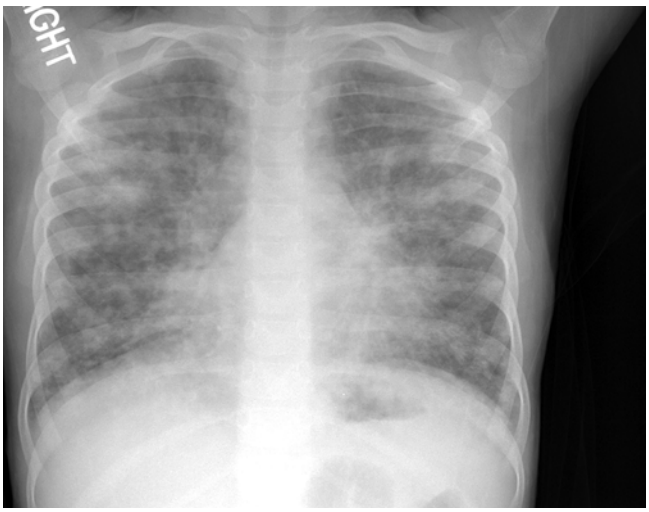


Fig. 6.1 Viral pneumonia. This CXR of a previously healthy 6 year-old child with varicella pneumonia shows diffuse alveolar infiltrates consistent with a viral pneumonia

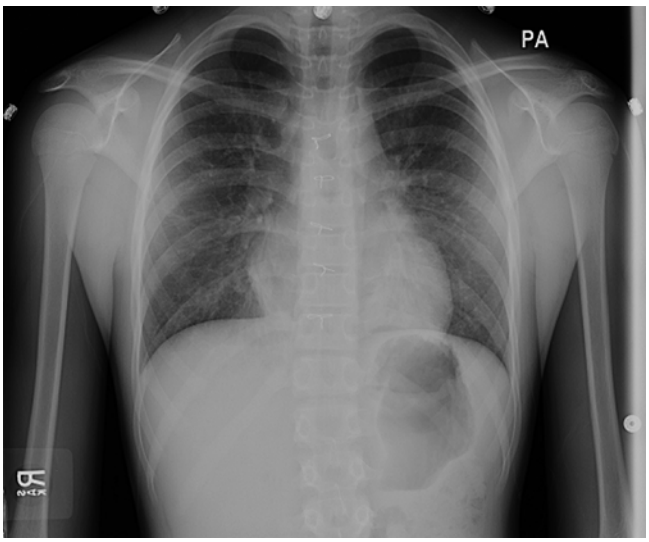


Fig. 6.2 Atypical pneumonia. This CXR of a 13 year-old boy with Mycoplasma pneumonia shows diffuse interstitial infiltrates (Reprinted from Swami and Shah [43]. With permission from McGraw-Hill)

interstitial infiltrates are characteristic though other findings include lobar consolidation, small bilateral pleural effusions, perihilar and peribronchial opacities that resemble butterfly wings, or a bi-lobar reticular pattern (Fig. 6.2) [42, 43].

The etiology of pneumonia in the immunocompromised patient can be difficult to determine though further imaging can help elucidate the cause. Respiratory failure in an immunocompromised child frequently necessitates a chest CT to better visualize the pattern and extent of disease, aid in diagnosis of the etiology, determine the need for more invasive procedures, and to increase the sensitivity of assessing treatment response [11]. Fungal infections are more difficult to diagnose; classic findings include pulmonary nodules on chest CT (Fig. 6.3).

Non-invasive Pathogen Identification

The "gold standard" diagnosis of pneumonia is microbiological identification of a pathogen from the lower respiratory tract [2]. Obtaining a LRT specimen can be difficult, especially in children, as it may require an invasive procedure and can be contaminated with oropharyngeal bacteria. Most children younger than 8 years of age cannot produce a sufficient sputum sample, defined as <10 squamous or epithelial cells and >25 polymorphonuclear white blood cells per low power field. Therefore, most samples are obtained through either an endotracheal tube via aspiration or bronchoalveolar lavage [44].

Other laboratory tests helpful in identifying the causative agent in CAP can include blood cultures, viral polymerase chain reaction (PCR) tests, and bacterial serologies. Commonly used diagnostic methods available for an individual microorganism may be found in Table 6.2 [8]. The clinician may also be limited by the capabilities of the laboratory in their institution for performing these tests.

Because of the difficulties in determining the etiology of pneumonia, non-microbiologic approaches have been sought to differentiate serious bacterial infections from nonbacterial pneumonia [21]. Many studies have evaluated markers including serum C-reactive protein (CRP), blood white cell count (WBC), serum procalcitonin (PCT), and erythrocyte sedimentation rate (ESR), attempting to find a test, or combination of tests, that would differentiate viral pneumonia from serious bacterial pneumonia necessitating antibiotic therapy [8, 45–49]. All of the aforementioned tests have limited utility in reliably differentiating viral from bacterial pneumonia, but when one or more of the markers are significantly elevated, a bacterial etiology is more likely. Thus, taken together with the clinical examination and radiologic findings, these tests can aid the clinician in deciding which patients require antibiotic therapy. PCT levels appear to be more sensitive than WBC, ESR, and CRP in identifying children with bacterial pneumonia and have been used to identify children who may benefit from a longer duration of antibiotic therapy [50].

Invasive Pathogen Identification

When non-invasive identification techniques are inadequate, or when identifying the cause is especially important, such as when treating an immunocompromised host, invasive diagnostic procedures may be necessary. Fiberoptic bronchoscopy with bronchoalveolar lavage (BAL) is the preferred diagnostic procedure in an immunocompromised host with an unknown

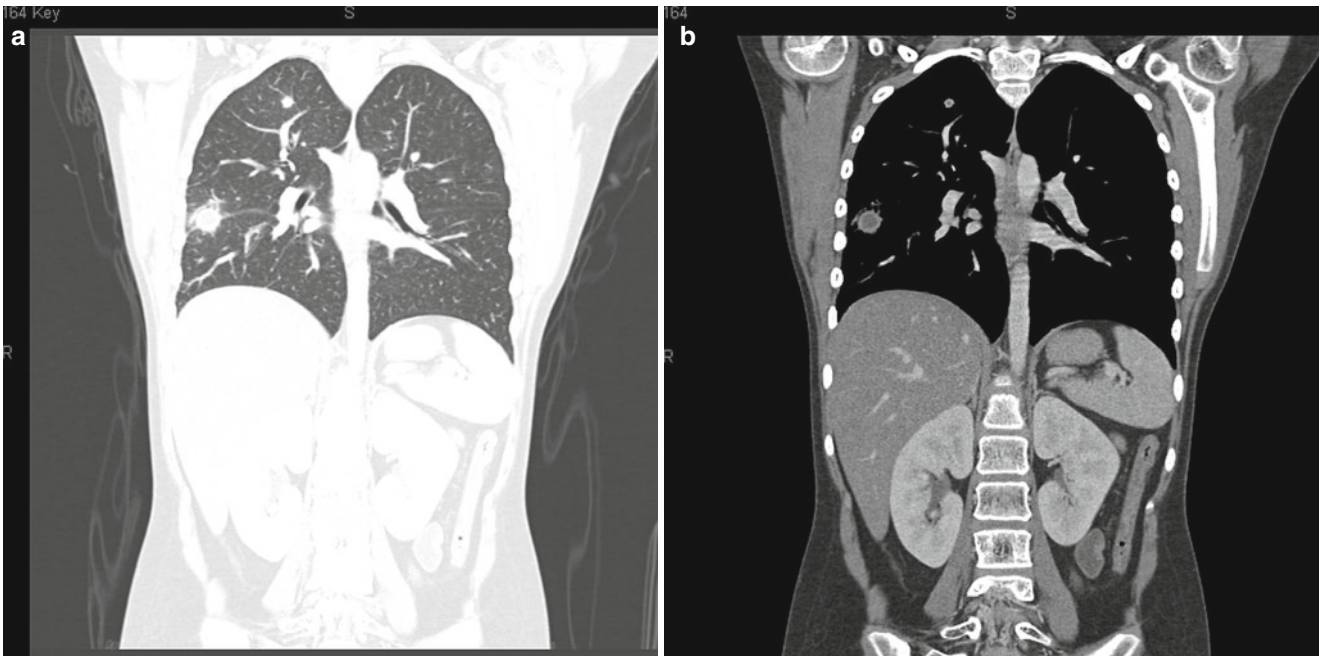


Fig. 6.3 Aspergillus pneumonia. Ten-year-old girl with AML and biopsy proven aspergillosis. (**a**, **b**) The chest CT (shown with two different window views) demonstrates a 0.6 cm nodule in the right upper lobe as well as a 1.5 cm × 1.5 cm centrally low attenuating mass lesion with peripheral enhancement noted in the posterior aspect of the right upper lobe, adjacent to the major fissure, consistent with an abscess

pathogen [51]. The sensitivity for diagnosis varies and depends on the host, pathogen, and the post-collection microbiologic detection methods employed. While many atypical organisms may be difficult to culture, *P. jiroveci* and *Mycobacterium* infections are more easily detected in BAL because of high organism burden in the lungs. The diagnosis of aspiration pneumonia is mainly clinical, often based on historical or witnessed events or conditions, and thus can be difficult to ascertain. If a BAL is performed in suspected aspiration, the presence of lipid-laden macrophages can help diagnose the aspiration of lipophilic foods such as formula [52]. A lipid-laden macrophage index can be obtained using the oil red O stain and when high, can be very sensitive and specific for aspiration [53].

Other invasive procedures include transbronchial biopsy if diffuse infiltrates are present but the BAL is negative, or CT-guided needle biopsy of a focal lesion. The improved diagnosis with these invasive procedures must be balanced against the risks to critically ill patients [54]. Important non-infectious etiologies to rule out with these invasive procedures include lung rejection (if transplanted), post-engraftment syndrome, idiopathic pneumonitis, graft versus host disease, and bronchiolitis obliterans.

General Treatment Principles

Antimicrobial Therapy

Children with severe pneumonia requiring admission to the PICU are likely to receive intravenous antimicrobial therapy even if only until the possibility of bacterial infection can be excluded. In critically ill children with respiratory failure from pneumonia, prompt initiation of broad-spectrum antimicrobials is crucial. One study in pediatric patients with CAP showed that longer delays in receipt of antibiotics were independently associated with adverse outcomes [55]. However, antibiotic resistance is increasing and the principles of appropriate antibiotic utilization must be adhered to: use of drug with narrowest spectrum, aiming for high tissue penetration, short half-life, and abiding to a short, intense duration of therapy [7]. The duration of therapy is typically 7–14 days, with 10 days being the best studied. A 7-day course may be reasonable in non-severe cases of pneumonia [12]. The choice of antimicrobial agent is based on many things including the patient's age, the type of pneumonia, and clinical and epidemiologic factors. Recent guidelines published by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America offer guidance for empiric antibiotic selection in children hospitalized with CAP (Table 6.3) [12].

Anti-inflammatory Therapy

Pneumonia causes a profound inflammatory response in the lungs and it has long been postulated that regulating this inflammation with steroid therapy may help to modulate local tissue damage and accelerate recovery for the patient. In addition, steroids are frequently utilized in other pulmonary inflammatory conditions such as reactive airway

Table 6.2 Microbiologic diagnosis of pneumonia in children

Microorganism	Preferred diagnostic method	Comments
Viruses		
Respiratory syncytial virus Influenza A or B Parainfluenza viruses Adenovirus Human metapneumovirus	Polymerase chain reaction (PCR) of nasopharyngeal secretions has the highest sensitivity; other options include immunofluorescence assay and solid-phase immunoassay	Viral culture has a high sensitivity but is less clinically useful as results may not be available for several days. In cases of adenoviral infection, serotyping may be helpful
Rhinovirus	PCR of nasopharyngeal secretions	The etiologic connection is not well established
Measles virus	Identify the virus by immunofluorescence assay or measure at least a quadrupling of serum antibody levels between acute phase and convalescence	The clinical diagnosis is specific
Varicella-zoster virus	Identify the virus by PCR or immunofluorescence assay of skin lesions,	The clinical diagnosis is specific. Diagnostic testing is useful to confirm the diagnosis. A four-fold increase in serum antibody levels between acute phase and convalescence is also diagnostic but clinically impractical
Hantavirus	Identify virus in nasopharyngeal secretions or antibody in serum. IgM or IgG antibodies may be found at presentation	Hantavirus infection is sufficiently uncommon that the finding of antibody in one serum sample is essentially diagnostic of acute infection
Cytomegalovirus (CMV) Epstein-Barr Virus (EBV)	Serologic studies: IgM and IgG for CMV; elevated IgM or IgG viral capsid antibody and absence of Epstein-Barr Nuclear Antigen (EBNA) confirms acute EBV infection	Finding virus in upper-airway secretions is not valuable with respect to diagnosis, since both CMV and EBV may be found in normal subjects. CMV antibody testing has poor specificity as past and recent infections cannot
Chlamydia		
Chlamydia trachomatis	Identify virus in nasopharyngeal secretions by culture or PCR assay	An IgM antibody test may be helpful
Chlamydophila pneumoniae	Identify virus in nasopharyngeal secretions by culture or PCR assay, or measure at least a quadrupling of serum antibody levels between the acute phase and convalescence	Etiologic connection in young children is not yet well established. The evidence is more convincing with respect to adolescents. No FDA tests exist for *C. pneumoniae* detection
Chlamydia psittaci	The finding of at least a quadrupling of serum antibody levels between the acute phase and convalescence	
Mycoplasma		
Mycoplasma pneumoniae	The finding of IgM antibody in serum late in the acute phase or early in convalescence is helpful, as is a positive PCR assay of secretions from a throat or a nasopharyngeal swab	Rapid IgM assays can provide results within 10 min. In younger children, an elevated IgM titer is often diagnostic; in older children, the finding of at least a quadrupling of serum antibody levels between the acute phase and convalescence is diagnostic. Cold agglutinin titers lack sensitivity and specificity and thus are no longer recommended
Bacteria		
Streptococcus pneumoniae *Haemophilus influenzae* *Streptococcus pyogenes* *Staphylococcus aureus* Gram-negative enteric bacteria Mouth anaerobes Group B streptococci *Neisseria meningitides*	Identify bacteria in culture of blood or pleural fluid; Pneumococcal urinary antigen tests accurately identify *S. pneumoniae* in pleural fluid	Culture of blood and pleural fluid lack sensitivity, especially in the setting of antibiotic treatment prior to culture. *S. pneumoniae* antigen tests may help confirm the diagnosis of S. pneumoniae when performed on pleural fluid; however, *S. pneumoniae* urine antigen test is not recommended because false-positives occur in the setting of pneumococcal colonization. PCR tests are accurate and increasingly available for *S. pneumoniae* and *S. aureus* detection in pleural fluid

(continued)

Table 6.2 (continued)

Microorganism	Preferred diagnostic method	Comments
Bordetella pertussis *Bordetella parapertussis*	Identify bacteria in culture, immunofluorescence assay, or PCR assay of nasopharyngeal secretions	PCR tests may be negative 3–4 weeks after illness onset. In such cases, serologic testing is recommended
Legionella pneumophilia and other legionella species	Identify bacteria in culture of sputum or tracheal aspirate or antigen in urine; or measure at least a quadrupling of serum antibody levels between the acute phase and convalescence	Culture of the organism requires special medium. Urinary antigen tests can detect only *L. pneumophila* antigen
Mycobacterium tuberculosis	Identify bacteria in acid fast culture of sputum or gastric aspirates, with or without a positive test for tuberculosis with purified protein derivative	Culture of bronchoalveolar lavage fluid is also specific but somewhat less sensitive. A PCR assay is more useful for the identification of the bacterium than for the detection of it. Interferon gamma release assays have modest sensitivity in children; a positive test can be diagnostic while a negative test does not exclude tuberculosis
Fungi		
Histoplasma capsulatum *Blastomyces dermatitidis* *Coccidioides immitis*	Identify organism by staining or culture of respiratory tract secretions; or measure IgM antibody or at least a quadrupling of serum antibody levels between the acute phase and convalescence	Histoplasma antigen is sometimes detectable in urine
Aspergillus spp.	Identification by culture or staining of respiratory washings; or serum EIA for Galactomannan antigen	Nested-PCR of serum may be useful if available. A single positive galactomannan test result should be clinically correlated by testing a separate serum specimen because some agents (e.g., piperacillin-tazobactam) may cross-react with the assay. If invasive aspergillosis is suspected in high-risk patients, serial sampling is recommended. The false positive rate is higher in children than adults [91, 92]

Adapted from McIntosh [6]. With permission from Massachusetts Medical Society

Table 6.3 Suggested initial drug therapies for pneumonia in children admitted to the PICU

	Community-acquired birth to 3 months	Community-acquired 4 months to 15 years	Immunocompromised	Aspiration
Typical pathogens	*S. pneumoniae*, *S. aureus*, Group B streptococci, Gram-negative enteric bacteria, *Listeria monocytogenes*, *Chlamydia trachomatis*, RSV, CMV	RSV, parainfluenza, influenza, rhinovirus, other respiratory viruses, *H. influenzae*, *S. pneumoniae, Mycoplasma pneumoniae*	In addition to typical pathogens: *Aspergillus*, *Candida*, herpes viruses, adenovirus, CMV, *P. jiroveci*	Typical aerobic flora and anaerobic flora including: *Peptostrepto-coccus, Fusobacterium* and *Bacteroides spp*
Recommended initial therapy	IV ampicillin and gentamicin in infants <20 days of age IV cefotaxime if >20 days of age	IV cefotaxime or IV ceftriaxone OR levofloxacin; addition of vancomycin or clindamycin for suspected MRSA; IV or PO azithromycin	In addition to antibiotics per age: amphotericin B or caspofungin, acyclovir for herpes, ganciclovir or foscarnet for CMV, trimethoprim-sulfamethoxazole or pentamidine for *P. jiroveci,* cidofovir for adenovirus	IV ampicillin-sulbactam or IV clindamycin; piperacillin-tazobactam if concern for gram negative enteric bacteria

Adapted from Refs. [8, 12]

disease (RAD) and acute respiratory distress syndrome (ARDS) [56]. The inflammatory responses in pneumonia and ARDS are similar with increases in pro-inflammatory cytokines concurrent with illness severity; severe pneumonia can often progress to acute lung injury (ALI) or ARDS [57–59]. While preclinical data support the use of steroids, current studies have not demonstrated a reduction in mortality among corticosteroid recipients compared with non-recipients. Several trials, however, have shown some secondary benefits of steroids, including reduced length of hospital stay and reduced inflammatory markers [60, 61]. In contrast, a multi-center, retrospective cohort study using administrative data found that among patients not receiving concomitant beta-agonist therapy (used as a proxy for wheezing), corticosteroid recipients had a longer LOS and higher readmission rate compared with non-recipients [62]. At present, the lack of high quality data supporting the efficacy of corticosteroids prevents the recommendation for the use of steroids in most patients with severe pneumonia. However, corticosteroids may provide benefit to certain subgroups of patients such as those with acute onset of wheezing and those who meet the criteria for ALI/ARDS [59].

Macrolide antibiotics have important anti-microbial as well as anti-inflammatory properties, though the relative importance of these two mechanisms in children with pneumonia is unknown. In adult studies, macrolides have recently been touted for their immunomodulatory effects and clinical benefit in multiple chronic pulmonary conditions such as asthma, chronic obstructive pulmonary disease (COPD), and cystic fibrosis (CF). The specific immunomodulatory effects are vast and include inhibition of intracellular signaling to suppress the production of transcription factors such as NF-κB and decrease production of inflammatory cytokines that recruit neutrophils [63, 64]. Several recent studies in adult patients with severe CAP and sepsis have shown a benefit in survival in patients treated with macrolide antibiotics in addition to the recommended antibiotics based on pathogen [63, 65–68]. The role of macrolides in children with pneumonia is unclear. In pediatrics, several small retrospective studies have shown that among children with atypical CAP, those treated with macrolides were less likely to have persistence of signs and symptoms after 3 days of therapy [69, 70]. Among children with *M. pneumoniae* infection, Lu et al. found a shorter duration of fever among macrolide recipients compared with non-recipients [71]. Finally, a large multi-center study of 690 patients with *M. pneumoniae* infection defined by discharge diagnosis codes, the median length of hospital stay was 3 days (interquartile range, 2–6 days); macrolide recipients had a 32 % shorter length of stay compared with non-recipients [72].

Complications

Empyema and Effusion

Pneumonia-associated complications such as empyema affect 7.5–15 % of children hospitalized with pneumonia [5, 73–76]. The progression from simple parapneumonic effusion to empyema occurs in stages that represent a continuous spectrum (Table 6.4) [77]. In the first stage, there is a rapid influx of exudative fluid into the pleural space as a result of increased pulmonary interstitial fluid traversing the pleura and an increase in vascular permeability due to pro-inflammatory cytokines. The pleural fluid is marked by the absence of bacteria, fluid pH >7.20, normal glucose, and LDH <3 times the upper limit of normal. At this stage, drainage is not generally required for resolution but if the effusion becomes large and

Table 6.4 Characteristics of pleural effusions and empyema

Category	Fluid characteristics	Bacteriology	Drainage
1	Minimal, free-flowing (<10 mm rim of fluid or less than ¼ of hemithorax opacified)	unknown	Not typically required
2	Small to moderate, free-flowing (>10 mm rim of fluid or less than ½ of hemithorax opacified)	Negative gram stain and/or culture	Not typically required unless respiratory compromise
3	Large, free-flowing (opacifies more than ½ hemithorax); or loculated effusion; or effusion with thickened parietal pleura	Positive gram stain and/or culture	Yes
4	Empyema	Pus	Yes

Adapted from Refs. [12, 78, 93]

impairs respiratory mechanics, drainage might become necessary. The fluid in the pleural space can flow freely and often layers along the lateral chest wall in decubitus films or along the posterior chest wall in supine films [37, 78] (Fig. 6.4a, b). If left untreated, exudative effusions can progress to fibropurulent effusions characterized by the new presence of bacteria or positive microbial cultures. Cellular lysis and phagocytosis in the fluid can result in pH < 7.20, higher LDH, and low glucose. Loculations begin to develop, causing these effusions to now be referred to as "complicated." A chest radiograph may be difficult to interpret with respect to evidence of complicated effusions. Thoracic US is more accurate than chest radiographs in distinguishing simple from complicated pleural effusions. Complicated effusions are associated with floating debris and echogenic material or septations. Ultrasound is also useful in guiding pleural aspiration and drainage. Chest computed tomography (CT) may be indicated to better define pulmonary and pleural anatomy. Thickening of the parietal pleura on a contrasted CT scan is suggestive of empyema, even if the effusions are small in size (Fig. 6.4c). Finally, stage three is the organizing phase where fibroblasts grow into the pleural space and eventually results in a pleural peel, restricting chest mechanics. This stage often necessitates surgical decortication, especially if there is restrictive impairment [78].

The typical organisms responsible for the development of an empyema include *S. pneumoniae* and *S. aureus*. Pleural fluid cultures identify an organism in only 20–30 % of children with empyema. Blood cultures are positive in 13–30 % of children with empyema [79–82]. *S. aureus* is most often identified in pleural fluid culture. However, molecular identification techniques reveal that most culture-negative cases are attributable to *S. pneumoniae* [83, 84]. Regardless of the type of effusion present, antibiotic coverage based on treatment guidelines for pneumonia are essential. A recent study on the impact of early antibiotic therapy on the laboratory analysis of pleural fluid found that pre-treatment significantly hindered a bacterial diagnosis but did not alter the biochemical parameters of the fluid [85]. However, delaying antibiotic treatment for a thoracentesis would not be recommended in a critically ill child with respiratory failure secondary to pneumonia.

The treatment of complicated effusions and empyema remains controversial but recent studies have better defined protocols. A complete list of the available treatments for effusions and empyema is found in Table 6.5. Small, uncomplicated pleural effusions do not routinely require drainage. Moderate or large pleural effusions as well as those with evidence of septations or loculations usually require drainage. The medical options include appropriate antimicrobials and chest tube insertion with or without fibrinolytic therapy. Surgical options include video-assisted thoracoscopic surgery (VATS) or open thoracotomy and decortication. Recent guidelines concluded that chest tube drainage with the addition of fibrinolytic agents and VATS are equivalent methods of treatment and emphasize the importance of local expertise in determining the optimal approach for individual patients [12, 86]. VATS has gained popularity over conservative medical therapy as a way to directly visualize the pleural space, mechanically disrupt the adhesions, and strategically place the chest tube for optimal drainage [73, 87]. The higher cost and risk of anesthesia with VATS must be balanced against the more frequent requirement for additional drainage procedures for those undergoing primary chest tube placement. Thoracotomy and decortication are rarely needed.

The argument of medical management versus surgical management remains controversial. To date, at least two prospective trials in pediatrics have been completed directly comparing these methods. Both trials failed to show any outcome superiority with surgical management [80, 88]. Certainly children who have a very high white blood cell count in their pleural fluid (>15,000), poor output drainage by chest tube, low pleural pH, the presence of bacteria in the pleural fluid and/or bloodstream, or failure of medical therapy alone may benefit from early VATS [86]. Patients who underwent VATS required fewer

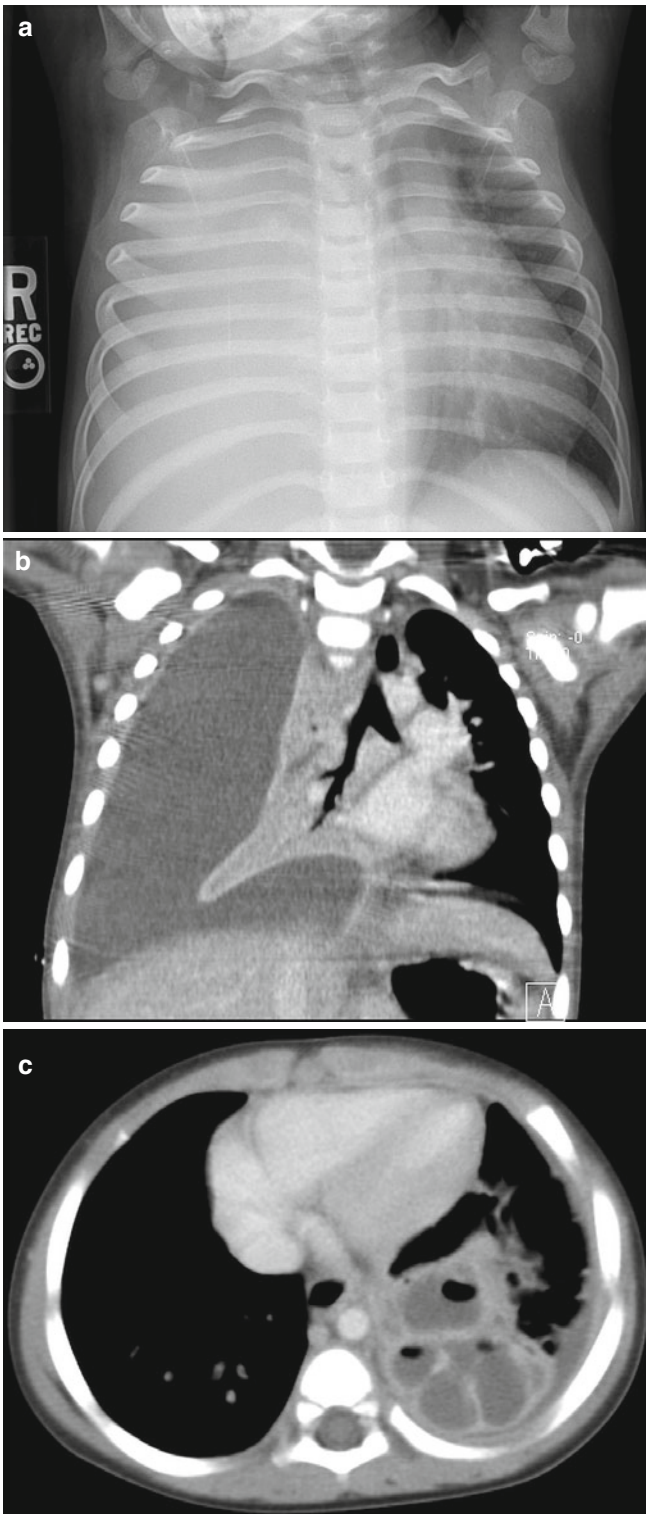


Fig. 6.4 Effusions and empyema. (**a**, **b**) A CXR shows complete opacification of the right hemithorax, with significant mediastinal shift to the left. The corresponding chest CT demonstrates a large right pleural effusion occupying the entire right hemithorax associated with leftward mediastinal shift. (**c**) A lobulated and loculated fluid collection with air-fluid levels is present in the left lower lobe measuring 4.5×4.4 cm with enhancing septations

additional drainage procedures, but had no difference in hospital length of stay [74]. However, one study of adults with empyema found that patients treated with a combination of tPA and recombinant human DNase required fewer surgical interventions and had a shorter length of hospital stay [89]. Cost-effectiveness, balance of risks, and availability of resources also plays a role in considerations for surgical management. A comparison of multiple strategies for pediatric empyema noted that the most cost effective method was insertion of a chest tube with fibrinolytic therapy [90].

Lung Abscess

Abscesses develop in localized areas of parenchymal infection that becomes necrotic and cavitates (Fig. 6.5a, b). Primary lung abscesses can develop either in previously healthy children or in children with underlying lung disease such as congenital cystic lesions, cystic fibrosis, or immunodeficiency. Mechanisms for abscess development can include direct aspiration of infectious material, embolic phenomena, hematogenous spread from septicemia, or local extension from abdominal or oropharyngeal processes. The most common organisms include Gram-positive bacteria such as streptococci, *Staphylococcus aureus* or anaerobes. Most abscesses resolve with intravenous antibiotics alone, but aspiration or drainage with a pigtail catheter may be necessary [37].

Prevention

Vaccines against specific bacteria that predominantly cause pneumonia in children, specifically pneumococcal conjugate vaccine (PCV-7) and *H. influenzae* vaccine (Hib) have drastically lowered the prevalence of infections causes by these strains. Since the introduction of PCV-7, several studies have documented its efficacy, and the decrease in cases of *H. influenzae* are equally striking [7, 21]. However, while PCV-7 has decreased the prevalence of invasive pneumococcal disease, the incidence of empyema is rising, the reason for which is unclear [76]. The licensure of pneumococcal conjugate vaccines that include even more serotypes (e.g., 13-valent) may further change the epidemiology of childhood pneumonia. Other vaccines, such as for measles (MMR) and influenza, can also aid to reduce these viral infections that so commonly lead to secondary bacterial pneumonia. While vaccines appear to be our greatest effort toward preventing pneumonia in children, more work needs to be done to increase their microbial coverage and availability throughout the world.

Table 6.5 Description of procedures for evacuating pleural effusion and empyema

Procedure	Description	Sedation requirement
Thoracentesis	Needle inserted between the ribs on the lateral chest wall into the pleural space, usually with ultrasound or computed tomography guidance	Local anesthesia, minimal (anxiolysis) or moderate sedation
Tube thoracostomy	Large bore, hollow, flexible tube placed between the ribs into pleural space though a 2 cm skin incision on the lateral chest wall. The tube is connected to a canister containing sterile water. Suction is applied to facilitate drainage	Local anesthesia, moderate or deep sedation
Video-assisted thoracoscopic surgery (VATS)	Operative technique in which a small camera and instruments are inserted into the pleural space through 2–3 small (1–2 cm) incisions of the skin and muscle on the lateral chest wall to mechanically remove purulent material and pleural adhesions. A thoracostomy tube is placed through one of the existing incisions following completion of the procedure	General anesthesia
Open thoracotomy	Operative technique where instruments are inserted into the pleural space through a single 5–8 cm incision of the skin and muscle on the postero-lateral chest wall to mechanically remove purulent material and pleural adhesions. A thoracostomy tube is placed through a second smaller 1–2 cm incision following completion of the procedure	General anesthesia

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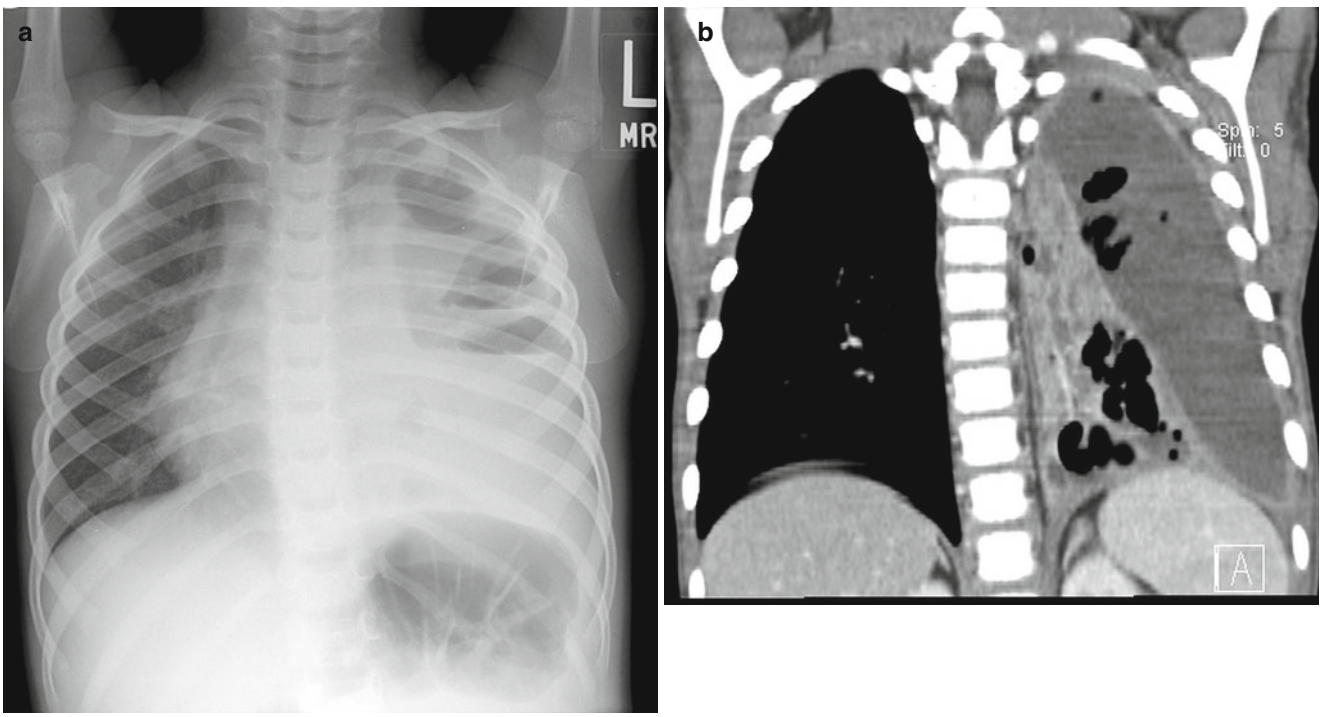


Fig. 6.5 Bronchial pneumonia with abscess. (**a**) The CXR shows a moderate left-sided effusion with fluid filled cystic spaces concerning for necrotizing pneumonia resulting in the shift of mediastinal structures to the right. (**b**) The corresponding chest CT shows a large loculated hydropneumothorax. The left lower lobe contains non-enhancing areas, multiloculated cavities, and air/fluid levels consistent with pulmonary abscesses and necrotizing pneumonia

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Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS)

7

Waseem Ostwani and Thomas P. Shanley

Abstract

Acute lung injury (ALI) and its most severe manifestation of *Acute Respiratory Distress Syndrome* (ARDS) is a clinical syndrome of inflammation of the lung triggered by both direct (e.g. pneumonia) and indirect (e.g. sepsis) inciting events that result in the loss of the capillary-alveolar integrity. As a consequence, patients suffer from high-permeability, non-hydrostatic pulmonary edema. Compensatory mechanisms regulating lung fluid flux are overcome and interstitial and alveolar edema develops leading to reduced lung compliance and alveolar collapse. These physiologic derangements cause ventilation and perfusion (V_A/Q) mismatch and consequently intrapulmonary shunting leads to hypoxemia that is the hallmark of ALI/ARDS. The incidence of ALI/ARDS places it among the most burdensome health care challenges in pediatrics. A complex interaction of cellular components, cytokine and chemokine mediators, and adhesion molecules of the immune system orchestrate the pathophysiology of ALI/ARDS. The mainstay of therapy is institution of positive pressure mechanical ventilation that requires careful attention to minimizing distending pressures responsible for ventilator-induced exacerbation of injury as well as optimal recruitment strategies to avoid repetitive opening and closing of lung units. Avoidance of fluid overload following adequate fluid resuscitation appears to be of benefit, while additional therapies such as prone positioning, corticosteroids, inhaled nitric oxide and high frequency oscillatory ventilation may improve arterial oxygenation, though none have been systematically proven to improve overall clinical outcomes in limited pediatric studies. Novel approaches to identifying new therapeutic targets for attenuating the pathophysiology of ALI/ARDS are discussed.

Keywords

Pulmonary edema • Cytokines • Chemokines • Adhesion molecules • Ventilation-perfusion mismatch • Ventilator-induced lung injury • Barotrauma • Atelectrauma

Introduction

Acute lung injury (ALI) is a clinical syndrome of inflammation of the lung resulting in the loss of the capillary-alveolar integrity. These patients suffer from high-permeability, non-hydrostatic pulmonary edema, reduced lung compliance, and alveolar flooding and collapse resulting in ventilation and perfusion (V_A/Q) mismatch and consequently intrapulmonary shunting leading to hypoxemia. In 1967, Ashbaugh and colleagues described a cohort of 12 patients who had

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the acute onset of tachypnea, hypoxemia, panlobular infiltrates on chest radiograph, and decreased lung compliance [1]. It was noted that this syndrome clinically appeared similar to the infant respiratory distress syndrome, so in 1971 these same investigators coined the name *Adult Respiratory Distress Syndrome* [2]. Over time, it became clear that this same condition occurred in children and consequently it was renamed in a manner agnostic to age as the *Acute Respiratory Distress Syndrome* (ARDS). While initially defined by characteristic clinical features, clinician-investigators aimed to identify objective criteria to define ALI/ARDS. In 1988 Murray and colleagues proposed to define ARDS via the Lung Injury Score (LIS) based upon chest radiographic findings, the degree of hypoxemia (defined by the PaO_2/FiO_2 ratio), the level of positive end-expiratory pressure (PEEP), and lung compliance (Table 7.1) [3]. Finally, in order to provide a consistent definition that would facilitate large, clinical trials in lung injury a joint American-European Consensus Committee (A-ECC) was convened in 1994 with the goal of developing a universally accepted, consensus definition of ALI and ARDS. This definition (Table 7.2) includes an acute pulmonary or non-pulmonary trigger of the disease process in previously normal lungs, oxygenation abnormalities as defined by the PaO_2/FIO_2 ≤300 for ALI and PaO_2/FIO_2 ≤200 for ARDS, radiographic findings of infiltrates, and the exclusion of left atrial hypertension when measured, but did not include positive end expiratory pressures, as described in the LIS [4]. Recognizing that many clinicians manage ALI and less severe ARDS patients with non-invasive monitoring, many groups have proposed and validated use of the pulse oximetry-determined SpO_2/FiO_2 ratio as an alternative method of quantifying hypoxia in determining the presence of ALI/ARDS [5]. While the proposed values vary slightly, a SpO_2/FiO_2 ratio < 253 indicated ALI and < 212 indicated ARDS in a pediatric ALI cohort [5]. Most recently the ARDS Definition Task Force developed the so-called "Berlin Definition" that proposes three mutually exclusive categories of ARDS based on the degree of hypoxemia as measured by PaO_2/FIO_2: mild = 200–300≤; moderate = 100–200≤; and severe 100 ≤ [6]. Of note, adding four ancillary variables for severe ARDS – radiographic severity, respiratory system compliance (≤40 ml/cm H_2O, PEEP ≥10 cm H_2O, and corrected expired volume added no discriminatory power for predicting mortality and were thus dropped [6]. Using either methodology, it is clear that ARDS is simply the most severe manifestation of ALI. Although highly useful in stratifying and identifying patients for clinical studies, it is currently being considered for revision as the predictive value of this definition in adults has been questioned. In contrast to adult studies, an epidemiologic study in pediatric ALI has demonstrated a correlation between the initial PaO_2/FIO_2 and mortality [7]. More importantly, this definition fails to incorporate any information about the amount of positive pressure ventilation being used to support a patient at a given fraction of inspired oxygen (FIO_2). As will be further emphasized below, the mean airway pressure (MAP) incorporates most of the parameters (PEEP, peak inspiratory pressure [PIP], inspiratory time [I_t]) utilized to support oxygenation deficits in the setting of ALI/ARDS. As a result, because

Table 7.1 Murray lung injury score

	Score
Chest radiograph	
No consolidation	0
1 quadrant	1
2 quadrants	2
3 quadrants	3
4 quadrants	4
Hypoxemia (PAO_2/FIO_2)	
≥300	0
228–299	1
175–224	2
100–174	3
<100	4
PEEP, CM H_2O	
≤5	0
6–8	1
9–11	2
12–14	3
≥15	4
Compliance, ML/CM H_2O	
≥80	0
60–79	1
40–59	2
30–39	3
≤29	4

The final value is obtained by dividing the sum of the individual component scores by 4
Scores: 0 = no injury
0.1–2.5 = Mild to moderate injury
>2.5 = Severe injury (acute respiratory distress syndrome)

Table 7.2 American-European consensus committee definition of ARDS and ALI

	Timing	Oxygenation	Chest radiograph	Pulmonary artery wedge pressure
Acute lung injury	Acute onset	PaO_2/FiO_2 ratio ≤300 mmHg (regardless of PEEP level)	Bilateral infiltrates seen on frontal chest radiograph	≤18 mmHg when measured or no clinical evidence of left atrial hypertension
ARDS	Acute onset	PaO_2/FiO_2 ratio ≤200 mmHg (regardless of PEEP level)	Bilateral infiltrates seen on frontal chest radiograph	≤18 mmHg when measured or no clinical evidence of left atrial hypertension

the Oxygenation Index (OI) incorporates the mean airway pressure in its equation: $OI = [(MAP \times FIO_2)/PaO_2] \times 100$, many clinicians feel this to be a more relevant parameter for stratifying ALI/ARDS patients for clinical studies as well as following the clinical response to therapeutic maneuvers. Because ALI/ARDS is one of the most common and challenging clinical entities the pediatric intensivist will face, it is crucial to possess a comprehensive understanding of the epidemiology, complex pathophysiology, and comprehensive management of this syndrome.

Epidemiology

The exact incidence of ARDS has been relatively difficult to establish. A 1972 population study in the state of New York by the National Heart, Lung, and Blood Institute reported the incidence of ARDS in adults to be approximately 150,000 cases/year. Other investigators have reported an incidence ranging from 1.5 to 75 patients/100,000 inhabitants/year [8–11]. In children, the exact incidence has also been difficult to establish [12]. Prospective epidemiological studies that made use of the A-ECC definition of ALI/ARDS provided more definitive data regarding the current incidence of ARDS. In a prospective, population-based, cohort study centered around Kings County, Washington, Rubenfeld et al. reported a crude incidence of ALI of 79 per 100,000 person-years and an age-adjusted incidence of 86 per 100,000 person-years, with an in-hospital mortality rate of 38.5 % [13]. Based upon this data, they estimated that there are over 190,000 cases of ALI/ARDS per year, which are associated with nearly 75,000 deaths and 3.6 million hospital days, providing evidence that ALI has a substantial impact on public health, both in this country and abroad. Unfortunately, as patients under the age of 15 were excluded from this most recent study, the burden of pediatric ALI/ARDS largely remains unknown.

Etiology

The variety of insults that lead to ALI/ARDS are diverse (Table 7.3). This heterogeneity of etiologies leading to a similar end-organ event in part likely reflects a common response of the lungs to injurious triggers. The pulmonary surface area that participates in gas exchange totals approximately 50–100 square meters [14] and by virtue of its anatomy and function must encounter the particulate and microbiologic environment of the outside world. This intimate connection, measured in micrometers, between the atmosphere and the delicate, capillary network of the pulmonary vasculature is separated by the interposed epithelial lining layer. Such anatomic proximity necessitates that the body's defenses be poised to react rapidly to pathogenic challenges directly encountered by the lung. Furthermore, the proximity of the pulmonary vasculature to the epithelial barrier explains the manner by which systemically manifested triggers readily affect the lung physiology and function.

Table 7.3 Common causes of ALI/ARDS

I. *Pulmonary* (*direct causes*)
A. Pneumonia
B. Aspiration of gastric contents
C. Hydrocarbon aspiration
D. Inhilation injury
E. Thoracic trauma (pulmonary contusion)
F. Sickle cell disease
G. Fat emboli
H. Drug related
I. Near drowning
J. Reperfusion pulmonary edema after lung transplantation or pulmonary embolectomy
II. *Extrapulmonary* (*indirect causes*)
A. Sepsis
B. Pancreatitis
C. Non-thoracic trauma
D. Transfusion of blood products
E. Disseminated intravascular coagulation
F. Cardiopulmonary bypass

This anatomical orientation has also led many observers of ALI/ARDS presentations to dichotomize cases on the basis of either a direct insult to the lungs (e.g. pneumonia or aspiration [so-called *pulmonary ARDS*]), or from remote or systemic injuries (e.g. sepsis or trauma [so-called *extrapulmonary ARDS*]). While initially suspected that the clinical presentation in either case resulted from similar pathophysiologic mechanisms, differences in the therapeutic responses to various strategies have raised the possibility that the pathophysiology of ARDS caused by pulmonary versus extrapulmonary triggers may in fact be different [15, 16]. It is intuitive that depending on the "side" (epithelial versus endothelial) of initiating insult, the injurious effect on the cell type comprising each component of the fragile epithelial-endothelial barrier may differ. For example, in the setting of a direct insult, alveolar epithelial cellular injury and dysfunction will be associated with an often focal or patchy intrapulmonary inflammatory response and accumulation of intraalveolar fluid, blood, and proteinacious materials. Conversely, in the setting of a systemic or extrapulmonary trigger, the generalized increase in pulmonary vascular permeability results from diffuse injury to the vascular endothelium via systemically released mediators of inflammation and thus more widespread and homogeneous alveolar edema [17]. Nevertheless, the subsequent similarity in the cascade of inflammatory events leading to the common clinical endpoint described in ALI/ARDS has led clinical investigators

to surmise a common pathway. However, this is countered by the observation that there are clinically measurable differences in pulmonary versus extrapulmonary ARDS in terms of the response to PEEP, respiratory mechanics, and findings on CT scan [18]. However, because no consistent differences in the response to ventilation strategies has been observed between pulmonary versus extrapulmonary ALI/ARDS, [19] it remains unclear as to whether clinicians should alter their therapeutic strategies in ALI/ARDS depending on the pathologic trigger – a key question that remains to be answered.

Risk Factors and Outcomes

Several risk factors for the development of ALI/ARDS in adults have been consistently identified, including sepsis and community acquired pneumonia. Fewer studies have been performed in children [20, 21] as the pediatric literature on ALI/ARDS has suffered from relatively small study size, variable exclusion criteria, examination of only individual patient populations [22], and variable adherence to the current consensus definition. These factors have made comparison between pediatric studies difficult. However, the presence of sepsis, septic shock, and multiple organ dysfunction have consistently had a very high association with the development of ALI/ARDS in both adults and children [21, 23]. The literature would suggest an approximate 40 % incidence of developing ARDS in patients with sepsis [24–27] with the incidence increasing in patients with additional risk factors such as witnessed gastric aspiration, multiple transfusions, and trauma [25]. Sepsis secondary to gram-negative bacteria portends a particularly high mortality rate in the setting of ARDS. In a series of 86 patients with gram-negative bacteremia by Kaplan et al., 20 patients developed ARDS (23 %) and the mortality rate (90 %) was substantially higher as compared to those that did not develop ARDS (50 %) [28]. Historically, prior reports on the incidence and outcomes from ALI/ARDS reported mortality rates that were substantially higher than more recent reports [29–31]. In one of the most recent epidemiologic studies of outcomes from ALI in pediatrics, Flori et al. reported on 328 PICU admissions (for 320 patients) with ALI/ARDS defined by consensus definition at two centers over a nearly 4 year time frame. The most common diagnoses were consistent with historical observations – pneumonia (35 %) and aspiration (15 %) as common direct injury triggers and sepsis (13 %), near drowning (9 %), and concomitant cardiac disease (7 %) as common indirect injury triggers [6]. Overall mortality of the group was 22 % (in contrast to adult outcomes of 35–55 %) with the highest rates observed among near drowning (54 %), associated cardiac disease (39 %), and sepsis (31 %). Importantly, hypoxemic respiratory failure was an uncommon cause of death which occurred more frequently as a result of either a *do not resuscitate* order or withdrawal of life support in the face of medical futility. Again, as mentioned above, in contrast to the majority of adult series, mortality did correlate with the initial PaO_2/FIO_2 ratio.

Clinical Course and Histopathology

The initial phase of ARDS (the *acute* or *exudative phase*) is manifested clinically by progressively refractory hypoxemia. The chest radiograph demonstrates bilateral patchy pulmonary infiltrates, similar to that observed during cardiogenic pulmonary edema (Fig. 7.1), while computed tomography (CT) of the chest reveals that alveolar filling, consolidation, and atelectasis occur predominantly in the dependent lung zones (Fig. 7.2). Histologic examination reveals alveolar epithelial cell damage characterized by cytoplasmic swelling, cell membrane fragmentation, and denudation of the cell lining in severe cases. As a result, the impermeability of the endothelial-epithelial barrier is abrogated, resulting in protein-rich alveolar fluid and parenchymal infiltration by neutrophils and monocytes in association with the loss of Type I alveolar epithelial cells.

While many patients recover after this acute stage, other patients will enter a second phase, known as the *fibroproliferative phase*. The time of onset of the fibroproliferative phase is highly variable (commonly thought to be 3–7 days after initial onset of ARDS) and is typically characterized by the onset of lung architectural changes and more refractory hypoxemia. Further translational research has provided evidence that the fibroproliferative response is driven by the proinflammatory cytokine, interleukin (IL)-1β and begins much sooner in the clinical course than previously believed

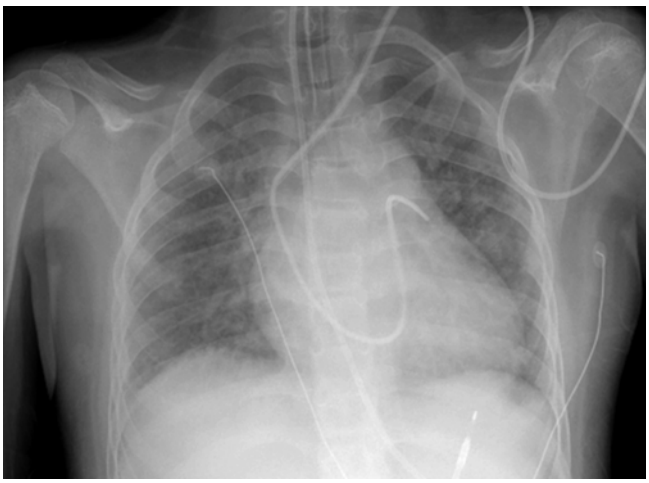


Fig. 7.1 Chest radiograph of a patient with ARDS illustrating bilateral diffuse alveolar infiltrates

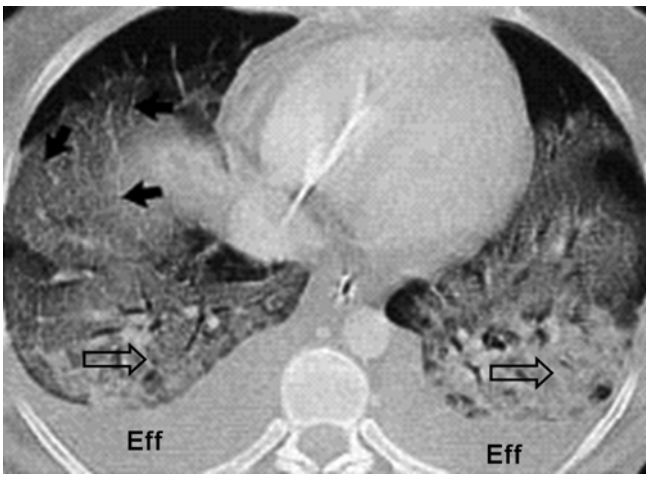


Fig. 7.2 Chest computed tomography of a patient with ARDS illustrating bilateral diffuse alveolar consolidation and septal fluid (➨), pronounced dependent edema (⇨) and pleural effusions (**Eff**)

[32, 33]. Histologically, this phase is characterized by prominent interstitial infiltration by fibroblasts, myofibroblasts, and inflammatory cells (mostly of the mononuclear lineage), and increased procollagen deposition. Of note, clinical studies have suggested that the type and amount of particular cells isolated in the bronchoalveolar lavage (BAL) fluid or ALI/ARDS patients may provide prognostic value. For example, the infiltration of immature monocytes occurs during this phase and correlated with persistence of hypoxemia [34] and having more than 6 % of fibrocytes in the BAL fluid in ALI/ARDS patients predicted worse outcomes [35]. Clinical features of the fibroproliferative stage include increased alveolar dead space and further decreases in lung compliance. Whether the process of fibroproliferation may be attenuated by the administration of corticosteroid therapy during this phase remains highly controversial [36–40].

The final phase is the *recovery phase*, characterized by gradual resolution of the hypoxemia and improved compliance as the lung architecture is restored to normal. The timing and duration of this stage is also highly variable. Lung repair is at least in part dependent on the ability of the type II pneumocyte to repopulate gas exchange surfaces. The type II pneumocyte, which is responsible for surfactant production, is the only epithelial cell type that appears capable of mitotic division and replication and must repopulate the alveolar lining and differentiate into type I pneumocytes for the lungs to recover. As a result, investigators are continuing to elucidate this and other reparative mechanisms in order to leverage this capacity therapeutically. Unfortunately, some patients will not recover and have histologic changes showing progressive lung fibrosis and cyst formation with irreversible loss of functional alveoli that ultimately leads to death secondary to refractory hypoxemia.

Pathophysiologic Mechanisms in ARDS

Development of Pulmonary Edema

As reviewed above, the hallmark of ARDS is the development of pulmonary edema and flooding of the alveolar space resulting in either alveolar collapse [36] or alveolar flooding [37, 38]. In either case, the result is an impairment of matching between ventilation and perfusion primarily as a result of impaired ventilation of alveolar units that remain perfused. The subsequent intrapulmonary shunt results in clinically significant hypoxemia and is most often refractory to supplemental oxygen. The numerous factors that contribute to the development of pulmonary edema may be best thought of in the context of the Starling equation which predicts fluid flux into or out of the pulmonary capillary system (Fig. 7.3). Intravascular capillary pressure (P_{mv}) can be an important driving force of fluid transudation into the airspace and is countered by interstitial pressure. This physiologic effect explains the finding of pulmonary edema that results from elevated left atrial as well as pulmonary venous pressure in the setting of congestive heart failure (CHF). For this reason, an elevated pulmonary wedge pressure remains an exclusion factor in defining ALI/ARDS. In contrast to hydrostatic pressure, increases in pulmonary capillary oncotic pressure serve to retain fluid within the intravascular space. Loss of plasma proteins (e.g., nephrotic syndrome) or impaired synthesis (e.g., liver failure) can result in decreased plasma oncotic pressure (π_{int}) and increase the flux of fluid into the interstitial space. This fluid transudation dilutes interstitial protein concentration and thereby decreases the interstitial oncotic pressure and diminishes the force driving fluid out of the vascular space. This process may provide a *safety factor* for interstitial fluid flux, though ultimately the capacity to resorb excess fluid is overcome, eventually resulting in alveolar flooding manifested as pulmonary edema.

In the context of ARDS perhaps the largest contributor to the development of pulmonary edema is a change in the permeability coefficient, Kf. For reasons elucidated below, numerous mediators affect the barrier function of the endothelium and epithelium which increase the permeability of these cell layers to both fluid and ultimately circulating proteins (Fig. 7.4). In this manner, the effect on the development of pulmonary edema attributed to a small increase in elevated P_{mv} (such as may occur in response to decreased myocardial compliance in sepsis) and/or a decrease in π_{int} will be amplified by increased permeability. The biologic causes of this change in permeability have been extensively studied over the past several years and inflammatory mediators (notably cytokines and chemokines) are key drivers of this increased permeability and pathophysiology.

Cytokines

The difficulty in elucidating the pathophysiology of ARDS relates to the multiple etiologies that have been associated with its onset. While initially it was believed that both direct/pulmonary and indirect/extrapulmonary causes of ARDS were characterized by a similar cascade of pathophysiological events, as noted above the varied responses to therapeutic interventions in the setting of different etiologies suggest they may differ. Nevertheless, the reason for surmising that the two shared a similar pathophysiology related to the consistent observation of increased cytokines measured either locally (from BAL samples) or systemically (in serum samples) in the setting of ALI/ARDS [39]. Because of their presence and multiple effects, cytokines have been extensively investigated as causative mediators in ALI/ARDS (Fig. 7.5).

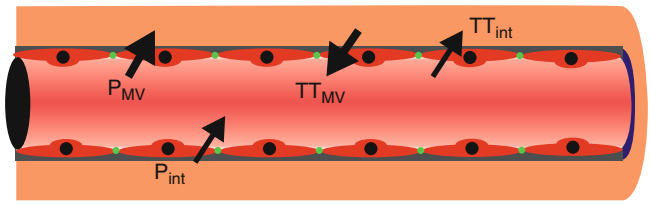


Fig. 7.3 Factors regulating fluid flux in the lungs as predicted by Starling's equation. LpA = Kf (*P* hydrostatic pressure, π oncotic pressure, *MV* microvasculature, *int* interstitial space)

Cytokines are soluble proteins synthesized by every cell type in the lung, including the alveolar epithelium, pulmonary vascular endothelium, alveolar macrophages, lymphocytes, and interstitial cells. They comprise a diverse group of peptides and glycoproteins that are key to intercellular communication, adhesion molecule expression, chemotaxis, leukocyte activation, generation of oxygen- and nitrogen-based radicals, all mediated via *de novo* gene expression regulated by intracellular signal transduction. Most of the effects of cytokines are mediated via binding to receptors on various target cells. The receptor-ligand interaction initiates any number of signaling cascades that can result in either

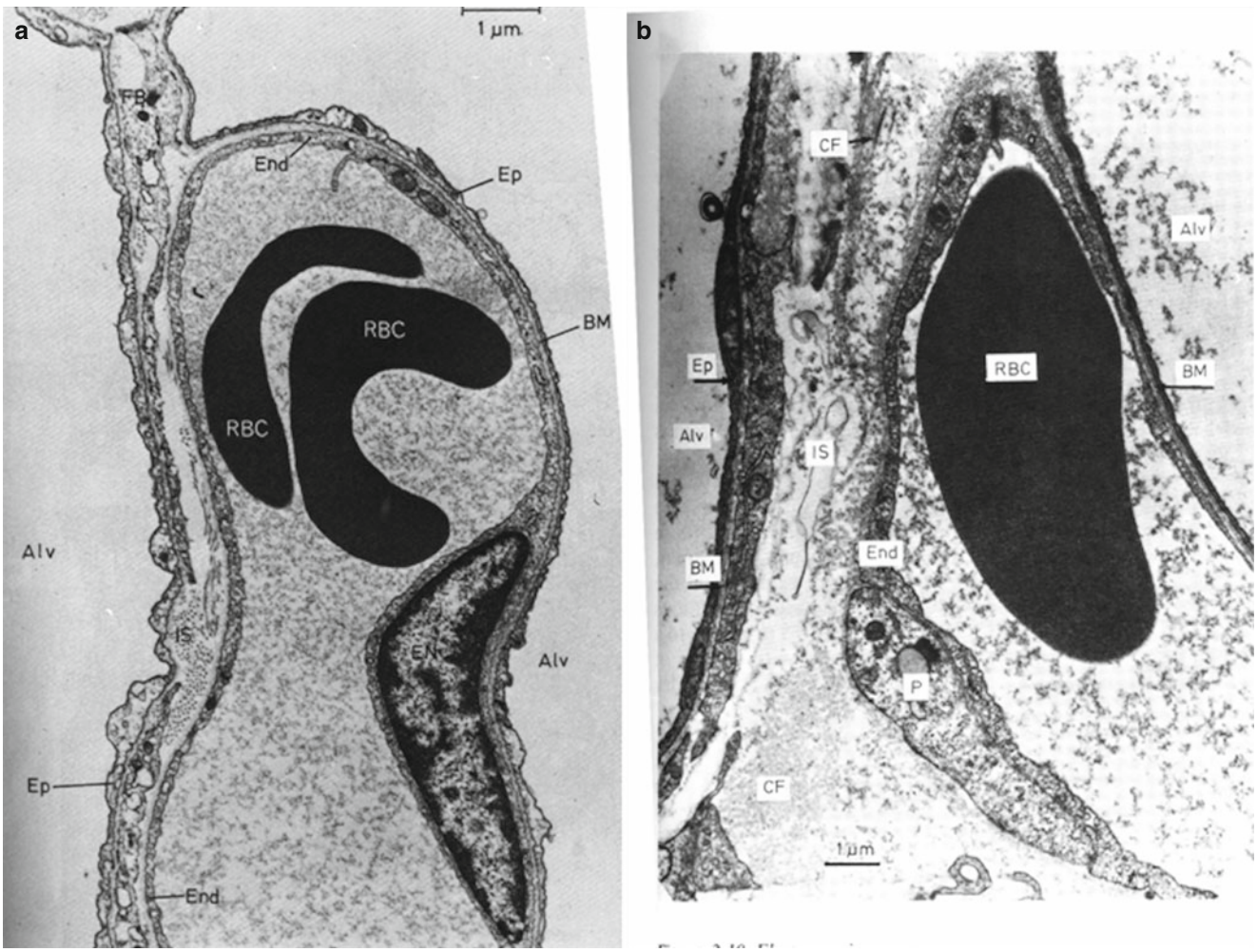


Fig. 7.4 Ultrastructure changes of endothelial/epithelial barrier between normal (**a**) and ALI/ARDS (**b**). Note the accumulation of collagen-enriched fluid (CF) within the interstitial space (IS) in ALI/ARDS. *Ep* epithelial cell, *End* endothelial cell, *BM* basement membrane, *Alv* alveolus, *RBC* red blood cell

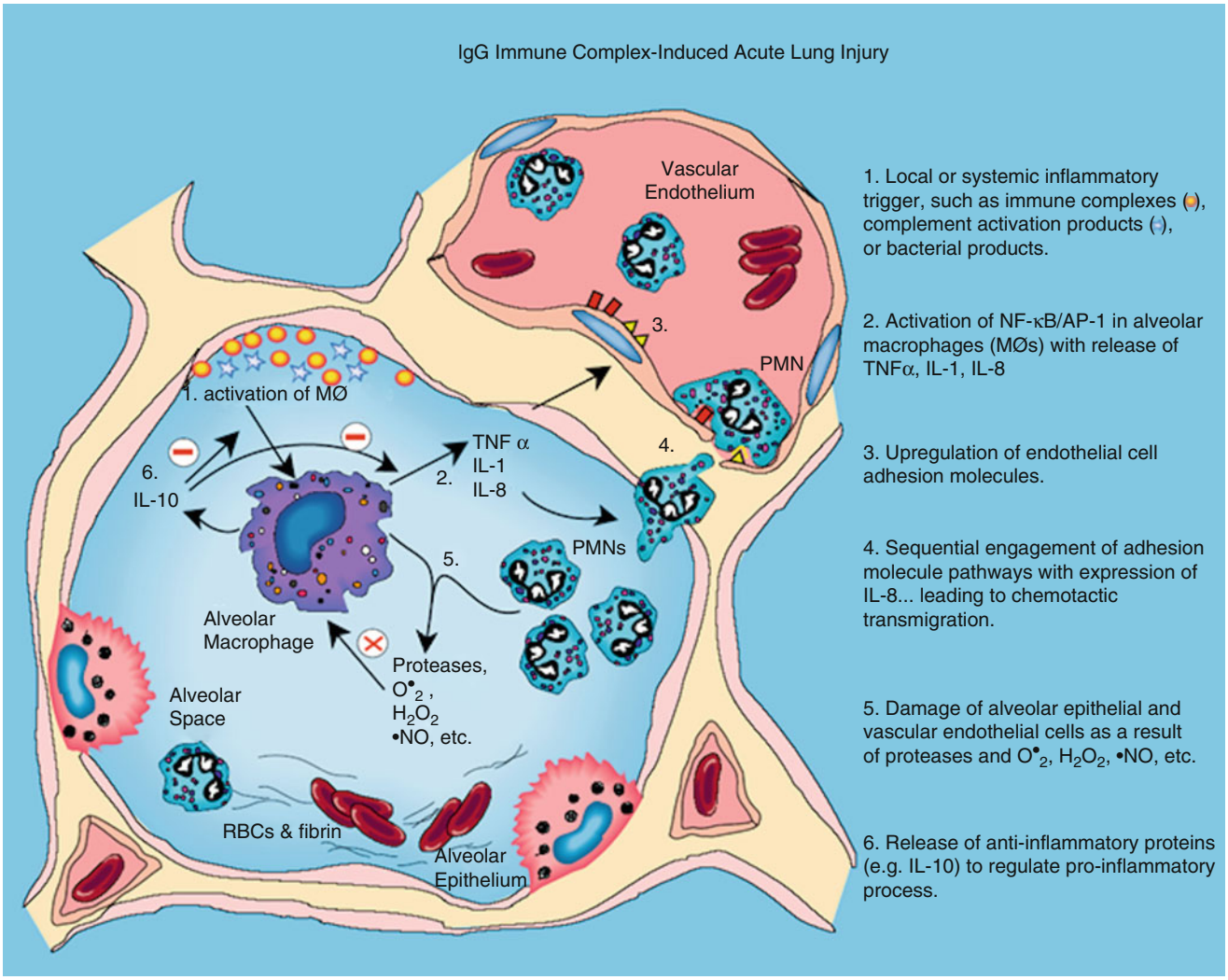


Fig. 7.5 Schematic of pathophysiologic mechanisms in ALI/ARDS

inhibitory or stimulatory responses by the target cell [40]. In the setting of ARDS, some of the most extensively studied cytokines include tumor necrosis factor-alpha (TNF-α) [41], interleukin-1β (IL-1β) [42], interleukin-8 (IL-8/CXCL8), and monocyte chemoattractant protein (MCP)-1/CCL2.

TNF-α and IL-1β are classically described as *early response cytokines* produced by cells of the innate immune system which evolved to protect the host from pathogen invasion. Microorganisms express a series of highly conserved molecular patterns that distinguish them from the host, e.g. double-stranded RNA of viruses, unmethylated CpG dinucleotides of bacteria, mannan binding proteins of yeast, glycolipids of mycobacteria, lipoproteins of bacteria and parasites, lipoteichoic acids of Gram-positive bacteria, and lipopolysaccharide (LPS) of Gram-negative bacteria [43–48]. These so-called pathogen- (PAMP's) or microbial-associated molecular patterns (MAMP's), are recognized by members of the Toll-like family of receptors (TLR's). As a result of TLR binding, cellular activation drives expression of these *early response cytokines* that are critical to inducing acute lung inflammation.

TNF-α is biologically active as a trimer and binds to one of two distinct receptors (55kD and 75kD forms) that exist on nearly every cell type studied. In early preclinical studies, administration of purified TNF-α caused fever, hypotension, and impaired endothelial barrier function characterized by the onset of pulmonary edema. Conversely, anti-TNF-α neutralizing antibodies prevented signs of sepsis, including ARDS, when Gram-negative bacteria or its toxic moiety, endotoxin, was administered to animals [41, 49–51]. Because of the frequent observation of ARDS in sepsis and increased levels of TNF-α in BAL fluid of ARDS patients, a causative role for TNF-α in ARDS was hypothesized [52, 53].

IL-1 is another early response cytokine that exists as one of two proteins, an α and a β isoform, which share little homology. IL-1β is synthesized as a proform that requires

proteolytic cleavage by caspase-1 (also known as interleukin-1β converting enzyme (ICE) to the bioactive form [54, 55]. Both TNF-α and IL-1β independently, and synergistically, are capable of regulating expression of other cytokines and mediators, perhaps most notably, CXCL8/IL-8 [56], CCL2/MCP-1, and adhesion molecules (e.g., Intercellular Adhesion Molecule (ICAM)-1). Of note, the induction of both pro- and anti-inflammatory cytokines from macrophages by IL-1β differs between children and adults in that there is a substantial anti-inflammatory response triggered in children's macrophages while only pro-inflammatory mediators are produced by macrophages from adults [57].

Both IL-8 (CXCL8) and MCP-1 (CCL2) are members of a large family of chemoattractant cytokines, or *chemokines* [58]. The nomenclature for classifying chemokines is on the basis of conserved cysteine motifs, thus, CXC, CC, C, and CX3C chemokine families exist as chemotactic factors for every type of leukocyte [59]. Relevant to ALI/ARDS, in the setting of a variety of inflammatory challenges in experimental models, CXC chemokines, notably IL-8 (CXCL8), mediate neutrophil infiltration into the lung [60–64]. There is also substantial clinical evidence that IL-8 is present in the lungs of patients with ARDS, and that increased BAL fluid levels of IL-8 correlate to the number of lung neutrophils, the severity of injury, and mortality [65]. It remains unclear, however, as to whether neutralization of CXC chemokines may be of benefit, as they are crucial to pathogen clearance. For example, Greenberger and colleagues observed that while depletion of MIP-2 (CXCL2/3) in a murine model of *Klebsiella* pneumonia reduced neutrophil recruitment to the lung, reduced bacterial clearance and increased bacteremia were also found [60]. In a similar fashion, investigators have attempted to target CXC receptors to determine the importance of CXC chemokine ligand/CXCR biology during bacterial pneumonia. These investigators found marked reductions in lung neutrophils in response to *Pseudomonas aeruginosa, Norcardia asteroides,* and *Aspergillus fumigatus*, which were accompanied by reduced clearance of the microorganisms and increased mortality, suggesting that impairing this key component of innate immune response in the setting of bacterial infections may not be of benefit [64]. Nevertheless, as described below, lung injury mediated by non-pathogen stimulation of CXC chemokine expression (e.g. barotrauma) may be inhibited with overall favorable outcomes [66].

The role of CC chemokines in ARDS has also been examined and studies have implicated a putative pathophysiologic role for CCL-2/MCP-1. Examination of BAL fluid from patients with ARDS noted increased monocytes presumptively recruited to the airspace. There was a correlation between the number of these cells and MCP-1 BAL fluid levels suggesting that MCP-1 may mediate the recruitment of this cellular population in ARDS [34]. In a murine model of sepsis-induced ALI, the presence of MCP-1 was also noted to mediate recruitment of neutrophils to the lungs that was attenuated by neutralization of MCP-1 [67, 68]. Thus, CC chemokines such as MCP-1 may be important contributors to the pathophysiology of ARDS.

Cytokines have a variety of biologic activities that modulate the inflammatory response of the lungs in a variety of ways. For example, cytokines can function as key amplifiers of inflammation through synergistic activity [69–71]. As an example, in an immune complex-mediated model of lung inflammation, blocking the CC chemokine, MIP-1α, decreased BAL fluid TNF-α content, suggesting that MIP-1α might function as an autocrine activator of TNF-α expression [72]. Therefore, targeting proximal cytokine mediators may dampen this auto-amplification observed during the acute inflammatory response.

One of the most important roles for cytokines is their facilitation of the endothelial cell-leukocyte adhesion cascade (Fig. 7.6). One of the pathologic hallmarks commonly observed in lungs from patients succumbing to ALI/ARDS is neutrophil infiltration. The mechanism by which leukocytes are recruited from the blood to the lung is now well understood [71]. The initial phase of leukocyte adhesion begins with a process called *rolling*, in which members of the selectin family of adhesion molecules (e.g. E-selectin) are upregulated on the endothelium and mediate an interaction with sialylated oligosaccharides that are constitutively expressed on neutrophils [73, 74]. In the second phase of adhesion, a firm interaction develops between cytokine-activated β2-integrins (e.g. CD11a,b,c/CD18) expressed on neutrophils and their counter-receptors, notably ICAM-1, expressed on the endothelial cell surface which anchors the neutrophil to the pulmonary vascular endothelium [75]. Finally, neutrophils (or other adherent leukocytes) migrate into the alveolar space via chemotactic gradients created by various chemokines [76]. Once in the interstitial and/or alveolar space, leukocytes release a series of oxygen- and nitrogen-based radical species, proteases, and arachidonic acid metabolites all of which can contribute to impaired endothelial barrier function and the pathognomonic development of non-cardiogenic pulmonary edema. Despite initial consideration of a therapeutic strategy aimed at blocking adhesion molecule function, the appreciation that this biologic response remains key to host pathogen clearance has dampened enthusiasm for this approach.

Leukocyte Chemotaxis Related to Acute and Transitional Inflammation

A key characteristic of the acute inflammation associated with the development of ARDS is the recruitment of leukocytes from the blood to the airspaces of the lung [77].

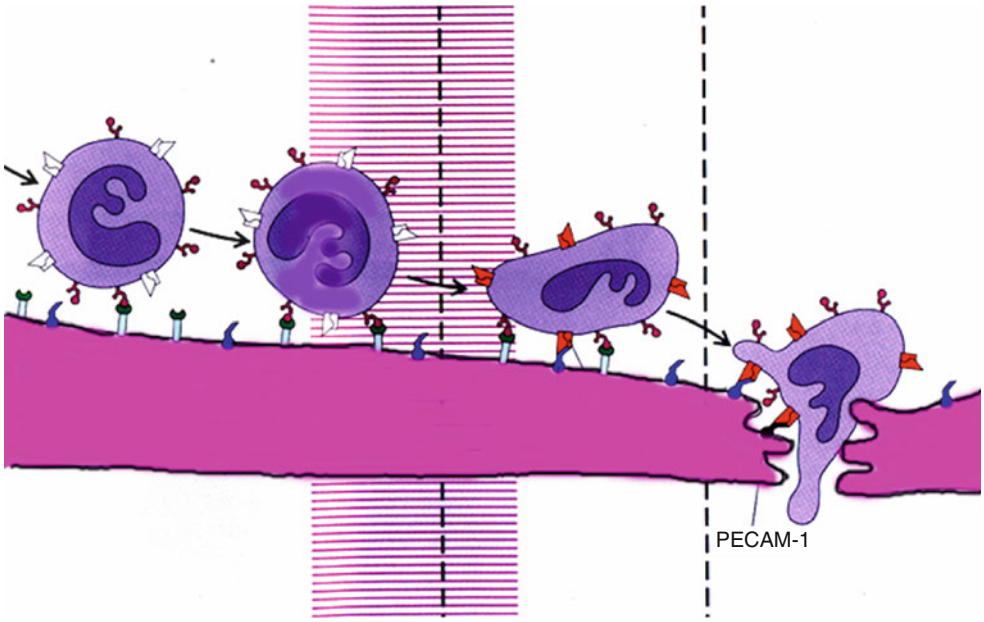


Fig. 7.6 Schematic depicting the leukocyte-endothelial cell adhesion cascade mediated by cytokine upregulation of both endothelial cell and leukocyte adhesion molecules. One adhesion has occurred, chemokine expression creates a chemotactic gradient to facilitate leukocyte homing and emigration to the site of inflammation

While this response is critical to eradication of an offending pathogen, an overly robust inflammatory response driving the release of mediators may amplify acute inflammation resulting in tissue injury. Additional investigations identified a series of non-specific chemotactic molecules such as N-formylmethionyl peptides from bacterial cell walls; the anaphylatoxin, C5a; leukotriene B4 (LTB4); and platelet activating factor (PAF) that are chemotactic for neutrophils [78]. While these molecules are critical to leukocyte extravasation, they do not exhibit the degree of specificity for leukocyte subsets. It has become apparent that the nature of the stimulus triggering lung inflammation variably determines the subpopulation of leukocytes recruited to the alveolar space. Thus, it was hypothesized that a more diverse set of chemokines existed which possess specific activity for subsets of leukocytes leading to the identification of the CXC family of chemokines (e.g. IL-8/CXCL8, MIP-2/GROα/CXCL2) and the CC chemokines (e.g. MIP-1α/CCL3, MCP-1/CCL2). Prospective studies in adult ARDS have suggested that acute infiltration of neutrophils is temporally followed by migration of mononuclear cells into the lung. Thus, both T-cells and monocytes may contribute to persistent lung inflammation and mediate subsequent fibrosis as has been observed in animal models of chronic lung inflammation. Recent clinical data suggest that late mononuclear cell recruitment, or so-called *transitional inflammation* is critical to the outcome of patients with ARDS [34]. Further understanding of the regulation of the expression of these chemokines may identify potential therapeutic targets for interrupting the inflammatory process later in the course of ARDS.

Role of Anti-inflammatory Cytokines in Regulating ARDS

Following their initial discovery most commonly in the context of a host response to a pathogen challenge, cytokines were characterized as proinflammatory based on their causal association with sepsis and ARDS. Subsequently, it became clear that a counter-regulatory host response characterized by expression of a number of anti-inflammatory cytokines occurs. Included among this group of cytokines are IL-10, IL-13, TGF-β, and in some model systems, IL-6 and a related cytokine, IL-11. Among the most well characterized of these cytokines is IL-10, which possesses potent anti-inflammatory effects by its ability to down-regulate cytokine production by macrophages in a myriad of ways [79]. In a rat model of ALI, blocking endogenous IL-10 caused increased inflammation and pulmonary edema in association with increased levels of TNF-α and IL-1β [80]. This finding was further supported by the observation that IL-10 knockout mice are exquisitely sensitive to inflammation as reflected by their response to sub-lethal endotoxin injection that results in 100 % mortality [81]. A correlative finding has been observed in humans where patients that mounted the lowest levels of IL-10 in their BAL fluid displayed the highest mortality rate from ARDS [82]. Similar findings have been observed in studies examining TGF-β and IL-13 as *monocyte deactivating agents* suggesting that these molecules also serve as important counter-regulatory molecules in the setting of acute inflammatory disease states such as ALI/ARDS. However, an over exuberant anti-inflammatory response may lead to an acquired, functional host immunosuppression thus impairing pathogen clearance. Such as response has been

described as the *Compensatory Anti-inflammatory Response Syndrome (CARS)* in contrast to the *Systemic Inflammatory Response Syndrome (SIRS)*, as a term that describes the pro-inflammatory, physiologic state [83]. This inability to regulate both necessary responses associated with the pathologic syndromes of ALI/ARDS and sepsis has been described as *immune dissonance*. Accordingly, as the field of critical care contemplates on-going interventional studies, it is imperative to recognize that patients afflicted with ALI/ARDS likely exist along a spectrum of inflammation (pro- to anti-) so that it is likely erroneous to presume that all ARDS patients exhibit any a single immunologic phenotype. The multitudes of clinical investigators who have witnessed the failings of proinflammatory cytokine inhibition to favorably impact clinical outcomes in ARDS helped to illuminate this concept [84, 85]. It may in fact be that some patients over-express anti-inflammatory cytokines that contribute unfavorably to overall outcome by impairing pathogen clearance. As a result, it is crucial for the host to maintain a homeostatic cytokine balance in its response to any number of inflammatory challenges. On-going and planned future clinical studies need to better stratify patients by immune status before considering novel approaches to therapeutically modulate a balance between pro- and anti-inflammatory cytokines.

Molecular Regulation of Cytokine Gene Expression

Because of the important role cytokines play in the development, propagation, and eventual resolution of ARDS, their molecular regulation has been a target of active investigation over the past decade. In this era of molecular biology and genomic science, it is necessary to possess a fundamental understanding of the mechanisms of gene expression and relevant signal transduction pathways that play fundamental roles in the expression of genes contributing to the pathobiology of ARDS. For the reader, these pathways have been reviewed in great detail [86] and are covered elsewhere in this text.

Conventional Therapeutics in ARDS

Therapy for ARDS begins by addressing any treatable, underlying cause of ARDS, such as sepsis, pneumonia, or pancreatitis [27]. Beyond this, with few exceptions, most therapies specifically directed at the pathophysiological mechanisms described above remain experimental or have not shown benefit in clinical trials [10]. Thus, at present, the majority of therapies for ARDS are primarily supportive in nature. Further consideration of any therapy for ARDS must take into account the fact that most patients with ARDS do not die from respiratory failure; rather, as mentioned previously, most patients with ARDS die as a result of multiple organ failure. Nevertheless, it is expected that therapies specifically directed towards ARDS have the potential to reduce the incidence of all causes of death associated with ARDS.

Conventional Mechanical Ventilation

Maintaining adequate oxygen delivery is the critical therapeutic goal in the management of ALI/ARDS. This goal is achieved with the usual strategies of fluid management, maintaining adequate hemoglobin concentration, achieving acceptable oxygen saturation, and using appropriate inotropes and vasopressors to maintain adequate cardiac output. Clearly the notable challenge in the patient with ALI/ARDS is the need for respiratory support, most typically in the form of mechanical ventilation, to address hypoxia. Positive pressure ventilatory support should be targeted towards achieving the greatest benefit while minimizing potential harm.

Among the options for a select group of patients with respiratory failure is the potential to be managed with noninvasive positive pressure ventilation (NIPPV). The most common indication for NIPPV is acute hypercapnic respiratory failure, particularly in the setting of chronic obstructive pulmonary disease [87, 88]. However, increasingly NIPPV has been suggested as a potential temporizing strategy in patients with hypoxemic respiratory failure, though some studies have suggested that such patients do not receive the same benefit from NIPPV as do patients with hypercapnic respiratory failure [89]. Nevertheless, there are reports of successful NIPPV in the setting of ARDS [90, 91]. Thus, NIPPV may be considered in some select patients with ARDS (i.e., patients with obstructive pulmonary disease and patients with milder forms of ARDS), but it should be understood that the vast majority of patients with ARDS require tracheal intubation and mechanical ventilation.

Increasing mean alveolar pressure (mPalv) is currently considered the key approach for reversing ventilation-perfusion mismatch and consequent hypoxemia in ARDS. Increased mPalv allows for recruitment of alveoli and for reduction of FiO_2 to *non-toxic* levels (still arbitrarily agreed to be <0.6). It is helpful to recognize that mPalv is derived from an area-under-the curve determination of a pressure-time curve (Fig. 7.7). As a result, there are several ways to increase this area, and thus mPalv: including increases in positive end-expiratory pressure (PEEP), inspiratory time (I_t), peak inspiratory pressure (PIP) and to some degree frequency (Fig. 7.7). Among these options, PEEP appeals to be the most clinicians as this can be instituted without augmenting PIP (expecting a consequent drop in tidal volume thus minute ventilation and permitting hypercarbia) and addressing potential de-recruitment (discussed below). Typically,

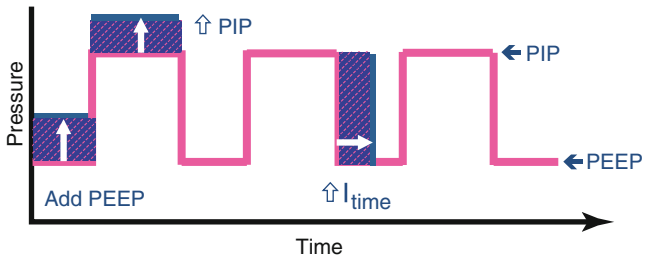


Fig. 7.7 Pressure-time curve demonstrating the area under the curve that correlates directly with the Mean Airway Pressure (MAP). A clinician can increase this AUC and thus MAP, by: increasing PEEP, lengthening the iTime or increasing PIP as shown. The consequence of increasing either PIP and/or PEEP are those risks associated with barotrauma, which limits an approach of increasing both pressures. (Note: PEEP can be increased safely provided the PIP is maintained at the same value. This will reduce the delta P and as a result the tidal volume resulting in increased CO_2. This latter strategy would be considered permissive hypercapnea.)

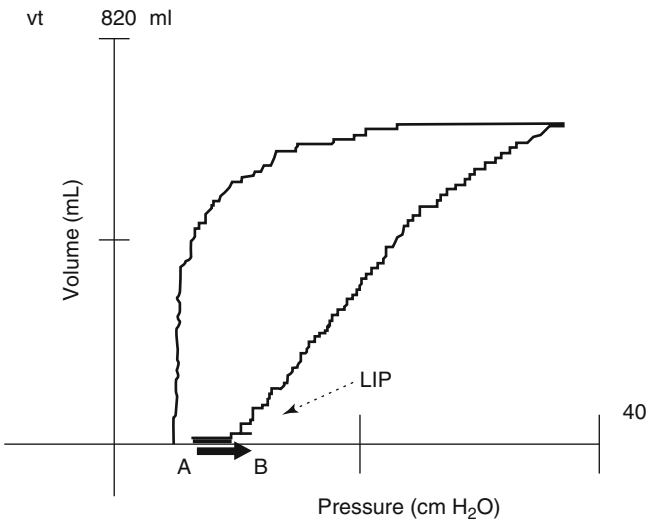


Fig. 7.8 Pressure-volume Loop demonstrating the lower inflection point (LIP). Pressure is applied (A to B) without volume expansion of the lung. The *open lung approach* advocates setting PEEP 1–2 cm H_2O above this point to avoid significant re-collapse upon exhalation thereby avoiding atelectrauma. While this can be estimated from a bedside P-V loop, precise determination of the LIP warrants the "super syringe" approach not commonly employed in routine practice

PEEP levels are increased incrementally until the FiO_2 can be reduced below 0.6 while maintaining a systemic oxygen saturation >90 %. Escalation in PIP typically above the 30–35 mmHg range is to be avoided given the concerns of ventilator-induced lung injury (VILI). Lengthening of I_t is also a commonly practiced approach that necessitates ensuring sufficient exhalation time it maintained for adequate CO_2 clearance and to avoid auto-PEEP, particularly when a reversal of the typical inhalation-to-exhalation (I to E) ratio is reversed.

Despite this common and logical approach based on sound physiologic principle, it is surprising that three large, randomized, controlled PEEP trials [92–94] have failed to demonstrate a reduction in mortality. The reasons for this are unclear, but may include ineffective individualization of the PEEP titration in these studies and/or insufficient power to detect a small absolute difference in mortality. A recent study by Caironi and colleagues [95, 96] based on a previously published cohort of patients with ALI/ARDS explored by computed tomography scan [97] constitutes the most comprehensive analysis of the possible therapeutic mechanisms of PEEP in ALI/ARDS to date. After stratifying patients within quartiles that received approximately the same ventilatory support with regards to PEEP and tidal volume, the authors observed a correlation between mortality and the amount of tidal opening and closing of lung tissue. Furthermore, they observed that increasing PEEP at a constant tidal volume improved outcomes on the basis of increased potential for lung "recruitability." Unfortunately, within common practice environments, it remains difficult to identify ARDS patients with this "high potential for recruitment" despite different methods having been proposed for bedside use, such as the pressure–volume curve technique. Nevertheless, a common strategy is to set PEEP at or above the *lower inflection point* of the pressure-volume curve (Fig. 7.8) with the goal of maintaining alveolar patency and eliminating repeated closure and opening of alveoli (so-called "atelectrauma") to be consistent with what has been coined as the *open lung approach*.

One of the limitations in escalating PEEP is the consequent increase in PIP that can only be limited to a level that maintains sufficient tidal volume [TV] (now accepted as 6 cc's/kg, though with no pediatric data) in a pressure preset mode or alternatively limited by the PIP achieved in a volume preset mode that targets 6 cc's/kg. However, in the context of non-compliant lungs as occurs in ARDS, it has been speculated that this high pressure delivered by the ventilator may not "reach" the alveolar tissue. In support of this hypothesis, it has been shown that measuring transpulmonary pressure using esophageal pressure monitoring can perhaps provide a better estimate of the alveolar pressure [98]. As a result, this approach has been suggested as a promising bedside tool with which to optimize PEEP management in patients with ALI/ARDS [99]; however, very little published pediatric data exist.

Given this emphasis on recruitment of non-ventilated lung, specific recruitment maneuvers (RM) have also been examined as a means to aerate collapsed and flooded alveoli to improve oxygenation while decreasing ventilator-induced lung injury from the shear stress of repetitive opening and closing of alveoli [98]. RMs are generally performed using high airway pressures (~40 cm H_2O) that are sustained for prolonged periods of time (~20–40 s). For example, in a trial conducted in Canada and Australia (the Lung Open Ventilation Study), one arm of the study used high PEEP

(20 cm H_2O) plus RM involving a 40–s inspiratory hold at 40 cm H_2O with subsequent reductions according to a PEEP/FIO_2 grid [92]. Results showed that this intervention group had significantly fewer episodes of refractory hypoxemia (4.6 % vs. 10.2 %; $p < .01$) and fewer deaths associated with refractory hypoxemia (4.2 % vs. 8.9 %; $p < 0.03$). Such promising results have not been substantiated in larger, randomized clinical trials so as yet, no consensus for the use of RMs in ALI/ARDS has been achieved; however in adult ICUs they are commonly applied to patients with significant and/or refractory hypoxemia. No efficacy data exists in pediatrics, however, small studies have demonstrated such an approach to be feasible and safe [100]; however, in their report of a small subset variable improvements in aeration of lung (3 %–72 %) as measured by CT scan and modest improvement in paO_2/FIO_2 was achieved (median of 14 %) and no adverse events were reported [101]. Thus, while apparently safe, whether RMs should be recommended as part of a management strategy for ALI/ARDS remains unknown. What is clear is that patients with ALI, and who do not reach the criteria for ARDS, frequently have a low potential for recruitment, and may respond poorly to high PEEP or RM [92, 93, 97]. In addition, patients with focal ARDS and heterogeneous disease may suffer more from over-distension with high pressures than they will benefit from lung recruitment [95, 102, 103]. Further bedside tools that can assist the clinician with these determinations may ultimately help in recognizing which patients most benefit from this strategy.

It is important to identify patients who will benefit from RM and/or high PEEP given the potential negative consequences that include barotrauma, alveolar over-distension with CO_2 retention, and decreased cardiac output secondary to increased intrathoracic pressure and as a result, impaired venous return and preload [104, 105]. Fear of barotrauma and VILI should not preclude the aggressive use of RM and/or high PEEP a priori, given the potential benefits. Increases of $PaCO_2$ secondary to alveolar distension can be well tolerated physiologically (*permissive hypercapnia*), or when excessive can be corrected by lowering PEEP so long as it does not compromise oxygenation. Finally, reductions in cardiac output can be overcome by appropriate augmentation of preload and appropriate use of intravenous inotropes. In this setting, data derived from a pulmonary artery catheter or a less precise, but potentially useful method of monitoring superior vena cava oxygen saturation, might provide valuable guidance in understanding the ramifications of PEEP changes on the overall oxygen delivery as reflected by a mixed-venous oxygen saturation measurement [106]. Given these hemodynamic caveats, it is not recommended to apply RM and/or high PEEP in patients who are in shock. It is wise to prepare the patient with adequate volume resuscitation as well as adequate sedation to ensure patient–ventilator synchrony [107]. Furthermore, if there is no improvement – notably in oxygenation parameters – then repeating RMs is probably unwarranted.

Inverse Ratio Ventilation and High Frequency Ventilation

Apart from PEEP, there are other additional means for increasing mean airway pressure in the setting of ARDS. Inverse ratio ventilation (IRV) is a strategy that makes use of supraphysiologic, prolonged inspiratory times such that the ratio of inspiratory time to expiratory time is greater than 1:1 [108]. This strategy substantially increases mPalv, thereby increasing alveolar recruitment and improving oxygenation while not effecting peak inspiratory pressure. Whether improvements in oxygenation are due to increased inspiratory time per se, or increased intrinsic PEEP, is a matter of debate. Studies using historical controls suggest that IRV can improve the outcome of ARDS [109–111]; however, when considering the use of IRV, it should be kept in mind that there are no large, prospective randomized trials comparing IRV to conventional ventilation in ARDS.

Perhaps the most simplistic, yet intuitive manner in which to apply mean airway pressure to manage severe ALI/ARDS is with the use of high frequency ventilation (HFV) either in the form of high frequency jet ventilation (HFJV) or high frequency oscillatory ventilation (HFOV) [112]. HFV has theoretical appeal in ARDS because it makes use of small tidal volumes, while maintaining alveolar recruitment, thus potentially reducing VILI. In the most recent (2005) adult trial comparing HFOV to conventional mechanical ventilation, showed no significant differences in survival, despite earlier improvements in the HFOV group [112]. Interestingly, the authors noted in a post-hoc analysis that HFOV appeared to confer a treatment effect on mortality in those with the most severe ARDS as quantified by an oxygenation index >30 suggesting that the sickest ARDS patients may benefit most by HFOV. Large multicenter clinical trials, including the OSCAR (ISRCTN10416500) and OSCILLATE (ISRCTN87124254) trials are either closed or currently being completed and are designed to compare clinical outcomes of patients who receive HFOV to those who receive a conventional lung protective ventilation strategy. Experience in pediatric patients, however, suggests that HFOV may provide some benefit [113, 114] particularly when instituted early on in the disease course [115]. Overall, there is continued enthusiasm for the use of HFV in the setting of severe ARDS, but its true benefit remains to be established. There are several reviews and published protocols available to direct management approaches [116–118].

Lung Protective Strategies

The use of mechanical ventilation presents a clinical paradox. On one hand, it provides life-sustaining support to allow sufficient time for recovery. On the other hand, the use of high concentrations of oxygen and the stretching forces of positive pressure ventilation (responsible for ventilator-induced lung injury [VILI]) can directly injure the lung. Lung toxicity related to high concentrations of oxygen (hyperoxia) has been recognized for many years. Hyperoxia is directly toxic to lung parenchymal cells by the generation of oxygen-related radicals and by impacting the signal transduction pathways of lung parenchymal cells [119]. Although the *safe* level of delivered inspired oxygen during ARDS is not known, a reasonable goal appears to be an $FiO_2 < 0.6$ which is why the recommendation of titrating PEEP to a level that allows reduction of FiO_2 below this level is espoused. Whether this concept will extend to the practice of allowing the systemic arterial oxygen saturation to fall to 85–90 % while maintaining adequate tissue oxygen delivery in order to avoid prolonged exposure to high FiO_2 levels (so-called *permissive hypoxemia)* remains to be seen [120]. VILI is a manifestation of direct physical damage to lung parenchyma, as well as stretch-induced changes in lung parenchymal signal transduction pathways. This latter concept is embodied in the term *mechanotransduction*, which describes how the physical force of positive airway pressure change gene expression patterns in the lung, thus leading to potentially important negative consequences such as increased inflammation and alterations of ion channels [121]. Multiple experimental models and clinical studies have documented the physiologic relevance of VILI [122–134] and supported the hypothesis that the mode of ventilation may impact the development of organ injury remote from the lungs [121, 128, 135].

As a result of the recognition of the influence of VILI on the course of ARDS, the clinical use of lung protective strategies that attempt to use minimal forces (whether pressure- or volume-triggered) have been espoused as a means to limit VILI. Examples described above include the appropriate application of PEEP to prevent cyclic opening and collapse of alveoli (*atelectrauma*) and the use of HFOV. Much of the clinical support for these approaches stem from the successful implementation of a lung protective strategy in which tidal volume was reduced to 6 mL/kg in contrast to a tidal volume of 12 mL/kg as reported by the ARDS Network. This study provided the most definitive evidence that a high tidal volume (12 mL/kg) is harmful to patients with ARDS (see www.ardsnet.org) [136]. Because half the patients in this trial were randomized to a conventional ventilation group in which the preset tidal volumes were often increased to 12 mL/kg tidal volume from more *conventional* 8–10 mL/kg, it remains unclear as to what the safest, minimal tidal volume in adults should be, and with greater uncertainty – children. Nevertheless, though this study was perhaps the largest trial to test this hypothesis, numerous studies have suggested clinical benefits of a low tidal volume strategy [130, 137–139].

Permissive Hypercapnia

An obvious consequence of limiting tidal volume is a reduction in minute ventilation and increase in carbon dioxide (hypercapnia). Although potentially exacerbating pulmonary hypertension, increased intracranial pressure, and cardiovascular dysfunction, hypercapnia appears to be well tolerated in patients with ALI/ARDS similar to what has been observed for years in neonatal respiratory distress syndrome [139–142]. In fact, several studies have suggested a possible protective role for hypercarbia in models of ALI/ARDS [140, 143–146]. In current common practice, most clinicians tolerate a pH of ~7.25 allowing gradual increase in $PaCO_2$ to avoid acute severe acidosis [147]. When pH drops below this level clinicians choose a myriad of approaches, including tolerating the lower pH, increasing minute ventilation by increasing frequency, or administering intravenous base agents (e.g., sodium bicarbonate, tris-hydroxymethyl aminomethane (THAM)) to raise the pH. Sodium bicarbonate infusions are often used in critical care units to manage life-threatening acidosis, but caution must be employed in hypercarbic respiratory failure as the partial pressure of CO_2 is increased in the process of buffering HCO_3 by carbonic anhydrase [148]. Another strategy to treat life-threatening acidosis is administration of trishydroxymethyl aminomethane (THAM) a non-bicarbonate buffer that does not increase CO_2 production. In a small observational study, THAM improved pH and $paCO_2$ in patients with ALI/ARDS and severe acidosis [149]. However, THAM infusions are contraindicated in patients with renal insufficiency as its risks include volume overload, hypoglycemia, and hyperkalemia. Which of these three approaches is most appropriate remains to be determined, and the choice of one method over another currently is generally dictated by individual patient scenario and physician experience or preference. Additional consideration with regards to permissive hypercapnea includes the observation that deep sedation may be necessary to reduce air hunger and dyspnea. Furthermore, it is important to note that permissive hypercapnia is contraindicated in children with suspected increased intracranial pressure and in those with sickle cell disease.

Prone Positioning

Chest computed tomography often illustrates how heterogeneously affected the lung parenchyma is in patients with ARDS (Fig. 7.2). When in a supine position, the dependent areas (dorsal) tend to be fluid filled and/or collapsed, while the non-dependent areas (ventral) tend be well ventilated, thus reflecting significant mismatch of ventilation and perfusion. Various mechanical factors have been identified to suggest that changing the position of the patient may facilitate the recruitment of these air spaces. Prone positioning has been considered as an inexpensive, non-invasive, and generally safe approach for potentially improving lung physiology for patients with ALI. While there can be complications from prone positioning (e.g., accidental extubation, pressure sores, facial edema, conjunctiva hemorrhage, catheter dislodgement, and in some cases worsening oxygenation), prone positioning has generally been found to be both well tolerated and clinically feasible in nearly any patient with minimal complications when attention is paid to potential dislodgement of tubes and/or access catheters.

Reviewing CT imaging, lung collapse is predominant in the dependent regions (Zone III) whereas ventilation is preferentially distributed to the non-dependent regions (Zone I). Furthermore, perfusion to the airspaces is lowest in the non-dependent regions and increases progressively in dependent regions (the concept described in West's depiction of lung zones). As a result, patients with ARDS in a supine position have maximal maldistribution (or mismatch) of ventilation and perfusion with subsequent physiologic shunt and resultant hypoxemia. Conversely, it is now appreciated that placing a patient in the prone position may be associated with a reduction of perfusion to collapsed regions providing a non-invasive means to improve V/Q matching and thus, oxygenation. Re-direction of perfusion from non-ventilated regions to newly recruited areas of lung regions in the prone position had been demonstrated in initial studies [150]. Such observations led to further studies in which prone positioning was found to (i) improve V/Q matching, (ii) decrease heterogeneity in the transpulmonary gradient related to heterogeneous lung diseases, (iii) improve alveolar recruitment, (iv) influence chest wall compliance and (v) potentially prevent VILI by decreasing the expand/collapse interface between recruited and de-recruited airspaces. While these physiologic benefits have been documented, an impact on what has been deemed important clinical outcomes (mortality and/or ventilator-free days [VFD]) has not been consistently demonstrated. For example, Curly et.al. demonstrated an immediate, improvement in oxygenation as measured by either P/F ratio or OI at various time-points during the first 24 h of prone positioning and this improvement was maintained in immediate responders upon returning to the supine position, however the primary outcome of VFD's was not changed [151]. In contrast, Casado-Flores et al. showed that the improved oxygenation was not sustained after returning to the supine position [152]. These seemingly discordant data are typical of the reported variability in the response to prone positioning such that predicting who will respond and derive benefit from proning is difficult. Unfortunately, despite evidence to show that prone positioning can be applied to improve oxygenation and respiratory mechanics, given the inherent complexity of ARDS studies, proving this to be a therapeutic intervention that alters mortality (and other end-points) in this patient population has been challenging, as neither of the large trials in either pediatric or adult ARDS patients demonstrated clear benefit beyond improved oxygenation [153, 154]. While reasons for this have been the subject of great speculation, an important confounder remains the heterogeneous patient population captured in large ARDS studies. Regardless, it has become increasingly clear that oxygenation may be an insufficient outcome to exclusively exam in interventional ALI/ARDS studies. From a practical standpoint, most intensivist's anecdotal clinical experience suggests that the response to prone positioning is variable from patient to patient, with some patients achieving greater improvements in oxygenation than others and that it can generally be done safely. Furthermore, there is a suggestion that "prolonged proning" (e.g. >18 h) may be a better strategy than the frequent repositioning (every 6–8 h) that has been employed in all large studies to date. Given this, it remains reasonable to consider prone positioning in patients with severe and/or refractory ALI/ARDS.

Fluid Management

As predicted by Starling's equation that dictates fluid flux across a semi-permeable cell layer, pulmonary alveolar edema will result from increased capillary permeability, and worsen as intravascular hydrostatic pressure rises and oncotic pressure falls. The onset of pulmonary edema behooves the clinician to optimally manage the fluid status of the patient with ALI/ARDS. Unfortunately, fluid management in the setting of acute lung injury remains widely debated with strategies ranging between conservative and liberal fluid approaches [155–157]. In addition to the "static" component of pulmonary edema during ALI/ARDS that results from alveolar-epithelial permeability and/or hydrostatic pressure, it is now understood that an "active" component of alveolar fluid clearance by the lung epithelium can also be impaired contributing to pulmonary edema [158, 159]. In fact, patients with ARDS who demonstrate relatively normal alveolar fluid clearance have a better survival rate than patients who have a lower than normal clearance rates [159].

As a means of addressing the debate over fluid management strategies in ALI, the National Heart, Lung, and Blood

Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network conducted the Fluids and Catheters Treatment Trial (FACTT) [160]. 1,000 patients with established ALI and "optimized" hemodynamics were randomized to a conservative versus liberal strategy of fluid management using explicit protocols applied for 7 days. Patients in the liberal treatment arm received therapies targeting higher filling pressures (CVP of 10–14 mm Hg or pulmonary artery occlusion pressure of 14–18 mm Hg), whereas those in the conservative arm were provided therapies targeting lower filling pressures (CVP <4 mm Hg or pulmonary artery occlusion pressure of <8 mm Hg). Although there was no significant difference in the primary outcome of 60-day mortality, the conservative strategy resulted in ~7 l less fluid accumulated over the week, improved lung function (as measured by compliance), and shortened the duration of mechanical ventilation and intensive care all without increasing non-pulmonary organ failures or shock. It is noteworthy to mention that pulmonary artery catheter guided fluid management of patients with ALI did not improve hospital outcome and increased costs with no patient benefit with a year follow up study compared to patients who managed using central venous catheter [161]. This latter result is one of many, notable reasons that PA catheter use has virtually disappeared from practice. Nevertheless, a conservative fluid strategy, perhaps even with the use of diuretic provocation, along with appropriate caution to preserve organ perfusion and avoid metabolic derangement, should be instituted in patients with acute lung injury.

Corticosteroids

Therapeutic use of corticosteroids in ARDS (and septic shock) has been practiced since the early 1960s. This strategy is based on the pathophysiologic concept that the organ injury observed in these clinical syndromes is a manifestation of dysregulated inflammation. Because corticosteroids are potent anti-inflammatory agents, it has been postulated that they might attenuate organ injury associated with ALI/ARDS [34–36, 162–164]. Despite this sound hypothesis, a consistently beneficial effect of corticosteroids has been difficult to establish in ARDS studies, despite promising smaller trials [165–167].

Meduri and colleagues performed a randomized trial involving 24 patients with *unresolving* ARDS and observed that administration of corticosteroids to these patients had several benefits, including improvement in the Murray lung injury score, improvement in the PaO_2/FiO_2 ratio, decreased multiple organ dysfunction, and decreased mortality [163]. As a result, this approach was subjected to a larger, multi-institutional study called the Late Steroid Rescue Study or *LaSRS* Trial conducted by the ARDS Network [168]. In the study, 180 patients with ARDS of at least 7 days' duration received either methylprednisolone or placebo. Despite earlier success, no change in 60-day mortality (the primary end point) was found. In fact, methylprednisolone treatment was associated with significantly increased 60- and 180-day mortality rates among patients enrolled late: at least 14 days after the onset of ARDS. Methylprednisolone did increase the number of ventilator-free and shock free days during the first 28 days and was associated with an improvement in oxygenation, respiratory-system compliance, and blood pressure with fewer days of vasopressor therapy. As compared with placebo, methylprednisolone did not increase the rate of infectious complications but was associated with a higher rate of neuromuscular weakness. While these results support not using steroid therapy late (>7–14 days) in the course of ALI/ARDS, whether earlier administration is beneficial remains unclear.

Two additional small, randomized trials also examined the effects of corticosteroids in early hypoxemic respiratory failure attributable to either ARDS (91 subject trial) and severe pneumonia (46 subject trial) and reported significant improvements in hypoxemia and lung injury scores observed as early as days 1 and 2 in the treatment group as compared to placebo [169, 170]. Thus, based on the current literature, low dose corticosteroids (1 mg/kg/day) are often considered within the first week for patients with severe ARDS with daily assessment of lung compliance and oxygen requirement and continuing corticosteroids with patients who show improvement in those parameters after few days of therapy. Corticosteroids therapy should be assessed with consideration of weaning over few days to a week as soon as patient status permits. Importantly, intensivists must be aware of the risks of prolonged steroid therapy especially critical illness myopathy/neuropathy. Corticosteroid treatment has been shown to be associated with a number of neuromuscular complications, including myosin loss in critically ill patients with the duration of steroid treatment as a predominant risk factor [171].

Inhaled Nitric Oxide (iNO)

In the lung, nitric oxide (NO) is produced by a variety of cell sources. As discussed in the chapter on Pulmonary Hypertension, NO is produced by pulmonary vascular endothelial cells and is a powerful vasodilator. In the airways, NO originates from epithelial cells and adventitial nerve endings to induce smooth muscle relaxation. Activated macrophages can also produce large quantities of NO during activation typically directed towards pathogen eradication. In the normal pulmonary circulation, NO not only mediates vasodilation, but also opposes vasoconstriction, prevents platelet adhesion, controls smooth muscle growth and influences the composition of the extracellular matrix.

In patients with ALI/ARDS who are exposed to hypoxia, impaired endothelial NO production contributes to the increased vasomotor tone and vascular remodeling leading to sustained pulmonary hypertension. Inhaled NO (iNO) is preferentially delivered to ventilated airspaces to cause pulmonary vasodilation thereby redistributing blood flow to ventilated regions to improve matching of ventilation to perfusion (V/Q) resulting in improved arterial oxygenation (without causing concomitant systemic vasodilation) [172–178]. As such, iNO's effect on improving oxygenation and reducing pulmonary artery pressure should theoretically hold tremendous potential for reversing the pathophysiologic processes associated with ALI/ARDS.

Despite this theoretic potential, several randomized clinical trials in adults with ARDS from various causes have failed to show a survival benefit for iNO [179–183]. This has been disappointing since the vast majority of patients demonstrate improved oxygenation that can last up to 4 days. Nevertheless, a recently published meta-analysis of 12 randomized, controlled trials found no significant effect of iNO on hospital mortality, duration of ventilation, or VFD. iNO improved oxygenation until day four. Patients receiving iNO had an increased risk of developing renal dysfunction [184]. Likewise, in children with severe hypoxemic respiratory failure, although iNO at 20 ppm acutely improved oxygenation and lowered mean pulmonary artery pressure [185], there was no clear effect on survival [186]. As 35 % of children who initially did not respond to iNO did so after lung volumes were increased by HFOV, combined use of HFOV and iNO may provide more predictable improvement in children with ARDS [187], though this approach has yet to be tested in a formal study.

The failure of iNO to consistently demonstrate a longer-term, beneficial effect may be related to the conversion of NO to peroxynitrite (ONOO–), a toxic moiety to cellular respiration. Additional adverse and potential toxic effects of iNO include: methemoglobinemia, increased nitrogen dioxide, platelet inhibition, increased left ventricular filling pressures and rebound hypoxemia and pulmonary hypertension upon discontinuation [188, 189]. These side effects are mostly seen with higher concentrations of iNO (>20 ppm), prolonged usage and in the setting of high FiO_2.

Despite the lack of beneficial evidence, iNO is still often considered in children with persistent, life-threatening hypoxemia that fails common interventions, including HFOV, and often to achieve a temporary improvement in oxygenation while preparing for cannulation necessary for Extracorporeal Life Support (ECLS). Because of the substantial cost of iNO, most institutions now have policies regulating its use. Under typical guidelines, the common practice is to initiate iNO at ~10 ppm and titrate up until an improvement in oxygenation is observed. If there is no immediate (within 1 h) response, then protocol typically suggests gradually discontinuing its use. If there is a response, FiO_2 should be weaned to <0.6 and then iNO should be decreased to the lowest dose necessary to maintain the target oxygenation. Because of the potential safety concerns with longer term us as well as the lack of evidence of longer term benefit, iNO should not be used for longer than 3–4 days in ALI/ARDS unless underlying pulmonary hypertension is a known contributor to the pulmonary edema responsible for the persistent hypoxemia.

Extracorporeal Life Support (ECLS)

ECLS has been used for nearly 30 years as "rescue" therapy for pediatric acute respiratory failure; however, optimal use relies on appropriate patient selection. ECLS is considered when patients are refractory to previously mentioned therapies and yet, have potentially reversible lung injury. ECLS for severe ALI/ARDS uses either a veno-venous (VV) or veno-arterial (VA) circuit that removes blood from the patient and circulates it through a membrane oxygenator that both oxygenates blood and removes carbon dioxide thereby relieving the lungs of their gas exchange function and allowing the lungs to heal and repair without substantial positive airway pressure applied to them.

Current Extracorporeal Life Support Organization (ELSO) registry data (as of 2012) indicate that overall survival in the pediatric cohort has remained relatively unchanged over recent years at ~60 %, despite the modality being offered to increasingly medically complex children. VA ECLS is the most common mode of support in pediatric respiratory failure patients but recent years have witnessed a gradual increase in the use of VV ECLS with the advancement of technology for the circuit and cannulation catheters conferring significantly lower odds of injury as compared to VA support [190]. Clinical factors associated with mortality include: pre-cannulation ventilator support longer than 2 weeks and lower pre-cannulation blood pH [190]. The first factor stresses the need to institute ECLS before development of ventilator-induced lung injury as was demonstrated by several early studies in both pediatric [191, 192] and adult [193] patients. Due to the lower survival for patients with longer pre-ECLS ventilation times, accepted pediatric criteria for patient selection typically include mechanical ventilation of less than 7–10 days [191, 192].

In identifying patients to support on ECLS, most pediatric intensivists trend the oxygenation index (OI) [see above], the single measurement that characterizes oxygenation as a function of the intensity of ventilatory support. The OI is generally a reliable indicator of a patient's prospects for responding to a course of mechanical ventilation for ALI/ARDS, and serial measurements may assist the clinician in identifying those who may benefit from ECLS [113, 194]. The use of ECLS can be associated with significant risks,

mostly because of the need for systemic anticoagulation and large indwelling vascular devices including carotid arterial cannulation for VA support. Commonly reported complications include clots in circuit, hemorrhage at cannulation sites, and infection [195–197]. Given these risks, ECLS should be protocolized as practiced at all experienced medical centers and not considered for use in patients with contraindications to systemic anticoagulation (most commonly intracerebral hemorrhage) or for those who have been ventilated with high pressures for an extended time period (often >7–10 days) [198].

Experimental Therapies

Targeting Cytokine Production

Although a number of cells produce cytokines, the peripheral blood monocyte (in indirect lung injury) and the alveolar macrophage (in direct lung injury), appear to be principle sources. A number of agents have shown promise in *deactivating* these cells as a means of inhibiting cytokine production. Anti-inflammatory cytokines such as IL-10 [199] and TGF-β [200] and other pharmacologic agents such as ketoconazole [201, 202] and lisofylline [203] display potent monocyte deactivating properties and have been touted as potential therapeutic candidates in ARDS. IL-10 has demonstrated particular promise as it inhibits a variety of biological functions that are fundamental to the development and propagation of ARDS. IL-10 inhibits the synthesis of a number of cytokines [204], impairs the endothelial cell-leukocyte adhesion cascade [205], attenuates NF-κB activation [206, 207], increases the expression of endogenous cytokine antagonists (e.g. IL-1 receptor antagonist protein) [208], and destabilizes cytokine mRNA resulting in decreased translational expression [209]. In light of the multiple mechanisms by which IL-10 and other regulatory cytokines can regulate inflammation, exogenous administration of these molecules may be a potentially promising strategy, though this potential has not been realized in any studies performed to date.

Cytokine Neutralization

Because of the proximal role cytokines play in the inflammatory cascade associated with the onset of ALI/ARDS, investigators have attempted to directly block their activity either by antibody neutralization (e.g. anti-TNF-α antibody) or receptor blockade (e.g. IL-1Ra). While promising in preclinical trials, their ultimate clinical efficacy in human trials has been disappointing [84, 210]. There are many reasons for this observation, including inaccurate modeling of the human disease, poor identification of underlying risk factors, and limitations on statistical power analysis [211]. Other factors weighing against the success of this strategy include the fact that cytokines are likely to be increased prior to the clinical presentation of a critically ill patient. In addition, the cytokine cascade has been discovered to be highly redundant and interlinked, making it unlikely that inhibition of any single mediator will prove beneficial in the context of the clinical trials that are limited by size. One important and relevant exception to this approach has been the success observed with the use of the anti-TNF agent, etanercept, in idiopathic pneumonia syndrome (IPS) following bone marrow transplantation. Etanercept given early to children with this form of non-infectious ALI showed remarkable success in decreasing radiologic evidence of pulmonary edema that was associated with clinical resolution of ALI. These early phase trials were sufficiently promising to warrant a phase II/III trial sponsored by the national Bone Marrow Transplant Trials Network and Children's Oncology Group [212].

Modulating the Regulation of Lung Edema Clearance

As alluded to above, a critical component to maintaining homeostasis of lung function is the ability to continuously clear alveolar lining fluid. This process becomes more imperative in patients with ALI/ARDS in whom a progressive increase in interstitial fluid occurs early in the illness. Furthermore, because it has been observed that patients who have higher alveolar fluid clearance rates have improved survival as compared to patients with a lower than normal alveolar fluid clearance rate [159], it is critical to ascertain the important factors regulating this biology which continue to be defined [213, 214]. Resolution of alveolar fluid is known to be dependent on active ion transport by the lung epithelial cells [215]; thus, the most important factor that preserves the alveolar space from flooding is the resistance of the epithelial cells to injury. Even in the setting of endothelial barrier injury, preservation of epithelial function serves to keep extravasated fluid in the interstitium where lymphatic drainage can accommodate an increased need for fluid removal and sparing the air space from edema formation. In experimental settings of endothelial injury (e.g. systemic endotoxemia) not only is alveolar fluid clearance not impaired, it may in fact be augmented [216]. This observed increase in fluid clearance can be inhibited by amiloride and augmented by propranolol instillation. These data support the conclusion that this epithelial function is dependent on β-adrenergic agonist stimulation of Na+−K+−ATPase-dependent sodium transport [216]. Thus, if the integrity of the alveolar epithelium is maintained, fluid clearance can be augmented in the setting of interstitial and/or mild pulmonary edema although this process is modulated by various factors. For example, in

the context of raised left atrial pressure, fluid clearance is attenuated even with β-adrenergic stimulation because of excess production of atrial natriuretic factor (ANF) [217].

Depending on the trigger used to induce lung injury, numerous mechanisms augment the capacity for fluid transport. In hyperoxia, increased expression of Na+−K+−ATPase correlated to increased sodium transport in respiratory epithelial cells [218]. In experimental models of sepsis- or hemorrhagic shock-induced lung injury, increased clearance appears to be mediated by catecholamine-dependent stimulation of cAMP and subsequently sodium pump activity. Data has implicated multiple biochemical mechanisms including increased expression of, activity of, and/or epithelial membrane insertion of Na+−K+−ATPase, as well as increased expression of the epithelial sodium channel (ENaC) [219]. More recent data has suggested that glucocorticoids and other stress hormones may modulate expression of ENaC and/or Na+−K+−ATPase resulting in increased fluid clearance rates [220].

With this mechanistic understanding, researchers tested the hypothesis that agonist stimulation of this clearance mechanism would reduce pulmonary edema and improve lung compliance and reduce mortality in ALI/ARDS. The β-agonist lung injury trial (BALTI) was designed to examine this potential and recruited 40 patients in a phase II study that compared a 7-day intravenous infusion of salbutamol to placebo. While the trial showed significant reductions in extravascular lung water (measured by single indicator thermodilution), reduced alveolar capillary leak, and improved pulmonary mechanics in the group given salbutamol; no difference in 28-day mortality was observed [221]. Disappointingly, subsequent studies have continued to demonstrate this trend of no benefit in adult subjects. The BALTI-2, multicenter trial of 1,334 patients similarly tested the effect of a 7-day continuous infusion of salbutamol to improve 28-day mortality versus placebo. The study was stopped at the second interim analysis of the first 273 patients because of a significant increase in mortality in the intravenous salbutamol arm (risk ratio for 28-day mortality was 1.47 (95 % CI 1·03–2·08)). Salbutamol was poorly tolerated because of tachycardia, lactic acidosis, and arrhythmias [222–224]. Similarly, the Acute Lung Injury (ALTA) Trial of Aerosolized salbutamol, (282 randomized patients) was stopped because the primary endpoint of VFD had crossed predefined futility boundaries and clinical outcomes were worse in the salbutamol group, particularly in the most severely ill patients [222, 225]. Given these disappointing results despite the logic behind the pharmacologic approach, one has to consider that β-agonists may have a non-beneficial effect in the setting of ALI. As an example, in an oleic acid lung injury model, β_2-agonists increased cardiac index, and consequent microvascular pressure, thereby, aggravating capillary–alveolar macromolecular leakage [226]. Furthermore, β_2-agonists may have a direct effect on cardiovascular morbidity in patients with risk factors for cardiovascular disease, particularly with the high incidence of drug-related supraventricular tachycardia (SVT) observed in many studies [227]. It is therefore possible that some patients experienced adverse cardiovascular events, including occult cardiac ischemia during tachycardia or SVT. Finally, there was an observed trend towards a higher cumulative fluid balance in the albuterol arm in ALTA that may reflect adverse activation of the renin-angiotensin-aldosterone system, a recognized effect of albuterol [228].

While these results dampen enthusiasm for the use of albuterol in the treatment of established ALI, questions remain about the role of β-agonists in the prevention of pulmonary edema and ALI. Of note, the majority of preclinical studies that demonstrated a benefit of using β-agonists for lung edema, did so as a pre-injury treatment strategy. It was also noted that following prolonged hypovolemic shock or high tidal volume ventilation, there is failure of β_2-adrenergic receptor-mediated augmentation of alveolar fluid clearance [215, 229]. Two human studies further support the prophylactic use of β-agonists. Sartori and coworkers found that prophylactic salmeterol reduced the development of high-altitude pulmonary edema [230]. In addition, in patients undergoing lung resection, Licker and colleagues found that aerosolized albuterol reduced pulmonary edema and improved oxygenation [231]; together these data support the potential role of β-agonists in a prophylactic manner. Several studies are ongoing to investigate this possibility. The BALTI prevention Trial, a study of inhaled salmeterol as a prophylactic treatment given to patients undergoing elective transthoracic oesphagectomy to prevent the development of acute lung injury completed patient recruitment in June 2011 and will report the results in 2013 [231]. The Beta-agonists for Oxygenation in Lung Donors (BOLD) is designed to test the effect of nebulized albuterol on oxygenation and lung transplantation rates in brain-dead organ donors [232]. When the outcomes of these trials are known, a more complete understanding of the indications for β-agonists to stimulate active clearance of pulmonary edema is ALI may become clear.

In addition to β–agonists, there are a number of other factors that can upregulate the rate of fluid clearance in the injured lung. Thus, future therapies aimed at restoring and/or augmenting normal alveolar fluid clearance may hold the promise of more specifically managing the pulmonary edema associated with ARDS. Other agents that have been examined include certain growth factors (e.g. keratinocyte growth factor) that have been shown to increase fluid clearance and synergize with β-agonist effects [233]. However, inhibition by atrial naturietic factor (ANF), β-receptor desensitization, or down-regulation of endogenous inhibitors of cAMP may all impact on the eventual clinical utility

of this approach. Finally, future directions may consider application of gene therapy as pre-clinical studies have shown that over-expression of the α and β-subunits of Na+–K+–ATPase can decrease lung edema formation in mouse models [234].

Blocking Adhesion Molecules

As our understanding of the role of adhesion molecule expression has unfolded, the goal of anti-adhesion molecule therapy has become an intriguing pursuit. Numerous pre-clinical animal trials have demonstrated that anti-adhesion molecule antibodies, such as anti-ICAM-1 [235, 236], anti-E-selectin [237], anti-L-selectin [238], and anti-P-selectin [236, 239] were able to inhibit neutrophil accumulation in the lung and subsequent tissue injury. Despite these encouraging results, to date, no human trials have successfully used anti-adhesion molecule strategies.

It is important to recall that the leukocyte-adhesion molecule cascade is a highly conserved and adaptive host response necessary for pathogen clearance as evidenced by individuals who suffer recurrent bouts of infection as a result of leukocyte adhesion deficiency (LAD) syndromes 1 and 2. The molecular basis of the defects associated with LAD-1 and LAD-2 are absent expression of the β-integrins (the counter-receptors for ICAM-1) and absence of sialyl-Lewis X (the carbohydrate ligand for selectins), respectively [240, 241]. In light of these observations from *nature's* experiment, investigators must approach the strategy aimed at disrupting this cascade carefully, especially in the setting of an invading pathogen.

Blocking of Chemokines or Chemokine Receptors

As mentioned above, chemokines appear to play a central role in the activation and recruitment of neutrophils to the lung in ALI/ARDS and as a result chemokines have been therapeutic targets in many inflammatory states including ALI/ARDS. Monoclonal antibodies directed against IL-8 have been shown to decrease neutrophil influx and tissue injury in a number of animal models of lung injury [242–244]. Because of these encouraging pre-clinical results, anti-IL-8 antibody had been considered for testing in human ARDS, however, antigen-antibody complex formation between IL-8 and anti-IL-8 seem to trigger an increased inflammatory response and has been associated with higher mortality in preclinical studies [245, 246]. Thus, whether this approach will continue to have merit is debated and instead, alternative approaches to attenuating the effects of chemokines have been suggested. Besides antibody neutralization, targeting the chemokine receptors has become a novel therapeutic target for clinical investigators [247]. As a result, it is possible that chemokines may be successfully inhibited in both a selective and effective manner in the near future.

Application of Genomics to ALI/ARDS

ALI/ARDS is a highly heterogeneous disease process with respect to both etiology and outcome. Variable outcomes are particularly frustrating to the pediatric intensivist who is faced with the reality that one patient with ARDS may survive, while another patient of similar age, having an identical trigger with seemingly similar co-morbidities may die. These highly divergent outcomes may at times be explained by management strategies; however, recent progress in genomics suggests that part of the basis of these variable outcomes may relate to a genetic background that predisposes an individual to a more severe manifestation of ALI/ARDS.

The evolving field of genomics holds the promise of elucidating a genetic predisposition to ARDS (and other diseases) in critically ill children [248–250]. While no clear ARDS gene or marker has been established to date, there is good evidence that point mutations, so-called single nucleotide polymorphisms (SNPs), in surfactant protein genes can impart a phenotype characterized by the propensity to develop interstitial lung disease and/or ARDS [251, 252]. In addition, polymorphisms of cytokine genes have been associated with increased mortality in sepsis, a primary cause of indirect ALI [253, 254]. Because the development of sepsis is so closely linked, clinically and pathophysiologically, to the development of ARDS, is expected that similar associations will be found between cytokine gene polymorphisms and the course of ARDS.

Additional clinical investigations into "candidate" ALI/ARDS genes have included an examination of the role of aquaporin (AQP). Aquaporins play a key role in water transport in several tissues including the lung. AQP1, is expressed on apical and basolateral membranes of pulmonary microvascular endothelial cells of the lung and has been implicated in the regulation of lung vascular permeability [255]. In animal models of lung injury, AQP1 is substantially increased whereas null mutations in AQP1 in mice has been associated with protection from the development of lung edema fluid [256]. Although, it was interesting to note that AQP1–/– mice were not protected from acute lung edema formation triggered by an inflammatory stimulus [257, 258]. Work from the HopGene Program in Genomics identified 2 SNP's in the 3′-untranslated region of the AQP1 gene http://www.hopkinsgenomics.org/ali/abstracts/aqp1.html). In these studies, a higher proportion of the C allele substitutions at positions 525 and 578 was

found in patients with sepsis as compared to controls. Taken together, these data support the concept that AQP1 plays a role in regulating pulmonary vascular permeability. Similar efforts to link polymorphisms in selected genes with ARDS by this group are summarized on their web site (http://www.hopkins-genomics.org/ali/ali_snp.html).

Important tools for the application of genomics to the study of ARDS include the recent sequencing of the human genome, evolution of microarray technology, and expansion of powerful bioinformatics all the increase the promise of characterizing the host predilection to ALI/ARDS at the genomic level. These genome-wide association studies (GWAS) are eagerly awaited as they hold the promise of increasing our understanding of ARDS with that hope that individual patients responses can be more thoroughly characterized such that therapies can be more specifically tailored to the needs of the individual patient.

Conclusion

ALI/ARDS continues to be a major cause of mortality in pediatric critical care medicine. It is clear that cytokines contribute to this pathophysiologic state via receptor-mediated signaling pathways that effect target cell responses. The mainstay of conventional therapy is directed at reversing the ventilation-perfusion mismatch that arises from pulmonary edema and causes significant hypoxia. Non-conventional approaches are commonly used, however, with little large-scale clinical data to support their effectiveness. It is hoped that further application of molecular biology tools and better-designed clinical trials in ALI/ARDS will not only improve our understanding of this biological response but also identify additional novel therapeutic targets or strategies. Although preclinical data have demonstrated the amelioration of lung injury when targeting inflammatory-related pathways, agents that have been tested in humans thus far have proven ineffective in human trials. It is hoped that further understanding of the fundamental biology, improved identification of the patient's inflammatory state, application of therapies directed at multiple sites of action, and further insight derived from genomic studies may ultimately identify enhanced prove beneficial for patients suffering from ALI/ARDS.

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Mechanical Ventilation

8

Alik Kornecki and Derek S. Wheeler

Abstract

Mechanical ventilation is perhaps the cornerstone of contemporary critical care. Indeed, the history of critical care medicine, especially pediatric critical care medicine, is inextricably tied with that of mechanical ventilation. The first Pediatric Intensive Care Units (PICUs) arose during the polio epidemic with negative pressure ventilation (the so-called "iron lung"). However, while mechanical ventilation is clearly life-sustaining, one should remember that it is only a supportive modality and does not reverse the underlying disease process. Moreover, mechanical ventilation can be associated with a number of adverse effects, which in turn can be associated with significant morbidity and risk of mortality. A thorough understanding of the physiologic basis of mechanical ventilation is therefore essential to providing safe, effective care in the PICU.

Keywords

Mechanical ventilation • Pressure-control • Volume-control • Modes of ventilation • Respiratory physiology • Weaning • Cardiorespiratory interactions • PEEP

Introduction

Mechanical ventilation is perhaps the cornerstone of contemporary critical care. Indeed, the history of critical care medicine, especially pediatric critical care medicine, is inextricably tied with that of mechanical ventilation. The first Pediatric Intensive Care Units (PICUs) arose during the polio epidemic with negative pressure ventilation (the so-called "iron lung") [1]. However, while mechanical ventilation is clearly life-sustaining, one should remember that it is only a supportive modality and does not reverse the underlying disease process. Moreover, mechanical ventilation can be associated with a number of adverse effects, which in turn can be associated with significant morbidity and risk of mortality. A thorough understanding of the physiologic basis of mechanical ventilation is therefore essential to providing safe, effective care in the PICU.

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Physiology of Mechanical Ventilation

Respiratory System Equation of Motion

Conceptually, the respiratory system can be modeled as a balloon that is connected to a tube. The forces required to inflate the balloon must overcome an elastic element (the balloon in the box) and a resistive element (the resistance in the tube). Classic respiratory mechanics must obey the

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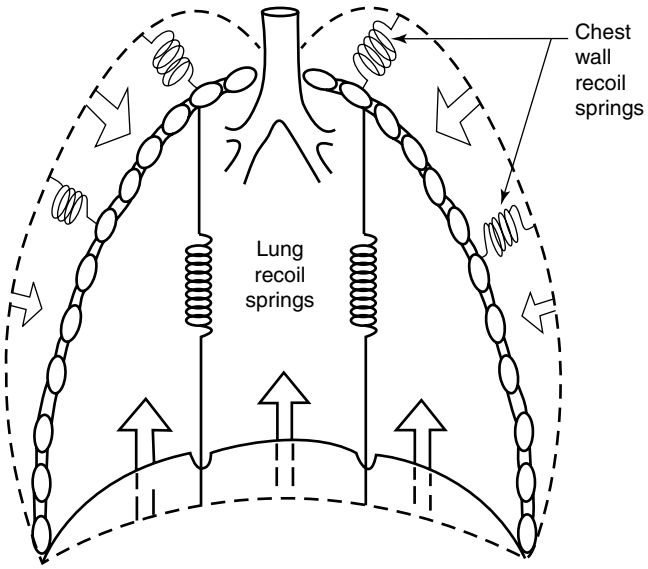


Fig. 8.1 Opposing forces in the respiratory system. Elastic recoil is the tendency of elements in the chest wall and lungs that are stretched during inspiration to snap back or recoil (*arrows*) to their original state at the end of expiration. At this point (at FRC or resting volume), the "springs" are relaxed, and the structure of the rib cage allows no further collapse. Opposing forces of the chest wall and lung balance out, and intrathoracic and airway pressures become equal (this further defines FRC) (Reprinted from Harris and Wood [2])

laws of Newtonian physics. The relationship between pressure, volume, and flow is therefore modeled by the equation of motion. Just like the balloon model, in order to "inflate" the lungs, the total pressure applied must exceed the opposing elastic ($P_{elastic}$) and resistance forces ($P_{resistance}$) of the lungs, chest wall, and conducting airways (Fig. 8.1). The total pressure applied to the respiratory system (P_{RS}) of a patient on mechanical ventilatory support is the sum of the pressure generated by the ventilator measured at the airway (P_{AWO}) and the pressure developed by the respiratory muscles (P_{MUS}).

$$P_{RS} = P_{AWO} + P_{MUS} = P_{elastic} + P_{resistance} \tag{8.1}$$

Note that during spontaneous breathing, P_{AWO} is equal to zero, as all of the pressure required to generate flow through the respiratory system is provided by the respiratory muscles. Conversely, if a patient is on full mechanical ventilatory support, P_{MUS} is equal to zero, as all of the pressure required to generate flow through the respiratory system is provided by the ventilator.

The total pressure applied to the respiratory system (P_{RS}) must exceed the opposing elastic and flow-resistive forces of the respiratory system. Recall that the normal tendency of the elastic forces of the lungs will result in lung collapse, while the normal tendency of the elastic forces of the chest wall is to expand. At functional residual capacity (FRC), these elastic forces are perfectly opposed. These elastic forces (also referred to as elastic recoil pressure, or elastance) reflect the relative stiffness of the respiratory system (i.e., the tendency of the respiratory system to return to its resting shape after deformation by an external force, in this case P_{RS}). Elastance (E) is the change in pressure (ΔP, or dP) for a given change in volume (ΔV, or dV).

$$E = dP/dV \tag{8.2}$$

The total elastance of the respiratory system is the sum of the elastance of the lungs and of the chest wall (the lungs and chest wall behave like elements in series). Elastance is the reciprocal of compliance. Practically, compliance is a measure of the distensibility of the respiratory system. It is therefore the change in volume (dV) for a given change in pressure (dP):

$$C = 1/E = dV/dP \tag{8.3}$$

Note that under most conditions, there is a linear relationship between pressure and volume (Fig. 8.2), such that compliance is the slope of the pressure-volume curve.

The resistive forces in the respiratory system include airways resistance (R), respiratory system inertance (I), and tissue resistance. Resistance is analogous to Ohm's Law of electricity, such that resistance is determined by the change in pressure (dP) over flow.

$$R = dP/\dot{V} = dP/\left(dV/dt\right) \tag{8.4}$$

where R is resistance, dP is the pressure gradient, and $\dot{V}$ is flow (i.e. the change in volume over time). Ordinarily, under most physiologic conditions, tissue resistance makes a very small contribution to these resistive forces and is therefore usually ignored. Inertance (I) is a measure of the pressure gradient required to cause a change in flow-rate with time, i.e. pressure divided by acceleration.

$$I = dP/d\ddot{V} = dP/d^2\ V/dt^2 \tag{8.5}$$

where I is the inertance, dP is the change in pressure, $d\ddot{V}$ is the change in flow over time (i.e., acceleration of the gas, or d^2V/dt^2). Inertance is negligible during quiet, passive breathing and during most forms of mechanical ventilation (with the notable exception, perhaps of high frequency ventilation). It is therefore frequently ignored.

Compliance therefore relates pressure to volume, resistance relates pressure to flow, and inertance relates pressure to linear acceleration. Putting all of these concepts together, the equation of motion for the respiratory system therefore becomes:

$$P_{RS} = \left(E \times V\right) + \left(R \times \dot{V}\right) + I = \left(V/C\right) + \left(R \times \dot{V}\right) + I \tag{8.6}$$

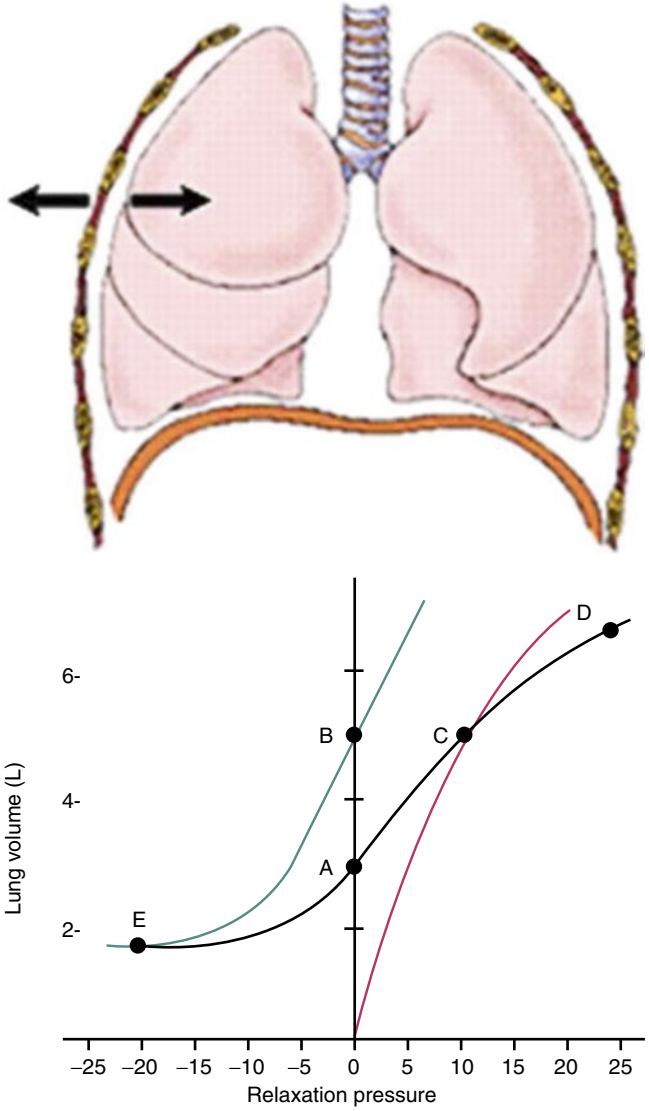


Fig. 8.2 Compliance of the lung, chest wall, and respiratory system. *Top*: diagram of the lung and chest cage. *Arrows* show the movement of the chest cage and lung. *Bottom*: Separate relaxation curves for the lung (*right*) and chest cage (*left*) along with the combined lung-chest cage relaxation curve (*middle*). The combined lung-chest cage curve is the algebraic sum of the separate lung and chest cage curves. The slope of each relaxation curve corresponds to the compliance for the structure(s). At end expiration (*point A*), recoil or relaxation pressure for the lung and chest cage alone are equal but opposite. At this point, lung volume corresponds to FRC. As additional air volume is inhaled into the lung, the lung is stretched further and exhibits a greater recoil pressure. At the same time, the chest cage is less compressed, so its negative recoil pressure diminishes as it approaches its equilibrium volume. When a slightly larger air volume is inhaled, the chest cage reaches its equilibrium volume (0-mmHg relaxation pressure, *point B*), and the lung and lung-chest relaxation curves intersect (*point C*). Thereby, at this lung volume, all measured relaxation for the lung-chest cage system is from the lung because the chest cage is at its equilibrium volume (*point B*), or the volume it would assume if the lung were not present. If an even greater air volume is inhaled (*point D*), both the lung and chest cage are stretched beyond their equilibrium volumes. Note that the compliance curve for the combined lung-chest cage becomes more flattened (less compliant) at this point because the lung and chest cage are both tending to recoil toward smaller equilibrium volumes. If the total lung-chest cage system is returned to resting end expiration (*point A*) and air is expelled, a negative relaxation pressure results for both the chest cage and combined lung-chest cage (*point E*). At this point, the chest cage is compressed as more and more air is expelled, with the negative recoil pressure resulting from the tendency of the chest to expand toward its equilibrium volume (*point B*). At the same time, the lung contributes little positive relaxation pressure because it is close to its equilibrium volume (i.e., 0-ml volume) because it is stretched very little (Reprinted from DiCarlo [3]. With permission of the American Physiological Society)

Note also that the equation of motion can be re-written as:

$$P_{RS} = E \times V + \int dV/dt + \int d^2V/dt^2 \quad (8.7)$$

Given that the inertance is negligible, the "I" term falls out. Substituting 1/C for the "E" term (compliance is the inverse of elastance), the respiratory equation of motion becomes:

$$P_{RS} = V/C + \int dV/dt \quad (8.8)$$

Children Are Not Small Adults!

While ventilation has been extensively investigated and characterized in preterm neonates and adults, there has been relatively few laboratory investigations and prospective clinical investigations of mechanical ventilation in infants and/or older children. As a result, age-based guidelines for the use of conventional mechanical ventilation in pediatric patients have not been well-established. Indeed, the recommendations for mechanical ventilation in children have been extrapolated from adult data [4]. Compared to adults, pediatric patients demonstrate a spectrum of lung and chest wall development. Maturation in the human lung continues well after the neonatal period until between 2 and 8 years of age [5]. Acute respiratory failure is one of the most common reasons that children are admitted to the PICU. The unique developmental differences between children and adults contribute to this prevalence and significantly impact the management of critically ill children [6–9]. For example, infants and young children have fewer alveoli compared to adults (approximately 20 million alveoli after birth to 300 million alveoli by the age of 8 years) [10–12]. The size of each individual alveolus is also smaller in children (150–180 μm diameter versus 250–300 μm diameter) [13]. Together, these two anatomic differences markedly decrease the surface area available for gas exchange by approximately 8 years of age.

The airways enlarge both in length and diameter with age. However, growth of the distal airways lags behind that of the

proximal airways during the first 5 years of life, accounting for the increased peripheral versus central airways resistance in children relative to adults [14]. Resistance is inversely proportional to the radius of the airway to the fourth power (by Hagen-Poiseuille's Law). Therefore, an equivalent reduction in airway caliber (e.g. by mucus, bronchospasm, edema, etc) in a child versus an adult will result in a greater relative decrease in the total cross-sectional area of the airway, as well as a greater relative increase in resistance. In addition, the cartilaginous support of the peripheral airways is less well developed, increasing the risk of dynamic compression with high expiratory flow rates (e.g. as occurs during crying, coughing, or respiratory distress). Finally, the pathways of collateral ventilation (e.g., pores of Kohn) are not fully developed in young children. These pathways allow alveoli to participate in gas exchange, even in the presence of an obstructed distal airway. Collectively, these important anatomic differences significantly increase the risk of atelectasis in children [7, 15].

The developmental influences on respiratory mechanics are also critically important [16]. The ribs are more horizontally aligned in young infants and children compared to adults, which makes it difficult to generate a greater negative intrathoracic pressure in the presence of poor lung compliance. The lung matrix of a neonate contains only small amounts of collagen. The elastin-to-collagen ratio changes during the first months and years of life and affects lung stiffness (i.e. elastance) and elastic recoil. Similarly, the infant's chest wall is soft and compliant, providing little opposition to the natural recoil (deflating tendency) of the lungs. These changes in elastic recoil pressure for both the lung and chest wall result in a lower functional residual capacity (FRC) in children versus adults [17], which may even approach the critical closing volume of the alveolus in neonates and infants (Fig. 8.3). In order to generate the same tidal volume per kg body weight, infants must perform a greater amount of work compared to adults, which is clinically manifest as severe retractions due to the highly compliant rib cage and contraction of the diaphragm during negative pressure generation [19]. Retractions represent a significant waste of energy – therefore, some infants will stop breathing from fatigue when faced with these excessive respiratory demands, which has been confirmed through electromyography performed in fatiguing infants who become apneic in the face of increased work of breathing [20, 21].

Ventilation-perfusion mismatching is one of the most common causes of hypoxemia in the PICU. As discussed in previous chapters of this textbook, due to the effects of gravitational forces, both ventilation and perfusion decrease significantly from the base (or dependent regions) of the lung to the apex (or non-dependent regions), though perfusion decreases to a greater degree compared to ventilation (Fig. 8.4). The regional differences in both ventilation and perfusion are greatly influenced by gravity. Intrapleural

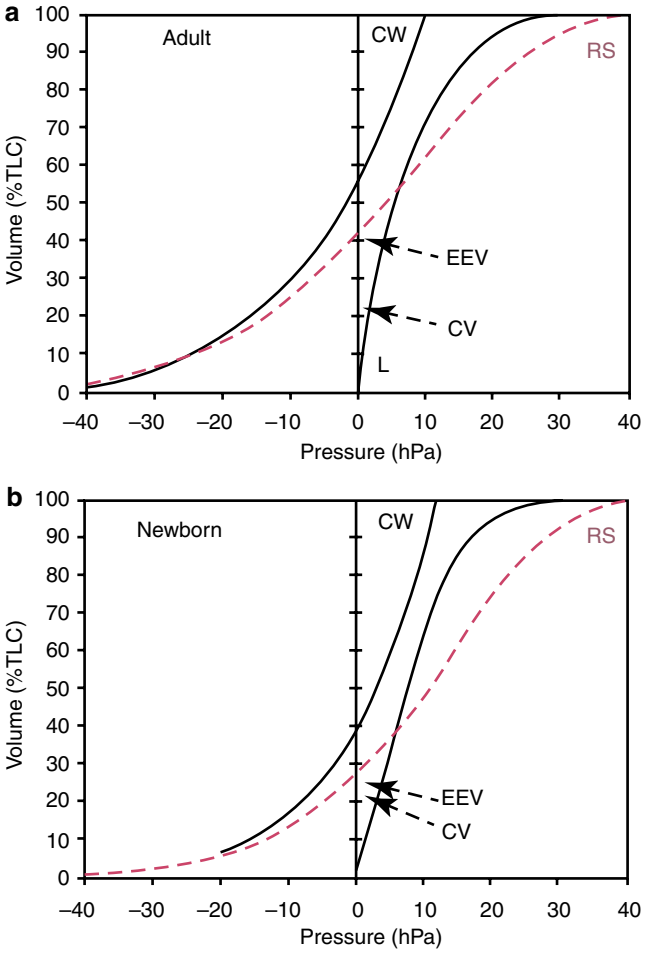


Fig. 8.3 Changes in total respiratory system compliance (*RS*), chest wall compliance (*CW*), and lung compliance (*L*) as a function of age. Two theoretical pressure-volume curves are provided for comparison – the *top curve* shows a pressure-volume curve in an adult, while the *bottom curve* shows a pressure-volume curve in a neonate. The normal elastic properties of the lung and chest wall are such that there is an inward elastic recoil of the lung (lung tends to collapse) and outward elastic recoil of the chest wall (chest wall tends to expand). At functional residual capacity (FRC) (depicted as the volume at which the airway pressure on the respiratory system pressure-volume curve is zero, EEV), these forces are in equilibrium. Note that the FRC is lower in children compared to adults. Also note that at FRC, the corresponding airway pressure on the chest wall curve is negative (i.e. at this volume, the natural tendency of the chest wall is to expand). The chest wall is in equilibrium (i.e. volume at which the corresponding airway pressure is zero) at a higher percentage of total lung capacity (TLC) in adults compared to children (due to increased chest wall compliance in children). Finally, also note that the closing volume (depicted as CV) approaches FRC in children compared to adults (Adapted from West [18]. With permission from John Wiley & Sons, Inc.)

pressure (P_{PL}) is less negative in the dependent regions of the lung (the base). Alveolar pressure (P_A) remains relatively constant. The transpulmonary pressure (P_L), or alveolar distending pressure, is therefore lower in the dependent regions of the lung:

$$P_L = P_A - P_{PL} \tag{8.9}$$

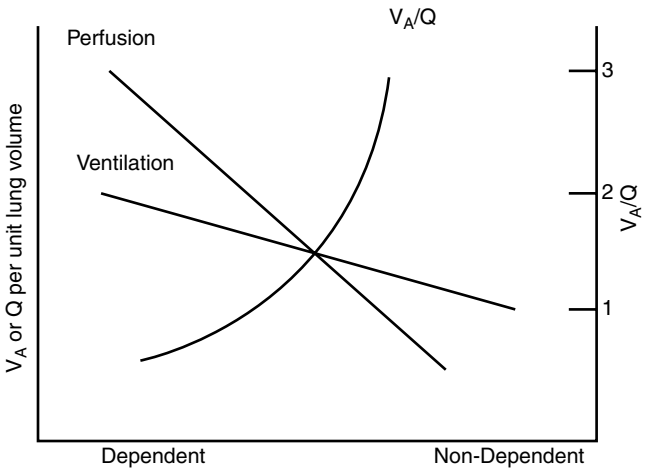


Fig. 8.4 Differential distribution of ventilation (V_A), perfusion (Q), and ventilation-perfusion ratio in the lung. The dependent lung regions preferentially receive better ventilation and perfusion compared to the non-dependent lung regions. However, the perfusion gradient is much steeper than the ventilation gradient, such that the ventilation-perfusion ratio is higher in the non-dependent (apex) regions compared to the dependent (base) regions (Adapted from West [18]. With permission from John Wiley & Sons, Inc.)

At functional residual capacity (FRC), the alveoli in the dependent regions of the lung will then tend to have a lower volume. At the apex, or non-dependent regions of the lung, the converse is true (higher transpulmonary pressure due to a more negative intrapleural pressure, leading to higher volumes). The higher volume alveoli in the non-dependent regions are therefore on a flatter portion of the compliance curve (i.e., less compliant). This creates a seeming paradox in the normal lung, where the lower volume alveoli at the base will have a greater compliance and are more easily inflated compared to the higher volume alveoli at the apex, because they are situated on the steeper segment of the pressure-volume curve [22]. These gravitational differences also result in a greater degree of lung perfusion at the base (dependent regions), compared to the apex (non-dependent regions).

Note also that the regional differences in ventilation also depend upon lung volumes. At FRC, the dependent lung regions are preferentially ventilated. At lower lung volumes (e.g., residual volume, RV, the volume left in the lungs at the end of a maximal forced expiratory effort), the converse is true. Dynamic compression of the airways, due to the effects of a maximal, forced expiratory effort (which often generates a positive P_{PL}), occurs in the lower (dependent) regions of the lung first. This leads to gas-trapping within the alveoli in the lower (dependent) regions of the lung. The alveoli in the non-dependent regions will therefore be on a much steeper portion of the compliance curve (i.e., increased compliance). Together, these two phenomena lead to preferential ventilation of the non-dependent lung regions first (in contrast to the situation at FRC).

Pulmonary edema and lung inflammation in critically ill children (and adults, for that matter) will exaggerate the gravitational effects on the intrapleural pressure gradient discussed above. As P_{PL} exceeds P_A, closure of lung units in dependent lung regions will occur during normal breathing. This inverts the normal distribution of ventilation causing the apex (or non-dependent region) of the lung to receive improved ventilation. These effects are compounded by the fact that the patients have a lower lung volume (recall the discussion above). While there are significant changes in the distribution of alveolar ventilation, perfusion is less affected. In other words, perfusion continues to be greatest at the base (or dependent region) of the lungs, leading to significant ventilation/perfusion mismatch in the dependent regions of the lungs. Chest CT and electrical impedance tomography (EIT) studies have elegantly shown the regional differences in lung consolidation in patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) [23–31].

There appears to be some important differences in children versus adults with regards to regional differences in ventilation (note that these studies were performed in spontaneously breathing patients). For example, in adults with unilateral lung collapse, ventilation and perfusion are better matched if patients are positioned with the "good lung" in a dependent position ("good lung down"). Conversely, in children with unilateral lung collapse, ventilation and perfusion are better matched if patients are positioned with the "good lung" in a non-dependent position ("bad lung down") [32–35].

Finally the ratio of lung volume to body weight is not constant and varies with development. In humans this ratio increase significantly with age in the first 2 years of life; therefore, when V_T is corrected to body weight, a smaller fraction of lung volume is inflated in young infant compared to older child. On this basis alone, adult guidelines for lung protective ventilation are unlikely to be applicable to the infant and young child.

The aforementioned developmental differences in lung pathophysiology may have significant implications on the management of critically ill children with acute respiratory failure. As an example, based upon the ARDS Network trial of low tidal volume ventilation [36], the current recommendation is to target a tidal volume of (V_T) of 6 mL/kg predicted body weight in critically ill adults with ALI/ARDS. There have been few studies on low tidal volume ventilation in critically ill children, though most authorities recommend such an approach [4, 37], based largely upon extrapolation from adult data. In addition, a low tidal volume ventilation strategy has been used in several multi-center, randomized, controlled trials in critically ill children with acute lung injury with acceptable results [38–40]. Adkins and colleagues [41] reported that the lungs of young, newborn rabbits were more susceptible to the development of ventilator-induced lung injury (VILI) due to increased lung and chest wall compliance and larger distending volumes at high peak airway pressures compared to adult rabbits.

However, several studies using a rodent model of VILI suggest that newborns may not be as susceptible to the adverse effects of VILI compared to adults [42–44].

A single center, retrospective study compared the mortality between critically ill children with ALI from a time period before low V_T ventilation was prevalent (1988–1992) with the current era, when the use of low V_T ventilation has become more established (2000–2004) [45]. Children in the more recent era had a lower mean V_T/kg (8.1 ± 1.4 vs. 10.2 ± 1.7, $p < 0.001$) and higher positive end-expiratory pressure (PEEP) (7.1 ± 2.4 vs. 6.1 ± 2.7, $p = 0.007$), with resultant lower peak inspiratory pressure (PIP) (27.8 ± 4.2 vs. 31.5 ± 7.3, $p < 0.001$) and higher $PaCO_2$ (47.2 ± 11.8 vs. 37.0 ± 5.0, $p < 0.001$). More importantly, children in the more recent era had a significantly lower mortality (21 % vs. 35 %, $p = 0.04$) and more ventilator-free days (16.0 ± 9.1 vs. 12.7 ± 10, $p = 0.03$). A recently published study in China also suggested that the use of lower tidal volumes are associated with better outcomes [46]. Conversely, a follow-up study failed to show a relationship between the tidal volume in the first 7 days and mortality [47]. Erickson and colleagues [48] published the results of a prospective, observational study of ALI which included nearly all of the PICUs in Australia and New Zealand. In contrast to the results above, increased tidal volumes were associated with decreased mortality. Finally, a single-center, retrospective study showed an association between higher V_T and increased ventilator-free days. In this study, 85 % of the children were ventilated with a target VT between 6 and 10 mL/kg, though a higher VT within this range was associated with increased ventilator-free days [49]. Regardless of what conclusions are to be made from these discrepant data, the main point that must be emphasized is that heedless extrapolation of adult data to critically ill children should be avoided, given the differences in respiratory physiology in children versus adults.

Indications for Mechanical Ventilation

The need for mechanical ventilatory support is one of the most common reasons for admission to the PICU, and acute respiratory failure is by far the most common indication for mechanical ventilation [50–53]. Although explicit indications exist (Table 8.1), they are not well validated. Thus, the decision to institute mechanical ventilation is made by the physician at the bedside on clinical grounds, and takes into consideration the underlying condition, the likely course of the disease, and the potential response to medical treatment. The indications for tracheal intubation (e.g. airway protection, relief of airway obstruction) are not the same as for mechanical ventilation and are discussed elsewhere in this textbook. However, children who require tracheal intubation will usually require mechanical ventilatory support, because of reduction in respiratory drive associated with sedation, the perceived benefits of positive end-expiratory pressure (PEEP), and the need to counter the resistance to airflow offered by the tracheal tube. In general, institution of mechanical ventilation is indicated when the patient's spontaneous ventilation is threatened or not adequate to sustain life.

Table 8.1 Indications for mechanical ventilation

Respiratory failure
Pump failure
Chest wall dysfunction (*e.g.* flail chest)
Neuromuscular disease
Central nervous dysfunction (decrease in respiratory drive)
Congenital (*e.g.* Ondine's course)
Acquired (*e.g.* trauma, drugs, infectors)
Pulmonary disease
Ventilation/perfusion mismatch (*e.g.* pneumonia)
Pulmonary shunt (*e.g.* acute respiratory distress syndrome)
Reduction in functional residual capacity
Others
Support an intubated patient (*e.g.* patient intubated for airway protection)
Decrease work of breathing and afterload
Optimized carbon dioxide levels (*e.g.* head trauma with increase in intracranial pressure)

Children usually require mechanical ventilation because of acute respiratory failure (or impending respiratory failure), which occurs when the system fails to meet the body's requirements in terms of oxygenation (acute hypoxemic respiratory failure) and/or elimination of carbon dioxide (acute ventilator failure). Acute respiratory failure may occur as a result of primary lung disease (e.g. reduction in functional residual capacity or compliance, worsened ventilation-perfusion mismatch) or pump dysfunction (e.g. reduced central drive, muscle disease). Beyond these pulmonary indications, mechanical ventilation may also be instituted in order to improve left ventricular function in case of heart failure or to optimize CO_2 in the case of increased intracranial pressure. As mechanical ventilation is not without complications, the goal should be to apply it only when necessary and with minimal injury to the lungs and maximal comfort to the patient. In other words, the goals of mechanical ventilation are to provide adequate oxygenation and ventilation (which necessarily includes maintaining alveolar recruitment and patient-ventilator synchrony), while minimizing alveolar overdistension, auto-PEEP (see below), and oxygen toxicity (i.e., using the lowest possible F_{IO2}).

Non-invasive Mechanical Ventilation

The interface between the ventilator and the patient may be classified into two categories: invasive and non-invasive. Invasive ventilation uses a tracheal or a tracheostomy tube, or for a limited period of time during a general anesthetic, a

Table 8.2 Adverse effects of invasive positive pressure mechanical ventilation

Respiratory
Upper airways
Nasal trauma
Nasopharyngeal and pharyngeal trauma
Laryngeal trauma – vocal cord fixation/paralysis
Subglottic edema/stenosis
Lower airways
Air-leak
Pneumothorax
Pneumomedistinum
Pulmonary interstitial emphysema
Atelectasis
Ventilation-associated Respiratory Infections (VARI)
Ventilator-associated Pneumonia (VAP)
Ventilator-associated Tracheobronchitis (VAT)
Nosocomial Sinusitis
Ventilation associated lung injury
Cardiovascular
Decrease venous return
Increase pulmonary vascular resistance
Central nervous system
Increase intracranial pressure
Renal
Decrease urine output (direct and indirect effect)

Table 8.3 Potential applications for noninvasive positive pressure ventilation (NIPPV) in children

More common
Nocturnal central hypoventilation
Chronic lung disease
Neuromuscular disease
Cystic fibrosis – bridge for transplant
Cardiac failure
Less common
Acute respiratory failure – likely to reverse within 24 h
Transient post-extubation upper airway obstruction
Pneumonia
Asthma – bronchiolitis
Pulmonary edema
Patients that refuse tracheal intubation

laryngeal mask airway (LMA). Non-invasive ventilation, on the other hand, does not require a tracheal device. Non-invasive ventilation may be administered with a positive pressure ventilator, sometimes termed non-invasive positive pressure ventilation (NIPPV), or as negative pressure ventilation. The main advantages of non-invasive ventilation are the avoidance of tracheal intubation or tracheotosmy, with the associated complications (Table 8.2). The presence of a tracheal tube increases the risk of airway trauma and ventilator-associated respiratory infections (VARI, which includes ventilator-associated tracheobronchitis, sinusitis, or ventilator-associated pneumonia), as well as an increased propensity for immobilization and need for sedation and/or neuromuscular blockade. In addition, important physiological functions such as speech, cough, and swallowing are impaired. Furthermore, non-invasive ventilation may be applied outside the critical care setting and outside the hospital as an optimal home ventilation solution.

Non-invasive Positive Pressure Ventilation (NIPPV)

Non-invasive positive pressure ventilation (NIPPV) refers to the delivery of positive airway pressure *via* a conduit other than a tracheal device, i.e. via either a facemask or nasal mask. It was first introduced to provide home ventilation for children with nocturnal hypoventilation caused by neuromuscular disease. Since the early 1990s, NIPPV has gained increased popularity for extended acute and chronic indications. For example, NIPPV is becoming a commonly used modality in the neonatal ICU for managing premature lung disease, with mixed results [54–56]. However, as with other modalities of ventilation there are fewer studies in critically ill children than in adults [57–69]. As a result, selection guidelines regarding the use of NIPPV in children are extrapolated from the adult literature (Table 8.3). While there are few randomized, controlled studies regarding the efficacy of NIPPV in critically ill children, there are several case series that describe its application in children with mild to moderate acute respiratory failure (e.g. bronchiolitis, asthma, pneumonia) and for chronic home ventilation (e.g. neuromuscular disease) [54, 58, 59]. The application of CPAP has been shown to increase FRC, improve lung mechanics, and increase arterial oxygenation in patients with ALI [70]. NIPPV in the early phase of ALI may reverse the disease process and prevent tracheal intubation in selected patients; however NIPPV is limited by difficulties in effectively applying high airway pressures, controlling airway secretions, and avoiding patient discomfort when utilized for prolonged periods. A trial of NIPPV should be attempted in any stable child with early or impending respiratory failure. However, one should not persist with its use if it becomes clear that the approach is only deferring the inevitable need for tracheal intubation [55, 71, 72]. The major contraindications for the use of NIPPV are clinical conditions in which upper airway protective reflexes are compromised, especially with reduced level of consciousness, or recent gastrointestinal surgeries in which increased bowel gas may compromise repair and/or recovery.

Non-invasive positive pressure ventilation may be administered through a nasal mask or an oro-nasal mask. The oro-nasal mask covers both the nose and the mouth. It may be less comfortable than the nasal mask; however, it abolishes the potential air leak through the mouth that commonly occurs during nasal mask ventilation. Controlled trials in adults

comparing nasal and oro-nasal masks show inconsistent results regarding the efficacy of gas exchange; however, the nasal mask is generally better tolerated. Another type of mask is called the helmet [60]. The helmet covers the patient's entire head, is similar to an over-sized hockey helmet, and is sealed using straps under the shoulder. The patients can better interact with the environment and it can be applied to any patient regardless of facial contour [58, 59, 73].

A relatively newer device that is being used with more frequency in the PICU is the high-flow nasal cannula (HFNC) system [74]. HFNC use higher gas flow rates compared to standard nasal cannula, and there is some evidence to suggest that HFNC does deliver some degree of continuous positive airway pressure [75–79]. There are reports that the increased use of HFNC in certain conditions (e.g. bronchiolitis) have led to a decrease in the number of children requiring invasive mechanical ventilation compared to historical experience [80–82]. However, HFNC has not been shown to be superior (or for that matter, equivalent) to either NIPPV in a prospective trial, so further studies are recommended.

NIPPV may be applied as continuous positive pressure airway pressure (CPAP) or combination of CPAP with pressure support ventilation (PSV). Any ventilator with high flow may be used to provide NIPPV. It can be delivered by volume or pressure-preset modes, or with a bi-level controlled or continuous positive pressure (CPAP) device. The more commonly used devices are portable bi-level ventilators that are designed for NIPPV and can operate successfully with a relatively large leak, providing high continuous flow. Pressure support ventilation is the most common mode of ventilation used with these devices. With bi-level devices (often erroneously referred to as BiPAP®, Respironics, Corporation, Murrysville, PA, which is one of several commercially available devices that can deliver bi-level positive airway pressure), the nomenclature may vary, but the inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP) are preset. The patient's spontaneous inspiration triggers the machine and the difference between IPAP and EPAP is the magnitude of the pressure support delivered with each breath. Because of the potential leak around the mask with high pressures, 15–25 cm H_2O is generally the highest pressure that usually can be achieved reliably and consistently. As certain ventilators do not have an inspiratory time limit, the preset pressure may be not attained in the presence of a significant air leak and the device will not therefore cycle *off* to expiration. In certain circumstances, only constant continuous positive airway pressure (CPAP) is provided throughout inspiration and expiration.

The key factor for effective initiation of NIPPV is a cooperative and relaxed patient. Patient coaching and gradual titration of the pressure may improve the rate of success. As a result, initiation of NIPPV is time consuming for the team as compared to conventional ventilation; this may be the major reason why some clinicians are reluctant to apply it. NIPPV is safe and can be delivered in any number of settings beyond the PICU. However, it can be associated with complications, such that it is generally the common practice to initiate NIPPV in the PICU setting where increased personnel and monitoring can provide constant attention to titrating adjustments to the patient's needs. Principle complications include skin ulceration and erosion in the area of contact between the mask and the skin, and once the skin has become eroded, application of the mask is extremely difficult. Drying of the nasal and pharyngeal mucosa, aspiration, and abdominal distension with gastric dilatation have all been reported as well.

Non-invasive Negative Pressure Ventilation

Until the mid-1900's negative pressure ventilation was almost the only method available to provide ventilation for the management of respiratory failure. Today, it is used only on rare occasions. It works by intermittently applying negative (i.e. sub-atmospheric) pressure to the chest, or to the chest and abdomen. This causes expansion of the chest, and decreases pleural and alveolar pressure, thereby creating a pressure gradient for inspired gas to move into the alveoli during inspiration. The expiration in most of the ventilators occurs passively by elastic recoil of the lungs, but in some the option of active expiration exists. The main two types of ventilators are the traditional *iron lung* where the torso (i.e. chest and abdomen, but not the head) are enclosed in a sealed solid cylinder and the Cuirass system, wherein a plastic shell is placed around the chest.

At present, negative pressure ventilation delivers negative pressure by four modes – cyclic negative pressure, so-called *negative-positive* pressure (*where expiration is actively assisted*), continuous negative pressure, and negative pressure with an oscillator. Most ventilators have the capacity to independently control the pressure and time during inspiration and during expiration. The role of such ventilation is not well established in either adults or children [83, 84]. Nonetheless, negative pressure ventilation is routinely applied in certain centers for chronic home ventilation when the non-invasive positive pressure is either unavailable or is not tolerated. The main factors that limit its widespread application include large unit size, noise, and potential upper airway collapse during inspiration [85].

When the entire body is exposed to negative pressure as occurs with the tank ventilators, non-invasive negative pressure ventilation has similar hemodynamic effects to conventional positive pressure ventilation. However, when the negative pressure is confined to the chest alone (e.g. using the cuirass-type, Hayek Oscillator) this modality of ventilation closely mimics the physiological dynamics of spontaneous ventilation and may have potential hemodynamic advantages

over conventional positive pressure ventilation (PPV). The deleterious effect on PPV on venous return is not present with negative pressure ventilation. On the contrary, negative pressure ventilation augments venous return, as in spontaneous inspiration. An appealing indication for non-invasive negative pressure ventilation was suggested by Shekerdemian and colleagues in a number of clinical studies [86–90]. During inspiration the right atrial pressure decreases, increasing the gradient for venous return. These investigators showed that following the Fontan operation or repair of tetralogy of Fallot, children had a significantly greater pulmonary blood flow and cardiac output when ventilated using negative versus positive pressure [86, 88, 90]. In summary then, while non-invasive negative pressure ventilation is a potentially attractive mode of ventilation, there are not enough physiological and clinical data to support its use as a first line approach. It may be applied on individual basis when venous return or pulmonary blood flow is especially tenuous.

Invasive Mechanical Ventilation

Since the 1960s, when negative pressure ventilation was almost completely abandoned (with the notable exceptions discussed briefly above), nearly all mechanical ventilators have employed the principal of intermittent positive pressure ventilation, where the lungs are inflated by applying a positive pressure to the airways. Most modern ventilators are equipped with a piston bellows system or use a high pressure gas source to drive the gas flow to the lungs. Ventilators used to be classified according to the termination of active inspiration and initiation of passive exhalation. Accordingly, the inspiratory phase may be terminated when a preset pressure is achieved (*pressure-cycled ventilators*), a preset volume is achieved (*volume-cycled ventilators*), or when a preset inspiratory time is reached (*time-cycled ventilators*). This classification has become somewhat irrelevant with time, as with nearly all modern ventilators currently in use, the clinician may separately control the tidal volume, the pressure delivered, and the inspiratory time (or indirectly with the flow). Some ventilators that are used for transport or for home ventilation are pure *pressure-cycled ventilators,* where the ventilator produces gas flow to the lungs until it reached a preset pressure, then inspiration is terminated and thereafter, the expiration valve opens, and expiration begins. The duration of inspiration and tidal volume varies according to the total respiratory system compliance (*chest and lung*) and the airway resistance. When lung or chest wall compliance is low or inspiratory time short, then the delivered tidal volume will be smaller. Furthermore, in case of an air leak, the preset airway pressure may not be reached thereby preventing the termination of inspiration. The above limitations restrict the use of these ventilators to children with relatively healthy lungs (e.g. neuromuscular disease, central hypoventilation).

Pressure Control Versus Volume Control

Mechanical ventilation is often classified by whether the ventilator is set to deliver a pre-determined tidal volume (volume limited, volume pre-set ventilation, volume-cycled ventilation, or volume control ventilation, VCV) or to achieve a pre-determined peak pressure (pressure limited, pressure pre-set ventilation, pressure-cycled, or pressure control ventilation, PCV) [91–93]. During Pressure Control Ventilation (PCV), the breath is delivered at a set rate with a decelerating flow pattern (Fig. 8.5). The tidal volume is determined by the preset pressure, inspiratory time and respiratory system mechanics. During the Volume Control Ventilation (VCV), a preset volume is delivered by the ventilator with each breath using a constant flow pattern (Fig. 8.5). The breath is terminated by a preset time (*time-cycled*) or after the delivery of the preset tidal volume (*volume-cycled*). During time-cycled, volume-preset ventilation, the inspiratory flow is regulated in order to deliver the preset tidal volume and the tidal volume and minute ventilation are guaranteed (regardless of resistance or compliance).

PCV has been associated with decreased patient work of breathing [94, 95], improved oxygenation at lower peak pressures [96, 97], and better outcomes (in terms of number of extrapulmonary organ failures and duration of mechanical ventilation) in critically ill adults with ALI/ARDS [98, 99]. In addition, in otherwise healthy children undergoing general anesthesia, PCV is associated with lower peak pressures [100–102]. Regardless of these studies, the choice of PCV or VCV is often dictated by institutional bias and/or physician preference.

Pressure Control Ventilation

During Pressure Control Ventilation (PCV), the breath is delivered at a set rate with a decelerating flow pattern and is terminated when a preset peak inspiratory pressure (PIP) is achieved (Fig. 8.5). The tidal volume is determined by the preset PIP and respiratory system mechanics. The inspiratory time is usually set by the operator. PCV is usually recommended in patients with leakage around an uncuffed tracheal tube, in cases of obstructive lung disease (e.g. status asthmaticus), neonates or small infants where measurement of the tidal volume is inherently inaccurate, or rarely, in the presence of a bronchopleural fistula. When the tidal volume is measured at the ventilator, instead of at the end of the tracheal tube, then changes in circuit compliance significantly influence the accuracy of the measurement. This is particularly the case with neonates and infants, where the tidal volumes are far smaller compared with the volume of the ventilator circuit. The main drawback of PCV is that tidal volume and minute ventilation are directly influenced by the respiratory system mechanics, and as these change, so too does the delivered tidal volume. As a result, in cases of rapidly changing respiratory

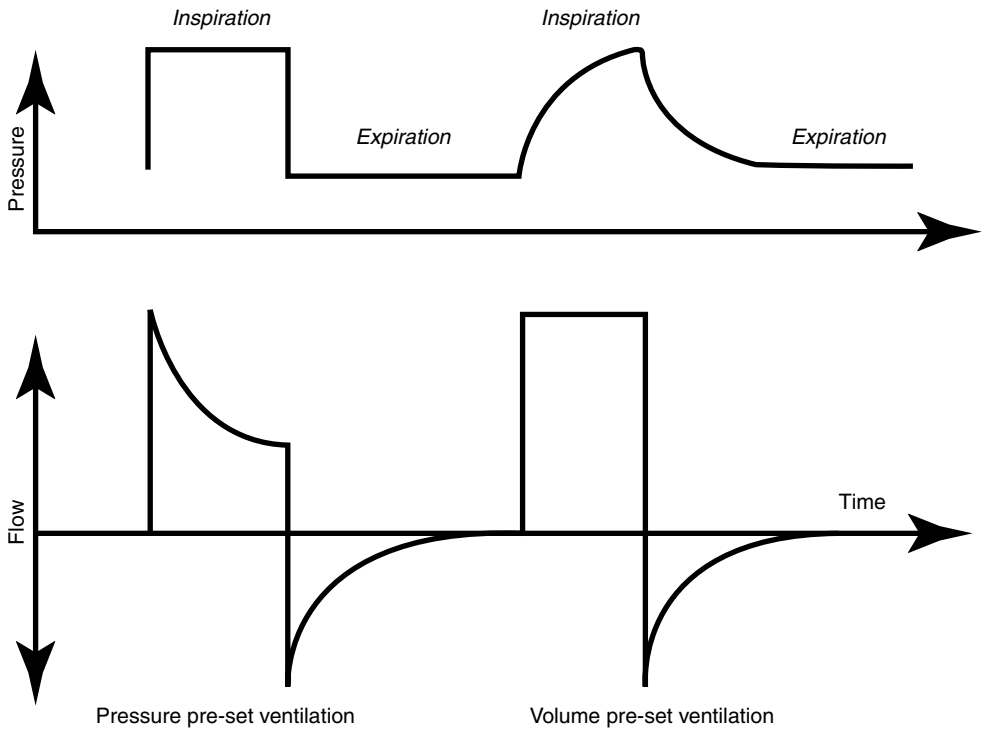


Fig. 8.5 Pressure limited breath (*left*) vs. volume limited breath (*right*). The same tidal volume is delivered in both modes. However, with a decelerating flow in limited pressure (*left*) or square wave flow in volume limited mode (*right*)

system mechanics (e.g. administration of surfactant), the patient may be at risk of inappropriate levels of ventilation. However, the same argument can be made about volume-preset ventilation and the potential risk of barotrauma with rapid changes in respiratory mechanics (see below).

Volume Control Ventilation

During Volume Control Ventilation (VCV), a preset volume is delivered by the ventilator with each breath using a constant flow pattern (Fig. 8.5). The breath is terminated by a preset time (*time-cycled*) or after the delivery of the preset tidal volume (*volume-cycled*). During time-cycled, volume-preset ventilation, the inspiratory flow is regulated in order to deliver the preset tidal volume and the tidal volume and minute ventilation are guaranteed (regardless of resistance or compliance). This mode of ventilation is commonly used in larger infants and children, but it is not generally recommended for neonates or small infants. The main drawback is variation in tidal volume delivery, due to either leaks in the system or inaccurate volume measurement. If compliance worsens, higher peak pressures will be delivered, which can be associated with areas of overdistension (e.g., areas of normal lung compliance) and ventilator-associated lung injury. In modern ventilators, the peak pressure can be limited during volume control ventilation (see next mode, below).

Adaptive Pressure Control Ventilation

Most of the newer ventilators have an additional mode of ventilation that combines the purported advantages of a decelerating flow pattern characteristic of the pressure-limited mode [94], as well as the guaranteed tidal volume associated with volume-preset ventilation. A preset tidal volume is delivered with the lowest pressure possible, using a decelerating flow pattern. After the first volume-limited breath, the plateau pressure measured by the ventilator is used for the next breath; this pattern is continued for each successive breath (Fig. 8.6). For each subsequent breath, the ventilator automatically adjusts the minimal inspiratory pressure required to guarantee the preset tidal volume. If the tidal volume increases above the preset value, the next breath is delivered with a lower pressure. This mode, called adaptive pressure-control ventilation, goes by a number of different names, depending upon the commercial brand of ventilator used: Pressure-regulated Volume Control (PRVC) (Servo-I, Maquet, Solna, Sweden), AutoFlow (Dräger, Telford, PA), adaptive pressure ventilation (Hamilton Galileo, Hamilton Medical AG, Bonaduz, Switzerland), Volume control plus (Puritan Bennet, Covidien, Dublin, Ireland), and volume-targeted pressure control or pressure controlled volume guaranteed (GE Healthcare, Cleveland, OH). Limited clinical trials have shown that lower levels of peak airway pressure are required to deliver the same tidal volumes using adaptive pressure control compared to classic volume control modes [94, 103, 104], though it is unclear whether this represents a meaningful advantage in the prevention of ventilator-induced lung injury (VILI). However, based upon what is known about the relationship between higher ventilatory pressures and worse outcomes [45, 48, 105, 106], it may be reasonable to hypothesize that this mode may be a better mode of ventilation for critically ill patients with ALI/ARDS.

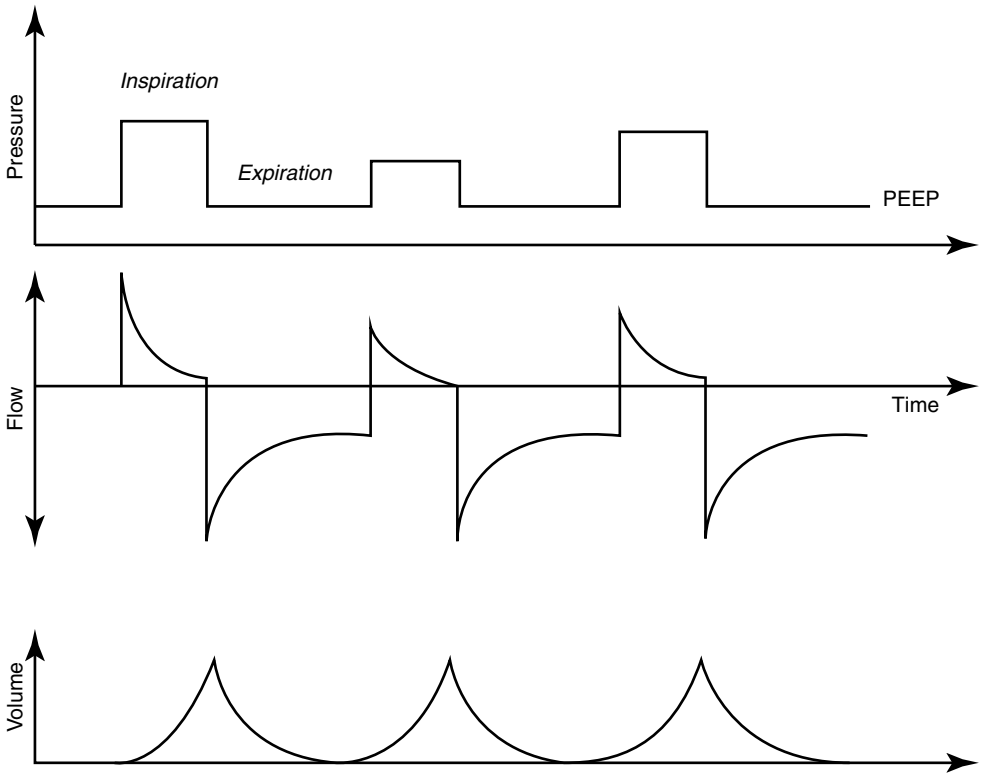


Fig. 8.6 Pressure regulated volume control (PRVC). A control mode in which the ventilator delivered a preset tidal volume, with preset frequency, and inspiratory time. The ventilator automatically adapts the optimal inspiratory pressure (lowest) in order to deliver the preset tidal volume

Ventilator Modes

The ventilatory cycle during mechanical ventilation is divided into an inspiratory and an expiratory phase. The different modes of mechanical ventilation are further classified according to the mechanism of the so-called patient-ventilator interaction during inspiration. This ranges from full ventilator control of the tidal volume and frequency, to provision of partial support only during a spontaneous breathing where the patient determines both the tidal volume and the respiratory rate. A classification of common modes of mechanical ventilation follows:

Control Mode Mechanical Ventilation (CMV)

In this mode of ventilation, the ventilator delivers a mechanical breath at a preset interval, irrespective of the patient's spontaneous effort (Fig. 8.7). The breath is either *volume-limited* or *pressure-limited*. In this mode of ventilation, the patient's spontaneous effort to breathe may interfere with the mandatory breath delivered by the ventilator. In order to prevent this, the patient's spontaneous breathing may be inhibited by decreasing the respiratory drive, either by administering sedative drugs or by hyperventilation to induce respiratory alkalosis. This mode of ventilation has almost been completely abandoned in children. It may be used rarely when a high rate of ventilation is required and the specific ventilator is unable to provide synchronized intermittent mandatory ventilation (SIMV) at such respiratory rates.

Assist/Control Mechanical Ventilation

This is a form of ventilation in which the ventilator provides a mechanical breath at a preset interval with a preset tidal volume or pressure in response to each spontaneous breath, regardless of the tidal volume desired by the patient (Fig. 8.8). Where the patient doesn't trigger the ventilator within the specified time interval, the ventilator will provide the preset tidal volume or pressure breath at the preset respiratory rate.

Synchronized Intermittent Mandatory Ventilation (SIMV)

This mode of ventilation was originally developed as a weaning mode but was quickly adopted as the main-stream mode of ventilation because of its apparent advantages over the control mode. It is a mixed ventilatory mode that allows both mandatory and spontaneous breathing (Fig. 8.9). The mandatory breaths can be pressure- or volume-regulated and the spontaneous breaths can be pressure-supported (or not). The SIMV algorithm is designed to deliver a mandatory breath in each SIMV breathe cycle, where the breath cycle is 60/[number of breaths per minute], in seconds. The mandatory breath is either patient- or ventilator-initiated. The SIMV cycle has two periods. The first period is the mandatory period that is reserved for the mandatory breath. If the patient doesn't trigger the ventilator during the mandatory period, then the machine will deliver the preset mandatory breath at the end of this period. When the patient triggers the ventilator during

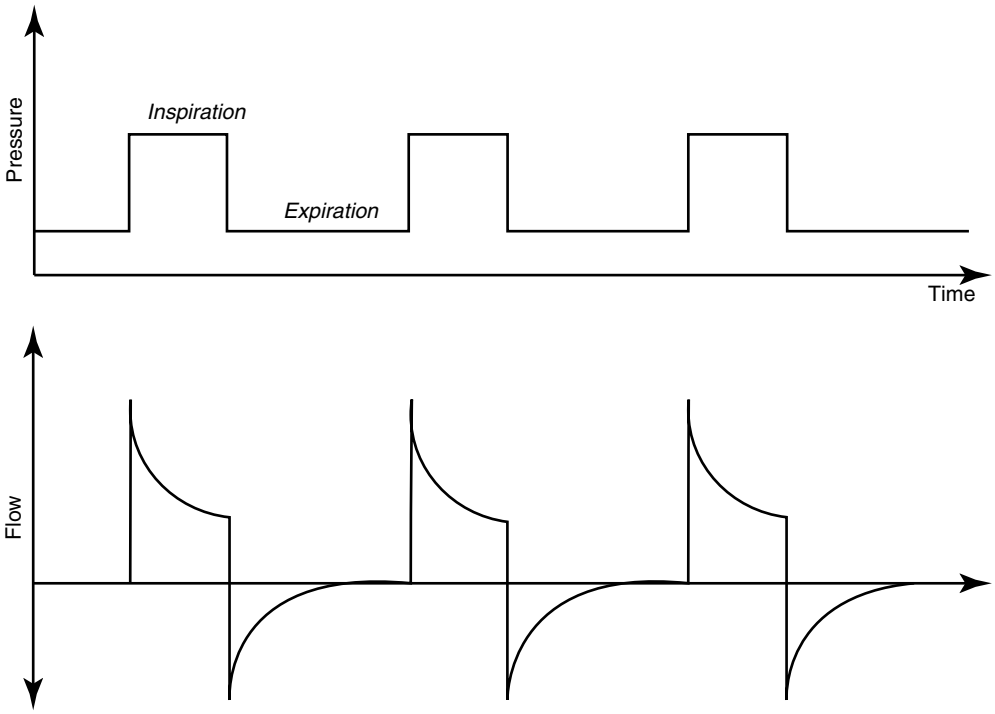


Fig. 8.7 Control ventilation mode. The ventilator delivers preset tidal volume or pressure with a preset inspiratory time and respiratory rate. End expiratory pressure (PEEP) may be kept over zero

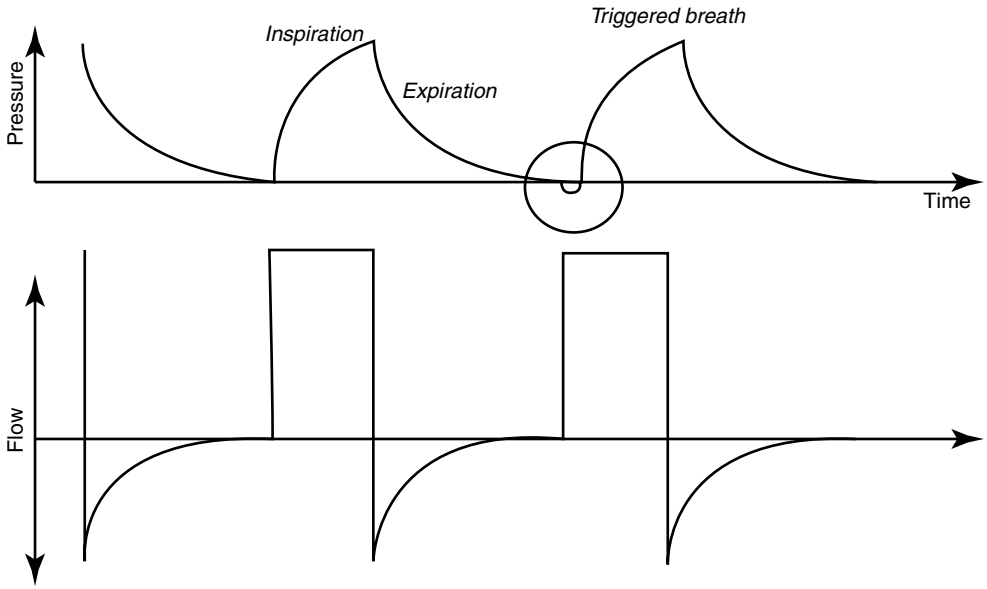


Fig. 8.8 Assist/control ventilation. When the patient doesn't trigger the ventilator within the specified time interval, the ventilator will provide the preset tidal volume at the preset respiratory rate (*left*). When the patient triggered the ventilator, a preset tidal volume in response to each spontaneous breath is delivered by the ventilator (*right*)

this period, a preset mandatory breath is delivered and the mandatory period is terminated. The second period is a spontaneous period which is reserved for the spontaneous breaths. The spontaneous period starts each time a mandatory period terminates. The main advantages of SIMV over CMV are maintenance of spontaneous respiratory activity which results in continuous use of the respiratory muscles and improved patient-ventilator synchronization. The result of the latter may be a reduction in the use of excessive sedation and neuromuscular blockade.

Pressure Support Ventilation

Pressure Support was designed as a spontaneous mode of ventilation that augments only spontaneous breaths (Fig. 8.10). The idea is that by doing so, the work of breathing imposed on the patient is reduced. It is a patient-triggered, pressure-limited, flow-cycled mode of ventilation. During pressure support ventilation, the ventilator delivers flow in order to provide a constant preset inspiratory pressure with each spontaneous breath. The patient controls the respiratory rate, inspiratory time, and the tidal volume (unless the preset

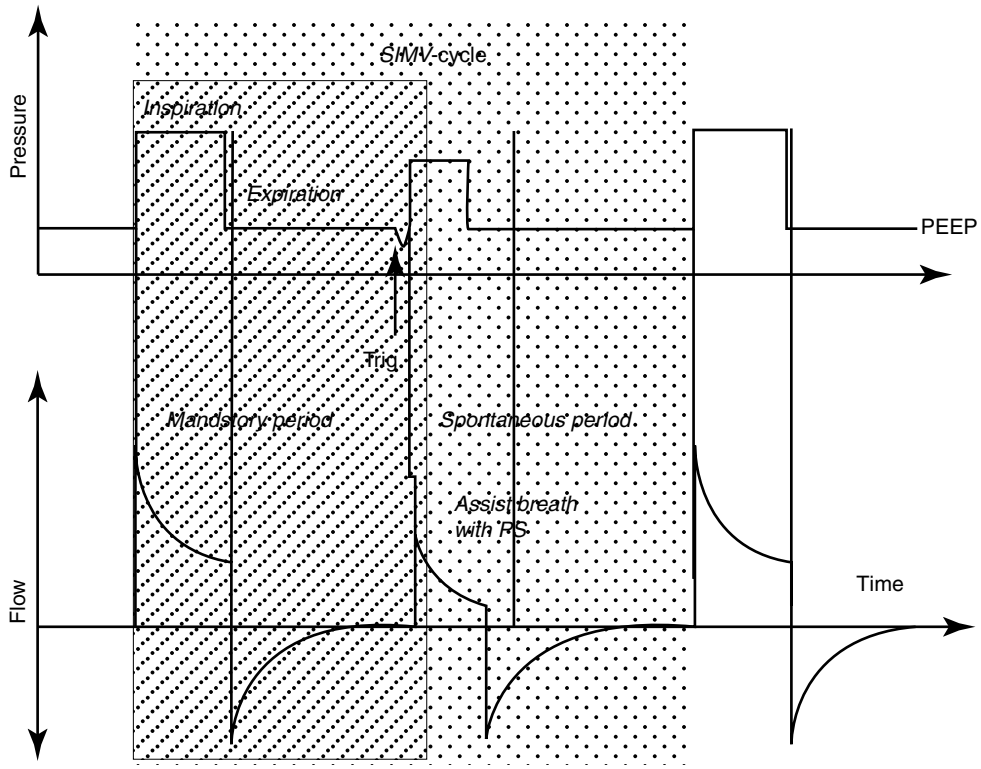


Fig. 8.9 Synchronized intermittent mandatory ventilation (*SIMV*). The SIMV cycle consist of a mandatory period and spontaneous period. A breath effort during the SIMV mandatory period will deliver a breath with a preset volume or pressure. A breath effort during the spontaneous period will delivered spontaneous breath in the absence of pressure support, or pressure/volume supported breath. In case the patient doesn't take a breath during the mandatory period the ventilator delivers a mandatory breath (volume limited or pressure limited)

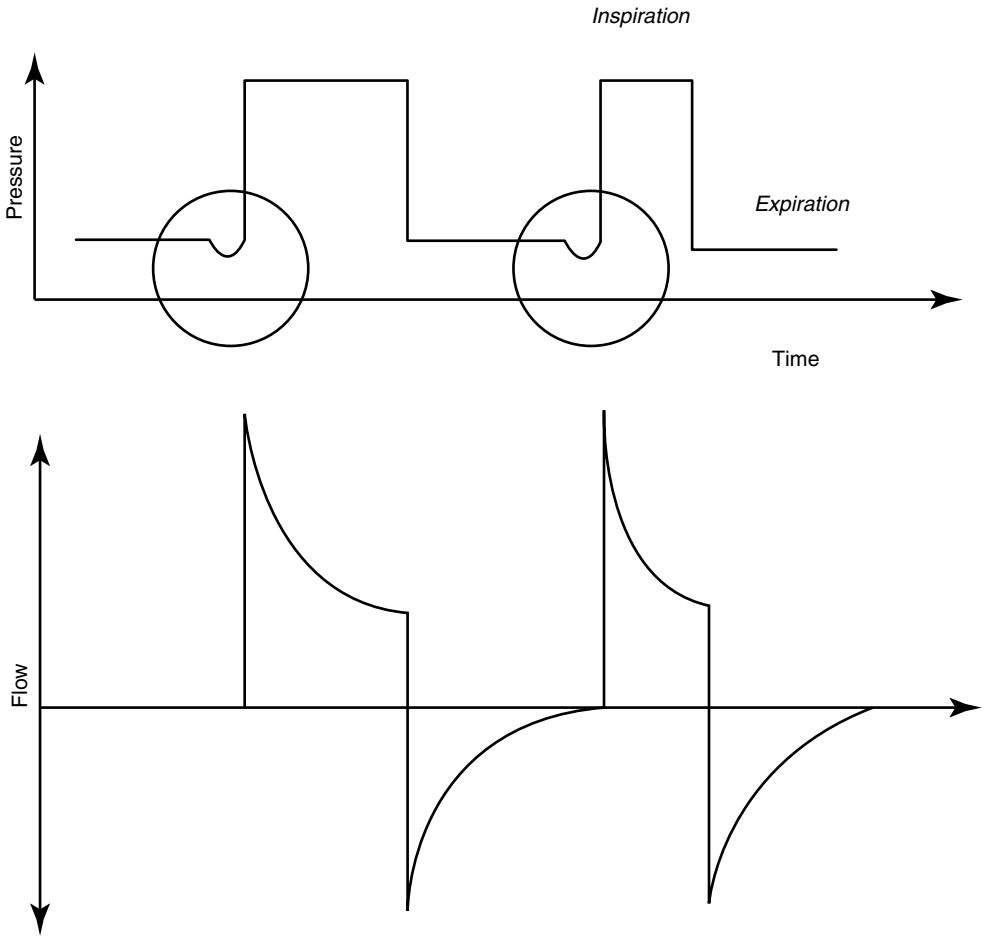


Fig. 8.10 A combination of control and pressure support ventilation

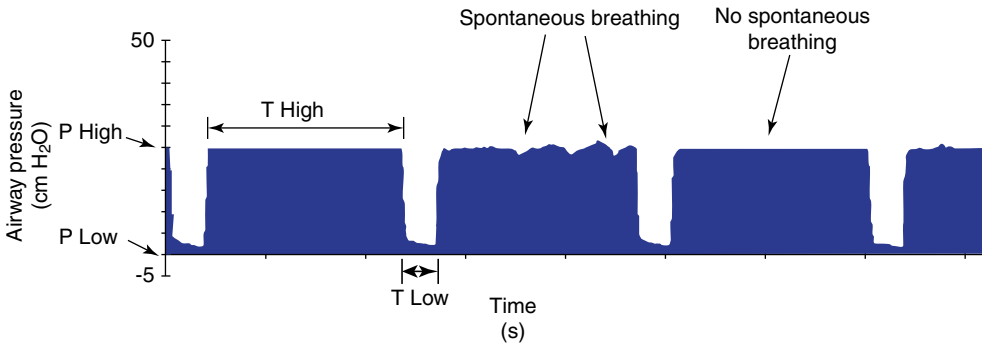


Fig. 8.11 Airway pressure release ventilation (APRV)

pressure is extremely high). To trigger the ventilator, the patient has to develop a minimum negative inspiratory effort that exceeds in magnitude the preset sensitivity (based on either pressure or flow). In order to reduce the effort of triggering to a minimum, most modern ventilators are equipped with very sensitive pressure or flow transducers that have a fast demand valve and a continuous flow. Since support ventilation is completely dependent on patient capacity to develop an inspiratory effort when this mode is used in isolation, the patient must have sufficient respiratory drive and muscle strength in order to trigger the ventilator. Furthermore, pressure support ventilation *per se* doesn't prevent apnea; however, virtually all modern ventilators have an alarm and backup mechanical support in the event of apnea.

The basis for determining or choosing the optimal preset pressure levels is not well established. In addition, neither the appropriate pulmonary disease states nor the use of adjunct SIMV have been determined for pressure support ventilation [107]. However, in practice, pressure support is usually used in combination with SIMV in order to improve patient comfort, or simply because practice has evolved that way. In addition, pressure support is commonly used during the weaning process.

One approach in implementing pressure support ventilation is to adjust the preset pressure to a level appropriate to achieve the desire tidal volume, and/or to achieve apparent patient comfort. The major drawback in this mode of ventilation, as with any pressure-preset mode, is that tidal volume is not guaranteed. The delivered tidal volume in pressure support ventilation depends on patient effort, which of course may continuously change. Changes in neurologic status (e.g. increased sedation which may reduce respiratory drive) or alteration in respiratory mechanics may affect the delivered tidal volume. Furthermore, oxygen demand (i.e. the requirement for O_2 due to fever, stress or pain) may change over time, and as a result, minute ventilation may change correspondingly while the preset pressure remains constant.

Volume Support Ventilation

In order to overcome the major drawbacks of pressure support ventilation (i.e. tidal volume is not guaranteed), some recent models have introduced the concept of volume support ventilation. Basically, this is a pressure support mode where the inflation pressure changes in order to maintain a constant (i.e. preset) tidal volume. Using a closed-loop control system, the ventilator alters the pressure level to deliver a preset tidal volume. The delivered tidal volume is used as a feedback control for continuous adjustment of the level of pressure. This way the ventilator continuously adapts to the changes in patient effort, respiratory system mechanics and oxygen requirement. The operator sets the desired tidal volume and also, by choosing the respiratory rate, the minute ventilation. Volume support ventilation is a commonly used weaning mode of ventilation (see further discussion below) [38].

Airway Pressure Release Ventilation (APRV)

Airway pressure release ventilation (APRV) is a modality that was first described in 1987, though it has had somewhat of a renaissance in the past few years [108–112]. Conceptually, APRV is really just the application of a relatively high CPAP (called P_{HIGH}) for a set period of time (called T_{HIGH}) to maintain adequate alveolar recruitment, with an intermittent release phase to a lower pressure (called P_{LOW}) for a set period of time (called T_{LOW}) to allow for expiration (Fig. 8.11). Inspiration can occur via one of two ways. Inspiration can occur via a mechanical breath (essentially the movement from P_{HIGH} to P_{LOW} generates a "breath"). Rather than producing a tidal volume by increasing the airway pressure above a preset PEEP, as in the conventional modes of positive pressure ventilation, the tidal volume is generated when airway pressure is reduced from the preset pressure. T_{HIGH} is usually much longer than T_{LOW}, such that in the absence of spontaneous ventilation, APRV is essentially pressure-controlled inverse ratio ventilation (see below). However, one of the major advantages to APRV is the ability to breathe spontaneously at either P_{HIGH} or P_{LOW}. Theoretically, spontaneous breathing (resulting from diaphragmatic contraction) during APRV results in preferential recruitment of the dependent lung regions (recall from the discussion above that the main of areas of consolidation in patients with ALI/ARDS are in the dependent lung regions). Therefore, overdistension of the better aerated (and more compliant) non-dependent regions is avoided [113]. Ventilation (i.e.

Table 8.4 Initial ventilator settings for APRV

1. Set P_{HIGH} at the desired plateau pressure (typically 20–30 cm H_2O), usually the plateau pressure obtained by an end-inspiratory hold maneuver if the patient was in VCV or the PIP if the patient was in PCV
2. Set P_{LOW} at 0 cm H_2O
3. Set T_{HIGH} at 3–5 s
4. Set T_{LOW} at 0.2–0.8 s

Adapted from Habashi [114, 115]
In order to improve oxygenation (i.e. increase SpO_2) – increase P_{HIGH} (usually in 2 cm H_2O increments) or both P_{HIGH} and T_{HIGH} (usually in 0.2 s increments)
In order to improve ventilation (i.e. decrease $PaCO_2$) – decrease T_{HIGH} or increase T_{LOW}
During weaning, decrease P_{HIGH} and increase T_{HIGH}

removal of CO_2) is also improved during the release phase of APRV [114, 115]. In addition, because spontaneous breaths do not trigger the ventilator (just as in CPAP), spontaneous inspiration during any phase of APRV results in lower pleural pressure and can therefore augment right ventricular filling [116]. The majority of the time is spent at P_{HIGH} (80–95 % of the "cycle"). The time spent at P_{LOW} must be short enough to prevent derecruitment, yet long enough to prevent air-trapping and auto-PEEP. Recommendations for initial ventilator settings and adjustments for APRV are listed in Table 8.4. Clinical studies demonstrate improved patient comfort, gas exchange, and cardiac output during spontaneous breaths with APRV [109, 114, 115, 117]. The theoretical benefits of APRV, however, have not been shown to be superior (or even equal) to any other ventilator strategy in critically ill children with acute respiratory failure.

Inverse Ratio Ventilation

Pressure-controlled Inverse Ratio Ventilation (IRV) uses inspiratory times which exceed expiratory times, usually resulting in I:E ratios of 2:1 or even 3:1 during otherwise conventional mechanical ventilation. IRV is thought to enhance alveolar recruitment, though at the expense of a significant increase in mean airway pressure (and the potential of auto-PEEP – see below). To date, there are no studies showing that IRV is superior (or even equivalent) to any other mode of mechanical ventilator support in the PICU [118]. This mode of mechanical ventilation has largely fallen out of favor [119].

Automatic Tube Compensation (ATC)

Although not technically a mode of ventilation, some ventilators offer the option of automatic tube compensation (ATC) in which the ventilator assists a spontaneous breath by delivering positive pressure, the degree of which is proportional to the inspiratory flow and tracheal tube resistance. This pressure compensates for the estimated flow-resistive work of breathing via a closed loop control of the calculated tracheal tube resistance [120–122]. The theoretical advantage of the system is that the work of breathing imposed by the artificial airway (e.g. tracheal tube, tracheostomy) is overcome. The system uses a known resistive coefficient of the tube, measures the flow through the tube, and then applies a pressure (during inspiration) or reduce the PEEP during expiration) proportional to the resistance throughout the respiratory cycle (inspiration and expiration).. Kinks or bends in the tube as it traverses the upper airway and secretions in the inner lumen may change the tube resistance and result in imperfect compensation. Some investigators have reported that ATC improves patient comfort and helps to eliminate dynamic hyperinflation [123]. There is very little data on the effect of automatic tube compensation on work of breathing, oxygenation, ventilation, or outcomes in critically ill children [124].

Proportional Assist Ventilation (PAV)

In the conventional mode of pressure support or assist control ventilation, the support delivered by the ventilator is fixed. In contrast, PAV is governed by the equation of motion that identifies the necessary pressure to be applied to the respiratory system in order to overcome opposing elastance and resistance forces that exist in proportion to the volume and flow, respectively [125]. During PAV, the ventilator output (i.e. flow and pressure) changes according to changes in the patient's effort (that is, the more the patient pulls, the more pressure the machine generates), which in turn reflects the resistance and elastance of the respiratory system [126]. There is limited experience with this type of mechanical ventilatory support in the PICU. In addition, there are no clinical trials to suggest that this mode of ventilation is superior or equivalent to any other modes of ventilation.

Neurally Adjusted Ventilatory Assist (NAVA)

In the NAVA mode of ventilation, continuous detection of the electrical activity of the diaphragm muscles are used as an index of inspiratory drive and the amount of support provided by the ventilator corresponds to the ventilatory demand. NAVA is currently only available with one type of ventilator (Servo-i, Maquet, Solna, Sweden). NAVA requires placement of an esophageal catheter that measures the diaphragm muscle electrical activity (EA_{di}), which is a measure of the patient's neurally-mediated respiratory effort. The degree of ventilator support provided by the ventilator is proportional to the EA_{di} signal. The ventilator is equipped with a safety mechanism, such that in the event of loss of the EA_{di} signal (e.g. dislocation or disruption of the catheter), the ventilator switches to a back-up pressure support ventilation mode. If the patient does not have a spontaneous respiratory drive (e.g. oversedation, brain injury, phrenic nerve damage, neuromuscular blockade, etc), the ventilator switches to a back-up pressure control ventilation mode. The level of

inspiratory pressure delivered by the ventilator is determined by the following equation:

$$P_{aw} = \text{NAVA Level} \times EA_{di} \quad (8.10)$$

where the EAdi is the instantaneous integral of the diaphragmatic electrical activity signal (measured in μV) and the NAVA level (measured in cm $H_2O/\mu V$) is set by the clinician. While NAVA is relatively new, there are several studies suggesting that NAVA improves patient-ventilator synchrony and is generally well-tolerated [127–134], even in premature infants [135, 136]. NAVA has also been used non-invasively. However, as yet there are no studies in either children or adults that demonstrate that NAVA is superior compared to other modes of ventilation, in terms of clinical outcomes [137, 138]. Given the potential and theoretical benefits, this is certainly a promising area for further research.

Determining Initial Ventilator Settings

The overall goal of mechanical ventilation is to provide acceptable gas exchange while causing the least amount of lung injury. Generally speaking, *aggressive* ventilation in terms of airway pressure, tidal volume, and FiO_2 results in better gas exchange but with a higher risk for the development of lung damage. Thus, one should always weigh the benefits of gas exchange against the injury caused to the lung in order to achieve oxygenation and ventilation targets [119, 139–141]. The definition of acceptable gas exchange is complex, and there are no validated values for $PaCO_2$ and SaO_2 towards which one should aim. In terms of $PaCO_2$, there has been a gradual acceptance of higher values as clinicians treating neonates with acute respiratory failure [142–148], children and adults with either asthma [149, 150] or ARDS have historically practiced [151, 152]. In these contexts, the higher levels of $PaCO_2$ are tolerated or *permitted* by the clinician, hence the term *permissive hypercapnia*. Such tolerance is not accepted where elevated $PaCO_2$ could be directly harmful, such as in the presence of intracranial hypertension or acute pulmonary hypertension. In addition, recent experimental work suggests that elevated $PaCO_2$ might be directly beneficial in certain situations, although these concepts have not been well tested outside the laboratory [153–155]. Although the risks associated with hypercapnia have received a lot of attention, the risks of hypocapnia are less well appreciated. While in some circumstances hypocapnia is valuable (e.g. evolving brainstem herniation), in many situations it is either of no benefit or potentially harmful [154, 156]. The lowest acceptable level of oxygenation is even more difficult to define. Although there is no consensus regarding how low one might aim with arterial oxygen saturation (SaO_2), a lower target level of SaO_2 >90–92 % ($PaO_2 \approx 55$ mmHg) appears physiologically safe. Indeed when high levels of PEEP, plateau pressure, and/or FiO_2 are required, clinicians will commonly accept lower target levels of SaO_2 (i.e. 85–88 %) [157, 158] (some clinicians have referred to this as *permissive hypoxemia*) [159–162].

As stated previously, in cases of parenchymal lung disease, lung compliance and the functional residual capacity (FRC) are usually reduced. Unfortunately, the parenchymal lung disease is usually heterogeneous in nature and different regions of the lung are differently affected – as a result the mechanical properties are inhomogenous. The gas delivered will preferentially go to the regions with lower resistance and higher lung compliance. The rationale behind the setting of the ventilator is to homogenize the otherwise inhomogeneous disease (recruitment), to keep the lung open throughout the respiratory cycle (with use of PEEP), and to avoid over distension (limited V_T and/or plateau pressure) of the relatively healthy lung regions.

At this stage the ventilator settings should be tailored to each patient and there are no proven formulaic guidelines. The basic principles for applying mechanical ventilation in a child with acute respiratory failure include:

1. Hemodynamic status should be optimized by assuring intravascular volume and inotrope support in order to tolerate relatively high levels of PEEP
2. The proportion of non-aerated lung should be minimized by recruitment
3. The transpulmonary pressure and tidal volume should not be excessive
4. Patient comfort must be ensured and some ventilatory effort ideally maintained.

The choice of Pressure Control (PCV) versus Volume Control Ventilation (VCV) is not well established and often depends more on the type of ventilator, physician preference, or institutional bias. Historically, VCV has been used in most adult critical care units, while PCV was the preferred mode in pediatric critical care units (largely due to the lack of available ventilators that could deliver such low tidal volumes to neonates and young infants and children) [163]. However, VCV has been used safely even in premature, low birth-weight neonates with hyaline membrane disease, and no study has demonstrated the clear superiority of PCV over VCV, or vice versa, even in this unique population [164–167]. The choice of PCV versus VCV will further dictate whether peak inspiratory pressures (PIPs) or tidal volumes are set by the clinician.

Tidal Volume (V_T)

The mortality associated with ALI/ARDS has declined steadily up to about 10 years ago. While it is likely that the

reasons for improved patient survival are multifactorial, the limitation of delivered V_T and airway pressure (see below) are the only interventions that have been demonstrated in prospective, randomized, controlled trials to improve outcome. Specifically the studies performed by Amato [168] and the ARDS network [169] comparing a protective ventilator strategy (V_T <6 mL/kg ideal body weight, plateau pressure <30–35 cm H_2O) *vs*. ventilation with high V_T (12 mL/kg) showed improved patient outcome. This outcome benefit was not reported in studies in which intermediate levels of V_T were employed [170, 171]. Although the clinical implementation of the ARDS network protocol in adults has been shown to be effective and to result in reduced mortality among adults ARDS patients [172] there is still much controversy over the extent to which V_T and airway pressures should be limited and whether low V_T, low Pplat or both are necessary in order to improve outcome [173]. While the optimal tidal volume in critically ill children has not been well established, it is generally accepted that high tidal volumes associated with high end-inspiratory pressures have a negative impact on outcome [37, 45, 46, 158, 174], as described in the sections above. Therefore, it seems reasonable to use the lowest V_T necessary to achieve acceptable gas exchange, without predisposing to atelectasis (i.e. derecruitment). Most clinicians target tidal volumes in the range of 5–8 mL/kg predicted body weight [158, 175]. While it is difficult to base recommendations in critically ill children from adult clinical data, the anecdotal experience and current literature would at least suggest that this is a rational and safe starting practice. Considerable difficulty may arise in the accurate measurement of delivered V_T, and this is especially the case with small children. Ideally circuit flow (hence volume, which is measured as the integral of the flow) should be measured as close to the airway opening as possible. In many ventilators the V_T is determined from the gas flow measured at the expiratory valve, i.e. on the ventilator. Measurement of V_T at the ventilator is inaccurate (up to 90 % measurement error in small infants). The magnitude of error varies between ventilators and is also affected by respiratory system compliance, the modality of ventilation employed and the circuit type. Stand-alone respiratory monitors which can measure V_T accurately are available and appear to be more accurate than using the exhaled tidal volume at the expiratory valve of the ventilator [176–178].

The administration of low V_T is not without drawbacks. Low V_T ventilation may promote atelectasis, increase intrapulmonary shunting, and promote VALI. It results in hypercapnia which predisposes to raised intracranial pressure, pulmonary hypertension and impaired myocardial contractility. Further, hypercapnia may increase the patient's work of breathing, and promote patient-ventilator dyssynchrony (described further below).

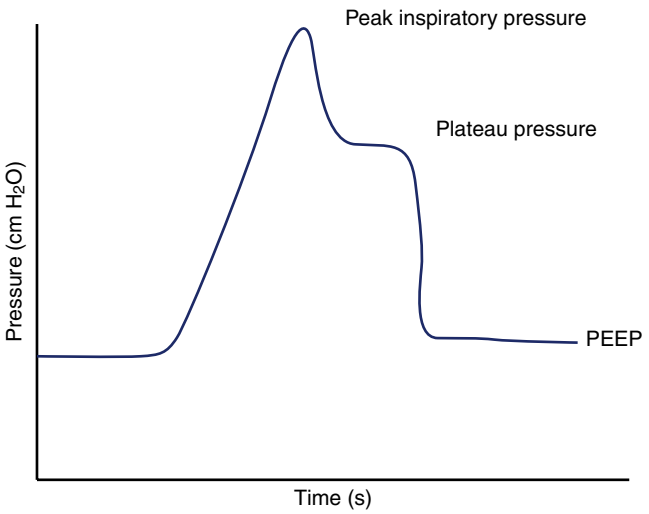


Fig. 8.12 Airway pressure waveform during volume control ventilation (VCV). An end-inspiratory hold maneuver is performed to measure plateau pressure (P_{PLAT}). The difference between PIP and P_{PLAT} is determined by the flow setting on the ventilator, as well as the resistance in the airways. An increase in the PIP–P_{PLAT} difference would (in the absence of other changes in ventilator settings) therefore suggest an increase in airways resistance

Inspiratory Pressures

With PCV, the clinician sets the peak inspiratory pressure (PIP), while in VCV, the PIP is determined by the patient's respiratory mechanics. The transpulmonary pressure (P_L) (by Eq. 8.9 alveolar pressure, P_A minus intrapleural pressure, P_{PL}) is the true alveolar distending pressure. However, P_L is not normally monitored in the clinical setting and its measurable analog may be the plateau pressure (static, i.e. no flow, end-inspiratory pressure (Fig. 8.12). Theoretically, in children because of the higher chest wall compliance, there is a better correlation between the PIP, plateau pressure (P_{PLAT}), and P_L than in the adult. The PIP is the pressure measured by the ventilator in the major airways and thus reflects airway resistance. Conversely, P_{PLAT} is the pressure that reflects the alveolar pressure and may be measured in most modern ventilators using an end-inspiratory hold maneuver for 0.5–1.5 s. In PCV, the inspiratory flow decreases to zero at the end of inspiration, such that P_{PLAT} and PIP are essentially the same. Importantly, P_{PLAT} can only be measured accurately when the patient is not exerting any respiratory effort and there is no leak around the tracheal tube. The difference between the PIP measured by the ventilator and P_{PLAT} is due predominately to airway resistance. Patients with a significant component of airway resistance (e.g. status asthmaticus) may have a large gradient between P_{PLAT} and PIP. The P_L is theoretically 10–30 % lower than P_{PLAT}. A P_L of 20 cm H_2O is generally safe and unless chest wall compliance is very poor (e.g. morbid obesity, ascites, fluid

Table 8.5 Setting PEEP based upon FIO_2

FIO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7	0.7	0.8	0.9	0.9	0.9	1.0
PEEP	5	6	8	8	10	10	10	12	14	14	14	16	18	≥18

Adapted from Curley et al. [182]. With permission from Elsevier
Summary of PEEP titration used in a pediatric prone positioning trial. Goal PaO_2 50–80 mmHg, SpO_2 88–92 %

overload, abdominal compartment syndrome), P_{PLAT} should probably be <30 cm H_2O [36, 105, 119, 175, 179, 180].

Positive End-Expiratory Pressure (PEEP)

The peak expiratory pressure (i.e. PEEP) has a pivotal role in maintaining the unstable lung units open throughout the respiratory cycle and increasing FRC. The overall effect here may be to limit the risk of VILI and improve oxygenation, thereby allowing the use of a lower FiO_2 and P_L. However, simultaneously high levels of PEEP have the potential to cause hemodynamic instability, and by increasing P_L and lung volume, may in turn contribute to overdistension and VILI. For example, a clinical trial in adults with ARDS that were ventilated with low V_T (6 mL/kg) and limited plateau pressure (≤ 30 cm H_2O) failed to show differences in mortality or length of ventilation between ventilation with high (13.2 ± 3.5 cm H_2O) and low (8.3 ± 3.2 cm H_2O) PEEP [181]. In this particular trial, PEEP was set based upon the FIO_2 required to maintain acceptable oxygenation levels (SpO_2 88–95 % or PaO_2 55–80 mmHg) (Table 8.5). There is no clear consensus, however, on the ideal method to set an optimal PEEP.

Some experts recommend determining the optimal PEEP by plotting the semi-static pressure-volume curve and setting the PEEP between the lower and higher inflection points. In this case, the lower inflection point (LIP) represents the pressure at which a large number of alveoli are recruited, while the upper inflection point (UIP) represents the pressure at which a large number of alveoli are overdistended [183–186]. With this in mind, the ideal PEEP would be just above the LIP. Unfortunately, there have been no studies assessing this particular method in critically ill children with acute respiratory failure.

Another method of setting PEEP is to start with a relatively normal PEEP (~5 cm H_2O) and increasing PEEP by a series of 2 cm H_2O incremental steps and watching for improvement in oxygenation and lung mechanics (compliance). The period of time required to observe clinically meaningful and sustained changes in oxygenation after a PEEP change is debatable, but most studies suggest it is on the order of 20–30 min after each change [187–189]. Alternatively, ideal PEEP could be determined by starting high and gradually lowering PEEP in 2 cm H_2O decrements, as derecruitment may occur faster than recruitment [189]. In addition, it has been shown that there is hysteresis in the pressure-volume curve (difference between inspiration and expiration) and that the ideal PEEP setting should be determined on the deflation limb [190, 191].

The stress index is another potential method of setting optimal PEEP [185, 192–195]. With this method, the shape of the pressure-time curve during constant-flow (i.e. classic) VCV is used to detect optimal recruitment versus overdistension (Fig. 8.13). With this method, worsening compliance (stress index > 1) suggests that the lungs are overdistended and the PEEP is too high. Conversely, improving compliance (stress index < 1) suggests there is further potential for lung recruitment and the PEEP is too low [193]. Importantly, the presence of a pleural effusion has been shown to impact the accuracy of this particular method [196].

The dead-space fraction (V_D/V_T) may also be used to determine optimal PEEP and is commonly measured using the Bohr equation:

$$V_D/V_T = \left(PaCO_2 - PeCO_2\right)/PaCO_2 \qquad (8.11)$$

where $PeCO_2$ is the mean partial pressure of expired CO_2 (expired gas is collected and compared) and $PaCO_2$ is the partial pressure of CO_2 obtained from an arterial blood gas. A normal V_D/V_T is 0.3 or less. Increased V_D/V_T has been shown to correlate with outcomes in both critically ill children [197] and adults [198–201] with ARDS. The optimal PEEP is defined as the pressure level with the highest compliance in conjunction with the lowest VD/VT [202, 203].

The use of esophageal pressure monitoring has recently been proposed to determine the optimal PEEP (as well as for detecting auto-PEEP). Esophageal pressure (P_{ES}) is measured using a thin-walled balloon which contains a small amount of air at the end of a catheter placed into the lower esophagus. P_{ES} is a surrogate measure for pleural pressure (P_{PL}). Indeed, P_{ES} has been used to estimate P_{PL} in the laboratory setting for many years [204]. However, it has only been within the last few years that P_{ES} has been used as a surrogate for P_{PL} in the clinical setting [205–208]. There are no studies currently in children using this method.

FIO_2

Levels of FiO_2 lower than 0.5 are usually consider safe. The initial FiO_2 should be 0.6 unless SaO_2 <92 %. After setting the PEEP, FiO_2 should be set to the lowest level required to

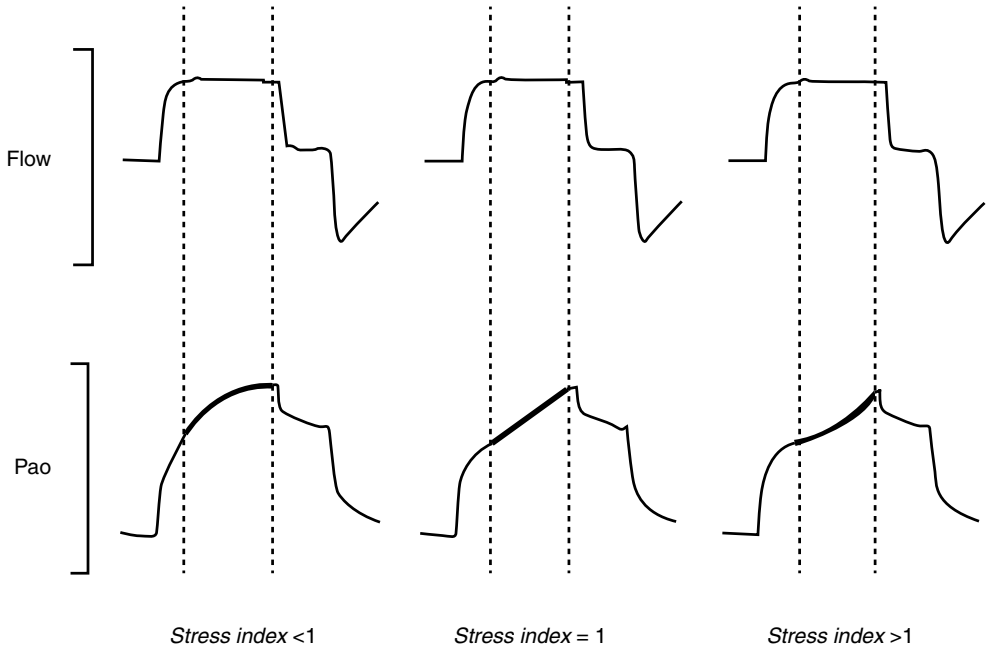


Fig. 8.13 Graphic representation of the stress index concept during constant-flow volume control ventilation. In this method, the shape of the pressure-time curve is used to determine and set optimal PEEP. If the compliance worsens as the lungs are inflated, the stress index will be >1 (shown as an upward concavity on the far right of the Figure). In this case, PEEP should be decreased. If the compliance is improving as the lungs are inflated, the stress index will be <1 (shown as a downward concavity on the far left of the Figure). In this case, PEEP should be increased further. The middle curve depicts ideal lung recruitment, when the stress index = 1 (there is a linear increase in pressure with constant-flow lung inflation) (Reprinted from Grasso et al. [193]. With permission of the American Thoracic Society. Copyright © 2013 American Thoracic Society. Official journal of the American Thoracic Society)

attain a SaO_2 >88–92 %. In a sick patient, FiO_2 <0.3 is not recommended for safety reasons (e.g. inadvertent extubation). When FiO_2 >0.6 is required despite high levels of PEEP, the tolerated SaO_2 limit may be reduced to 85–88 % (permissive hypoxemia) and/or additional methods for improving oxygenation considered (e.g., extracorporeal membrane oxygenation, a trial of prone positioning, etc) [160, 162, 209].

Rate (Frequency)

The ventilator rate is selected according the patient age and nature of the disease and is then adjusted according to the $PaCO_2$ and patient comfort. Recall that $PaCO_2$ is inversely proportional to minute ventilation (V_E).

$$V_E = V_T \times f \tag{8.12}$$

where f is the frequency or respiratory rate. The initial respiratory rate setting is ~40 breaths per minute in a neonate, ~20–25 breaths per minute in an infant and decreases further with age. The inspiratory time may be selected in order to provide a certain inspiratory: expiratory (I:E) ratio (usually 1:1.5 or 1:2) or to provide a preset inspiratory time. In neonates, the inspiratory time is usually set to 0.3–0.4 s and this usually increases with age. In heterogeneous lung disease with low compliance and variable time constants, the inspiratory time is usually longer in order to allow sufficient inflation. In contrast, in the case of obstructive lung disease (e.g. asthma, bronchiolitis), the expiratory time is set longer in order to allow the lung to fully empty, thereby avoiding air trapping and over inflation which can be confirmed by auscultation, time-flow loops, and auto-PEEP determinations using an expiratory pause (see further discussion below).

Triggering the Ventilator

In order to deliver a triggered breath the ventilator has to sense the patient's inspiratory effort. There are two principle mechanisms by which such sensing occurs – through either changes in pressure or changes in flow. In all modern ventilators designated for pediatric use, a continuous base flow exists in the circuit. Sensors measure the delivered flow and the exhaled flow and continuously calculate the difference between the two. If no leak exists in the system or around the tracheal tube, the flow measured is identical in both sensors unless the patient makes an inspiratory effort. As the patient inspires from the baseline flow, the delivered flow remains

unchanged, but the exhaled flow is reduced. When the differences between the delivered and exhaled flow equal or are greater than the preset flow sensitivity, the ventilator commences an inspiration. With pressure sensitivity, a drop in pressure below the preset baseline end-expiratory pressure is the signal to commence a ventilator breath.

Since a non-cuffed tube is commonly used in neonates, a leak may exist around the tracheal tube. The leak causes a drop in flow and pressure in the circuit, and may be detected as an inspiration; this will cause the ventilator to commence an inspiration commonly called *auto-cycling* or *auto-triggering*. In order to compensate for a leak, the operator may attempt to increase the sensitivity to flow or pressure. The differences between flow and pressure sensitivity are subtle. With flow-triggering, flow is experienced during the short interval between the start of the effort and the beginning of gas delivery. In contrast, with pressure triggering, a brief isometric effort is experienced. In clinical practice, there may be little significant differences between the two systems.

Patient-Ventilator Dyssynchrony

Suboptimal patient ventilator interaction (dyssynchrony) may adversely affect the comfort, work of breathing, gas exchange of the ventilated patient and if severe it can exacerbate lung injury. Patient-ventilator dyssynchrony is defined as a mismatch between a patient's underlying neurally mediated respiratory drive and the ventilator's inspiratory and expiratory times [137, 138, 210–213]. It occurs in up to 25 % of all patients on assisted mechanical ventilation in the ICU [214]. When patient-ventilator dyssynchrony is severe and frequent, it is associated with a higher risk of VILI, as well as a longer duration of mechanical ventilation (and all its associated complications) [215, 216]. In addition, patient-ventilator dyssynchrony contributes to disruption of sleep-wake cycles, higher sedation requirements, and delirium [210, 214, 216, 217]. While patient-ventilator dyssynchrony is a common problem in adults (25 %), its prevalence in pediatric practice is unknown. Clinical manifestations of patient-ventilator dyssynchrony include tachypnea, tachycardia, diaphoresis and sternal or costal retractions. Patient-ventilator interaction is determined by the success of the physician in reconciling the respiratory drive and lung mechanics of the ventilated patient with the design limitations of the ventilator. Two areas are of particular importance. First is the ability of the patient to initiate support from the ventilator, i.e. triggering. Second, is his or her ability to signal that support should be terminated so that expiration may occur (i.e. cycling). In addition, the support offered by the ventilator should be tailored to the patient's ventilatory demands. The evolution of ventilators has seen the emergence of support modes which utilize alterations in circuit gas flow to indicate the state of the respiratory cycle in the patient and by his effort determine the level of ventilatory support to be applied during inspiration.

The most common impediments to patient-ventilator synchronization are failure of patient inspiratory effort to trigger support from the ventilator and the development of intrinsic positive end expiratory pressure (auto-PEEP) through the use of ventilator patterns characterized by high respiratory rate and/or inadequate short expiratory time. The use of alteration in circuit gas flow to indicate a patient inspiratory effort (i.e. flow trigger; '*flow by*') has largely replaced the traditional *pressure* trigger in most ventilators. As discussed below, auto-PEEP can be detected with the end expiratory airway occlusion maneuver (expiratory hold in certain ventilators), but this particular maneuver requires a cooperative or paralyzed patient. It can be detected by analysis of flow-time curve, although the simplest method is by auscultation over the trachea for breath sounds that persist and do not stop for a short period of time before the next inspiration.

Patient-ventilator dyssynchrony is subclassified into trigger dyssynchrony, flow dyssynchrony, and cycle dyssynchrony. Trigger dyssynchrony is perhaps the most common and occurs when the patient is unable to trigger a supported breath or when the ventilator auto-triggers (i.e. auto-cycling or auto-triggering – see above). The ventilator trigger sensitivity should be set to be as sensitive as possible, without causing auto-cycling or auto-triggering. Aside from the wrong trigger sensitivity on the ventilator, failure to trigger a supported breath is usually due to a respiratory muscle weakness (which is especially common in patients on prolonged mechanical ventilatory support), auto-PEEP (see below), excessive condensation in the ventilator circuit, or leaks in the circuit or around the tracheal tube. Cardiac oscillations have also been shown to occasionally cause trigger asynchrony (auto-cycling) [218]. Flow dyssynchrony occurs when the inspiratory flow is set too low for the patient's demand. Clinical manifestations of flow dyssynchrony include tachypnea, retractions, and paradoxical breathing. Increasing the inspiratory flow or changing from VCV to either PCV or Adaptive Pressure Control mode (e.g. PRVC, Servo-i, Maquet, Solna, Sweden) should help alleviate some of these signs and symptoms [94–96, 213, 219, 220]. Alternatively, if the patient is already in PCV, increasing the rise time setting may help. Finally, cycle dyssynchrony occurs when the neurally mediated inspiratory time of the patient does not match the ventilator's inspiratory time. If the inspiratory time is too short, the patient may double-trigger the ventilator, leading to breath stacking. If the inspiratory time is too long, the patient will actively exhale while the ventilator continues to deliver a breath. Patient-ventilator dyssynchrony can be detected by clinical manifestations of respiratory distress or by examining the respiratory graphics on the ventilator [212, 213, 221–224].

Adjuncts to Mechanical Ventilation

Recruitment Maneuvers

A recruitment maneuver (RM) is performed in an attempt to re-open collapsed alveoli, thereby promoting better ventilation-perfusion matching. There are several ways of performing a RM that are described in the literature – however, to date there are no studies showing that RM improve outcome [225–227]. In addition, among the different approaches, there haven't been any studies showing the superiority of one RM method over another. In general, RM's have been shown to be safe and at least transiently improve oxygenation in critically ill children [228–232], though there are some studies that have demonstrated a transient and systemic release of pro-inflammatory cytokines after performing a RM [233, 234]. The significance of this latter finding is unknown. However, until there are studies showing that RM's improve outcome in critically ill children and/or adults, we suggest that RM's are probably best reserved for those children with refractory hypoxemia, as more of a rescue maneuver to improve oxygenation [235]. In addition, it is probably more important to maintain lung recruitment, once a RM has been performed, by setting an appropriate level of PEEP (see above).

Prone Positioning

Prone positioning has been shown to improve oxygenation transiently in both critically ill children and adults in multiple studies performed over the last decade. However, the effects of this improvement in oxygenation on mortality have been inconsistent [236–242]. Analysis of previously published trials suggest that there is a population of critically ill patients with severe ARDS who could benefit from prone positioning [241, 242]. Based on these data, a multicenter, prospective, randomized, controlled trial performed in critically ill adults with severe ARDS (defined as a PaO_2/FIO_2 ratio <150 mmHg with FIO_2 of at least 0.6) showed that early (meeting ARDS criteria for less than 36 h) and prolonged (at least 16 h per day) significantly reduced 28- and 90-day mortality [243]. Therefore, it would seem reasonable to keep prone positioning in the armamentarium for management of critically ill children with severe ARDS, at least as a rescue therapy for those patients with refractory hypoxemia.

Nitric Oxide

Inhaled nitric oxide (iNO), a potent short acting selective vasodilator, has been shown to have short-term effects on oxygenation in selected patients with ALI/ARDS. Unfortunately, these short-term improvements have no resulted in significant improvements in clinical outcomes, such as the duration of ventilatory support or mortality [244]. Therefore, iNO is generally reserved for patients with refractory hypoxemia with FiO_2 >0.6 and a significant pulmonary shunt in which a trial of iNO shows improvement in oxygenation. Inhaled nitric oxide is discussed elsewhere in this textbook.

Surfactant Administration

The role of surfactant administration in patient with ALI/ARDS has not been established. Several studies have been performed in adults and children with conflicting results. A prospective, multi-center, randomized, placebo-controlled trial in children showed that surfactant may improve outcome (i.e., ventilator-free days, mortality) of selected group of children with ALI [245]. However, a more recent trial was stopped early due to futility [246]. Based on these studies, exogenous surfactant administration cannot be recommended outside the context of a clinical trial.

Complications of Mechanical Ventilation

Mechanical ventilation is a lifesaving therapy in many circumstances. However, as mentioned briefly above (and discussed further in subsequent chapters of this textbook), mechanical ventilation is not a natural way of breathing and is associated with numerous complications and adverse physiological side effects which for the most part.

Respiratory Complications

Injury to the respiratory system can involve either (or both) the upper airways and lungs. Airway injury may be due to laryngoscopy, insertion of the tracheal tube, or the presence of the tracheal tube for a prolonged period of time. Lung injury is due to mechanical stretch caused by the continuous pressure and volume changes associated with positive pressure ventilation. Such injury may be macroscopic (i.e. extra-alveolar air leak) or microscopic. The latter is functionally and histologically similar to that observed in ARDS and is termed Ventilator-Induced Lung Injury (VILI). Additional pulmonary complications include Ventilator-Associated Respiratory Infections (VARI) and atelectasis.

Upper Airway Injury

Early complications related to tracheal intubation are mostly due to traumatic intubation and include tooth avulsion or damage, laryngeal trauma, and pharyngeal injury ranging from mild edema to laceration with severe bleeding. Tissue injury secondary to prolonged tracheal intubation is likely due to the pressure and shearing forces the tube exerts on the surrounding tissues which may be exacerbated by movement

of the head or neck. Nasotracheal intubation may cause pressure sores or necrosis of the ala nasi or nasal septum, and oral intubation may cause similar ulceration at the angle of the mouth. Prolonged ventilation in the neonate may cause grooves in the palate, and in extreme cases, a traumatic cleft.

Clinically apparent laryngeal injury is relatively rare and ranges from mild edema to ulceration of the mucosa. Significant vocal cord injury may be minimal, or in extreme cases, involve subluxation of the arytenoid cartilages with subsequent vocal cord fixation. The more frequent and clinically significant complications occur in the subglottic region (i.e. below the vocal cords). This region is a narrower region in children as compared with adults, and it is the only region with a complete circumferential cartilaginous ring that doesn't afford for expansion under pressure. Infection and ischemic necrosis may develop over time, and during healing granulation tissue, or in the absence of resolution, an organized scar may develop and evolve causing subglottic stenosis and clinically significant upper airway obstruction. Similar injury may develop deeper in the trachea at the tip of the tracheal tube or at the carina as a result of continuous epithelial injury from the suction catheter. Some of the injuries may be prevented by skillful tracheal intubation, with a proper size tube, and taking care with tube repositioning, taping and carefully measured suctioning lengths. When a cuffed tracheal tube is being used, the cuff should be deflated daily for assessment of a leak, and then inflated to a maximal pressure no greater than 25 cm H_2O.

Air Leak

Macroscopic air leak has been reported in up to 40 % of children receiving mechanical ventilation [247]. However, more contemporary studies suggest that with the open-lung approach to mechanical ventilation with the use of low tidal volumes and permissive hypercapnia, the incidence of air leak is much lower [45, 248]. Excessive transpulmonary pressure and overdistension leads to alveolar rupture and escape into the pulmonary interstisium (i.e. Pulmonary Interstitial Emphysema, PIE). Extension of this injury may involve the mediastinum (i.e. pneumomediastinum), the pleural space (i.e. pneumothorax) or pericardium (i.e. pneumopericardium), or it may propagate into the subcutaneous space (i.e. subcutaneous emphysema). Subcutaneous emphysema, pneumopericardium and PIE are usually not clinically significant, although the former may cause discomfort. Pneumothorax is generally the most important type of air leak. If continuous, air may enter the pleural space with each inspiration, and because it cannot exit the space, a net accumulation occurs, with steadily increasing pressure (i.e. tension pneumothorax). Over time, the volume of air and the pressure in the pleural space increase significantly causing collapse of the ipsilateral lung, shift of the mediastinum, obstruction of the venous return, and compromise of the cardiac output. Tension pneumothorax should be immediately suspected in any mechanically ventilated child who unexpectedly experiences an acute deterioration in oxygenation or cardiac output. Unless it is rapidly diagnosed and drained it may cause death. Air leak is rare in otherwise healthy lungs, in the absence of excessive airway pressures. Retrospective studies have shown the association of occurrence or air leak with high levels of PIP, PEEP, or tidal volume [45, 248–250]. Application of a protective ventilation strategy that limits plateau pressure and tidal volume may decrease the risk of air leak.

Ventilation Associated Respiratory Infections (VARI)

Nosocomial infections that are associated with tracheal intubation and mechanical ventilation include ventilator-associated tracheobronchitis (VAT), ventilator-associated pneumonia (VAP), and nosocomial sinusitis. VAP is a significant problem in the PICU and has been associated with significant increases in duration of mechanical ventilation, PICU length of stay (LOS), hospital LOS, costs, and mortality [251–260]. VAP is principally a clinical diagnosis based on the appearance of new infiltrates on chest radiography, purulent endotracheal secretions, and the presence of fever or leukocytosis. The microbiologic diagnosis can be confirmed by obtaining a tracheal aspirate for culture during suction, bronchoalveolar lavage (BAL), or bronchoscopic-protected specimen brush sampling, though the latter is rarely performed in children. When the diagnosis of VAP is established on clinical grounds, microbiological confirmation (i.e. BAL) should be sought, and therapy (directed by the local microbial sensitivity profile) commenced pending microbiologic confirmation. The antibiotics should be tailored according to the response and the subsequent microbiologic data. It is important to recognize the local resistance patterns when making empiric choices about initial antibiotic therapy. A bundle of measures that may reduce the risks of VAP include the following placing patients in semi-recumbent position (elevating the head of the bed), changing heat-moister exchangers, and maintenance of oral hygiene [256, 259, 261, 262].

Ventilator-associated tracheobronchitis (VAT) may be a precursor to VAP [263–266], and preliminary data has suggested that it also increases the duration of stay in the PICU (Wheeler, *unpublished data*). The diagnostic criteria for VAT are similar to those used for VAP, with the exception of a change in infiltrates on chest radiograph or worsening ventilator status. The use of VAP as a quality metric has been questioned [267–269], primarily due to the low specificity of the diagnostic criteria. For this reason, some authors have suggested that VAT and VAP should be considered in aggregate.

There have only been a few studies about nosocomial sinusitis in the PICU [270–272]. However, these studies suggest that sinusitis is likely underappreciated and underrecognized in this population.

Atelectasis

Injured lungs have a low compliance and a tendency to collapse [273, 274]. Mechanical ventilation increases the risk by direct lung injury, retention of secretions, de-nitrogenation during ventilation with 100 % oxygen, endobronchial placement of the tracheal tube, and intermittent suctioning. Furthermore, neuromuscular blockade, commonly used during mechanical ventilation, abolishes diaphragmatic tone and further decreases FRC. Because infants have a relatively lower FRC and less collateral ventilation than adult, they may be at even greater risk of developing atelectasis. It mainly occur in the left lower and right upper lobe Principi T et al. [248]). Atelectasis is important because it may compromise oxygenation, increase pulmonary artery pressure, and contribute to VILI by over-distension of the ventilated lung regions. It may be treated with positioning, physiotherapy, increasing the PEEP, and the use of routine, short recruitment maneuvers. Prolonged ventilation may contribute to *disuse atrophy* of the diaphragm, which has been demonstrated in animal studies, but not in humans. However, it seems that maintenance of spontaneous respiratory effort may mitigate against this problem.

Ventilator-Induced Lung Injury (VILI)

VILI is discussed in great detail in a subsequent chapter. Suffice it to say that positive pressure ventilation is not a natural form of breathing and can cause lung injury that is virtually indistinguishable from that of ALI/ARDS. Several types of VILI are relevant in the PICU. *Volutrauma* (lung injury induced by excessive tidal volumes, leading to repetitive stretch injury) can be minimized by avoiding the use of excessive tidal volumes (generally defined as tidal volume ≥10 mL/kg predicted body weight) and transpulmonary pressures – the so-called lung-protective strategy [36, 105]. *Barotrauma* (lung injury induced by excessive pressures, leading to alveolar overdistension and air leak) can be minimized by avoiding the use of excessive plateau pressures (see discussion below), generally less than 30 cm H_2O [105]. These high pressures cause injury by virtue of the fact that higher transpulmonary pressures cause excessive stretching and alveolar distension. Numerous animal models have shown, however, that limiting alveolar expansion, even in the face of very high transpulmonary pressures (e.g. with chest strapping) does not cause injury [275]. Therefore, patients with poor chest wall compliance (e.g. obesity, significant abdominal distension) may require increased transpulmonary pressures which can be done relatively safely as long as excessive tidal volumes are avoided [276, 277]. Atelectrauma (lung injury induced by the cyclical opening of alveoli during the inspiratory phase and closure/collapse during the expiratory phase) can be minimized with the so-called "open lung approach," which combines a lung-protective strategy of low tidal volume ventilation with optimal lung recruitment (using PEEP). Biotrauma (lung injury induced by the local production and systemic release of proinflammatory cytokines) can lead to a systemic inflammatory response and multiple organ dysfunction syndrome (MODS) [278]. Finally, a fractional inspired oxygen concentration (FIO_2) approaching 1.0 can lead to oxidative injury to the lung (oxygen toxicity). The safe range of FIO_2 is not exactly known, but most authorities suggest that FIO_2 ≤0.6 is preferable.

Auto-PEEP

Auto-PEEP (also known as intrinsic PEEP, inadvertent PEEP, endogenous PEEP, occult PEEP) is measured using an end-expiratory pause for 0.5–1.5 s during either VCV or PCV [279]. The measurement of auto-PEEP is only accurate when the patient is not exerting a significant respiratory effort. Auto-PEEP is caused by air-trapping (hyperinflation) in the alveoli at the end of expiration, which exerts a positive pressure, and it is usually due to an incomplete expiration prior to the initiation of the next breath [280–282]. The incomplete expiration is usually due to the presence of severe airflow limitation (e.g. increased airways resistance, as in children with asthma), though auto-PEEP can be present even in the absence of airflow limitation [283]. For example, setting the inspiratory time too high (e.g. inverse ratio ventilation) will result in too short of an expiratory time. Patients with dynamic hyperinflation and dynamic compression of the airways are also at risk. Dynamic hyperinflation is present when the end-expiratory lung volume exceeds FRC, usually as a result of airflow limitation (resulting in incomplete emptying of the alveoli during exhalation), but also from ventilation with high tidal volumes, use of short expiratory times, or presence of lung units with long time constants (resistance x compliance).

There are several other clues to the presence of auto-PEEP. The breathing pattern and respiratory graphics are particularly useful. If the patient is still exhaling when the next breath is delivered (observed directly or on the respiratory waveform), auto-PEEP is likely present (Fig. 8.14). Similarly, inspiratory efforts that fail to trigger a breath (i.e. trigger asynchrony – see above) also suggest the presence of auto-PEEP. Finally, signs and symptoms of increased work of breathing (tachypnea, nasal flaring, retractions) can also suggest the presence of auto-PEEP. Finally, an esophageal pressure monitor can also detect the presence of auto-PEEP [280].

Ideally, auto-PEEP should be as low as possible (preferably 0 mmHg), as there several associated adverse effects. First and foremost, auto-PEEP effectively acts as a threshold

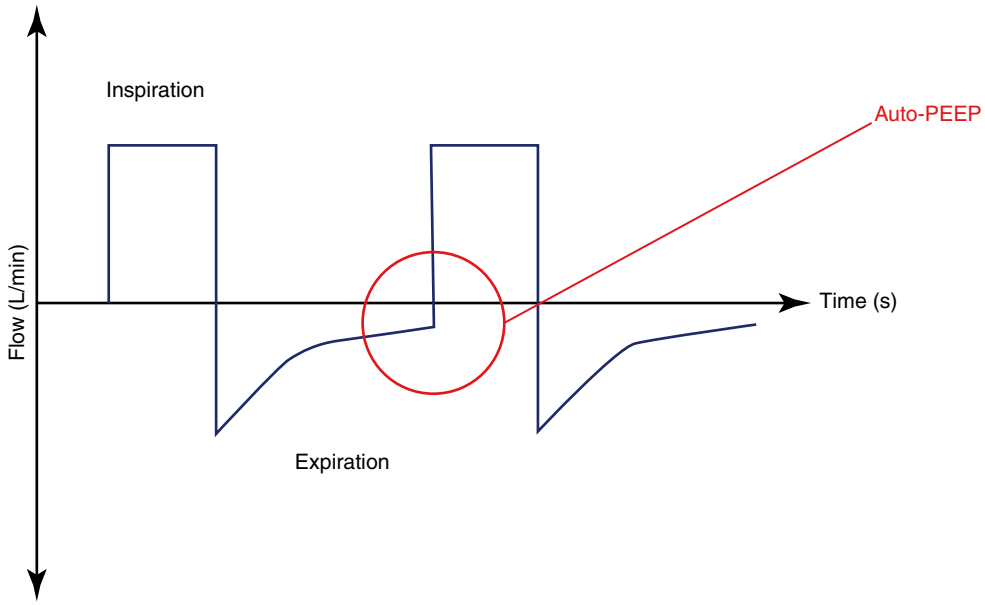


Fig. 8.14 Detection of auto-PEEP. Flow-time waveform in a patient showing persistence of airflow at the end of expiration, as well as an incomplete return to the baseline

pressure that the patient must overcome to trigger the ventilator, leading to patient-ventilator asynchrony (trigger asynchrony). Auto-PEEP represents an additional inspiratory load, as shown by the modified equation of motion below:

$$P_{RS} = V/C + (R \times V) + PEEP_i \quad (8.13)$$

where $PEEP_i$ is the auto-PEEP (intrinsic PEEP). In the presence of auto-PEEP, a negative intrapleural pressure equal to the level of auto-PEEP and the ventilator sensitivity threshold must be generated in order to generate inspiratory flow (Fig. 8.15). The application of extrinsic PEEP (set by the clinician) will improve the patient's ability to trigger the ventilator, by raising the trigger level closer to the total PEEP (so-called *waterfall effect*) [284]. Auto-PEEP also increases the risk of VILI (through overdistension) and worsens hemodynamics (through the cardiorespiratory interactions discussed below).

Central Nervous System Effects

The effects of positive pressure ventilation have been extensively studied in the context of head trauma, but the effects on intracranial pressure (ICP) and cerebral perfusion pressure are complicated. Some issues are apparent from several studies. The application of PEEP may directly increase ICP by transmission of pleural pressure through vertebral veins towards the cranium. Indirectly, PEEP may increase ICP by increasing the right ventricular afterload, decreasing right ventricular output, and decreasing venous return – including the venous return from the skull. These effects are more prominent in patients with normal ICP, and are minimal in the context of modestly elevated ICP [285–287]. Furthermore, increased PEEP may decrease cardiac output and systemic arterial pressure, and thereby reduce cerebral perfusion pressure.

There is a growing interest in the effects of sedation and neuromuscular blockade, which are frequently used in critically ill children on mechanical ventilation, on delirium and sleep [288]. The alarms on the ventilator, the need for suctioning, and poor patient-ventilator synchrony also contribute to the adverse effects of mechanical ventilation on sleep [217]. This is a relatively new area for research, and there will likely be more studies devoted to this issue.

Cardiovascular Effects

The heart is a pressure chamber within another pressure chamber, the thorax. Since the pulmonary vasculature, right ventricle, and the left atrium all exist in the same pressure chamber (i.e. thorax), the changes in pleural or intrathoracic pressure affects them identically. However, intrathoracic pressure will affect the pressure gradient for both blood draining into the heart (i.e. venous return) as well as for the blood flow leaving the heart (i.e. left ventricle ejection), independent of cardiac function. The overall effects of mechanical ventilation on cardiovascular function are discussed in much greater detail in the chapter on Cardiorespiratory Interactions. However, they will be reviewed in brief here as well.

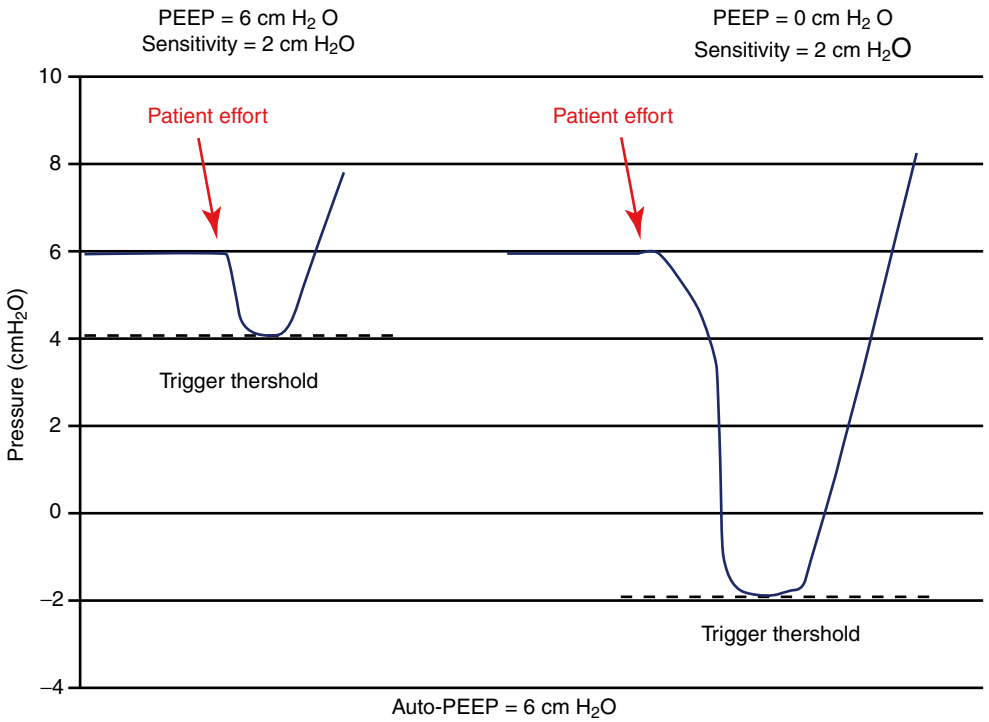


Fig. 8.15 Pressure-triggering in a child with auto-PEEP 6 cm H_2O. On the *left-hand side* of the graph, the trigger sensitivity is set at 2 cm H_2O and the extrinsic PEEP is set at 6 cm H_2O. The ventilator is triggered when the patient's own spontaneous inspiratory effort reduces the airway pressure to the set threshold level (in this case, 2 cm H_2O below PEEP, or 4 cm H_2O). On the *right-hand side* of the graph, the trigger sensitivity is set at 2 cm H_2O, but this time the extrinsic PEEP is set at zero. Now the patient must reduce the airway pressure to 2 cm H_2O below auto-PEEP, which requires a negative pressure of 8 cm H_2O

During inspiration with positive pressure ventilation, the thorax expands and the lung volume and intrathoracic pressure increase. In contrast, with a negative pressure (or spontaneous) inspiration, the changes are in the opposite direction – the volume of the thorax and lung increase, but the intrathoracic pressure decreases. It is important to understand that the pressure that the clinician usually observes during mechanical ventilation is the airway pressure, which is that pressure in the proximal trachea, not the pressure transmitted to the lung. During positive pressure ventilation, the volume of the lung increases only by increasing the airway pressure, only part of this pressure is transmitted to the lung. The pleural pressure may be monitored with an esophageal probe, but this is not routine in most centers. In cases where lung compliance is reduced (as in ALI/ARDS) or lung resistance is increased (as in asthma), the percentage of airway pressure transferred to pleural pressure is lower than when chest wall compliance is reduced. Generally, when tidal volume is kept constant, the changes in airway pressure reflect mostly the changes in mechanics of the lung and will not reflect changes in intrathoracic pressure [289, 290].

Venous Return

When intrathoracic pressure increases, right atrial atmospheric pressure also increases. The systemic venous return, which is the principal determinate of cardiac output in the normal heart, depends on the gradient between the upstream mean systemic pressure and the downstream pressure in the right atrium. An increase in the right atrial pressure therefore decreases the venous return to the right atrium, decreasing the filling pressure and stroke volume of the right ventricle. The reduction in venous return due to an elevation in right atrial pressure may be of a lower magnitude than the increases seen with a reduction in right atrial pressure. This occurs because during positive pressure ventilation the intra-abdominal pressure increases, increasing the mean systemic pressure. The hemodynamic effects of increased intrathoracic pressure are, under normal conditions, not clinically significant. However, in certain clinical conditions, the effect of elevated intrathoracic pressure may compromise cardiac output. These include hyopvolemia, relative hyopvolemia (e.g. septic shock), and obstructive right heart lesions and/or right ventricle failure. Often this effect is countered by effects on left ventricular afterload.

Left Ventricular Afterload

The left ventricle and thoracic aorta are also in the thorax and both are affected by changes in intrathoracic pressure. The pressure that left ventricular work is directed against is the transmural pressure and not the pressure measured outside the thorax. The transmural pressure of the aorta is the difference between the intravascular pressure (positive) and the intrathoracic pressure (negative during spontaneous respiration). During spontaneous inspiration, the intrathoracic pressure decreases (becomes more negative) and as a result the transmural pressure increases, thereby increasing the afterload of the left ventricle. Conversely, during positive pressure ventilation, the intrathoracic pressure becomes positive and as a result the transmural pressure decreases, thereby decreasing the afterload of the left ventricle. Thus, the application of positive pressure ventilation with PEEP (or just CPAP) has been shown to improve significantly cardiac output in patient with heart failure [291]. Most commonly these swings in intra-thoracic pressure are not clinically significant in otherwise healthy children under normal conditions. However, they may become clinically significant in extremes, such as the case of severe upper-airway obstruction where the intra-thoracic pressure significantly decreases, resulting in a substantial increase in the afterload of the left ventricle and contributing to the development of acute pulmonary edema (so-called negative pressure or post-obstructive pulmonary edema).

Cardiovascular Effects of Change in Lung Volume

A key effect of altered lung volume is on the pulmonary circulation, a low-resistance, low-pressure system. The pulmonary vessels can be classified as either alveolar or extra-alveolar vessels. The alveolar vessels are small vessels (i.e. capillaries, arterioles and venules) that are adjacent to the alveolar wall. The extra-alveolar vessels are the larger vessels in the interstitium. The total pulmonary vascular resistance (PVR) is the sum of the resistance in both the alveolar and the extra-alveolar vessels. A change in lung volume has different effect on both systems. In normal lung mechanics, ventilation around FRC is associated with the nadir of PVR. However, when the lung is inflated above FRC, the distended alveoli may compress the alveolar vessels and increase the PVR. Similarly, as lung volume falls below FRC, the extra-alveolar vessels become more tortuous, the transmural pressure increases, and the vessels tend to collapse, resulting in increased PVR. Thus, at least in the isolated perfused lung (although never conclusively demonstrated in humans), maintenance of the lung volume at physiologic FRC will yield optimal PVR. Furthermore, in case of ventilation with small tidal volumes, certain areas of the lung tend to collapse, causing alveolar hypoxia which in turn may activate hypoxic pulmonary vasoconstriction. Indeed, in contrast to the traditional beliefs outlined above, newer *in vivo* data suggests that during atelectasis, alveolar hypoxia, not volume loss, may be the key determinant of increased PVR [292].

Ventricular Interdependence

The right and left ventricles pump in series and share a common intraventricular septum. If the right ventricular volume increases, it shifts the septum to the left, reducing left ventricle filling volume and compromising left ventricle diastolic function. Ventricular interdependence is not a significant factor in positive pressure ventilation unless pulmonary vascular resistance is increased significantly. Some suggest that this phenomenon may become clinical significant in patients with acutely injured lungs where echo-cardiographic studies have revealed leftward shift with the application of PEEP, most probably because of the increase in pulmonary vascular resistance and right ventricle afterload.

Renal Effects

Mechanical ventilation with positive pressure induces a reduction in renal water and sodium excretion. This effect appears to be exacerbated by PEEP. The rise in intrathoracic pressure, administration of sedatives and analgesic drugs, and immobility reduce venous return, cardiac output, and may eventually lower mean arterial pressure. As a result, renal perfusion decreases, and the renin–angiotensin system is stimulated. Angiotensin II formation stimulates aldosterone production resulting in increased reabsorption of water and sodium. Low systemic blood pressure increases the secretion of antidiuretic hormone which also decreases urinary output Reduced venous return and decreased right atrial pressure results in reduced levels of atrial natriuretic peptide to further reduce diuresis [293–295]. These issues are particularly important when discontinuing mechanical ventilation, as in the presence of good cardiac function, a large diuresis may occur. Recently, the biotrauma hypothesis suggests that non-protective ventilation may release inflammatory mediators into the systemic circulation that potentially cause renal dysfunction [296].

Hepatic Effects

Blood flow to the liver represents the balance of flow through the hepatic artery and portal circulation. The reduction of cardiac output associated with positive pressure ventilation may reduce flow through the hepatic artery. In addition, positive pressure ventilation increases intra-abdominal pressure which may decrease portal vein flow [249, 297]. Indeed, positive pressure ventilation has been shown to reduce splanchnic blood flow in some [249, 297], but not all studies [298]. Many patients receiving positive pressure ventilation

demonstrate some degree of hepatic dysfunction; it is not clear whether positive pressure ventilation is causative here, or whether the dysfunction represents systemic underlying systemic disease. The precise clinical significance of the positive pressure on liver function in the critically ill is not clear.

Weaning from Mechanical Ventilation

Weaning is the usual word to describe termination of mechanical ventilation, because in most cases in adults it is a gradual and sometimes long process. However, in children the more appropriate description would be liberation or termination of mechanical ventilation, because in most children the process is short without either delay or significant problems [38]. Only small groups of children, usually those with underlying chronic pulmonary diseases required weaning. However, in those children with neuromuscular diseases, weaning as commonly practiced in adult ICU's may actually be counter-productive and potentially disadvantageous.

Premature termination of tracheal intubation and mechanical ventilation may result in the re-intubation of the patient and introduction of a second period of mechanical ventilation that is often associated with clinical deterioration and increased morbidity and mortality. There is no established strategy for successful termination of ventilation, though, it has been shown that faster and more successful weaning may be achieved with the implementation of weaning protocols designed to offer objective clinical parameters associated with successful extubation and complement of clinical judgment.

The gradual transition from full or almost full mechanical support to spontaneous breathing may be accomplished by gradually decreasing the mandatory breath rate with SIMV, the level of PEEP and/or the degree of pressure or volume support. Sedation should be reduced carefully in order not to compromise the respiratory drive, while at the same time not compromising patient comfort or precipitating drug withdrawal. Although objective measurements for successful termination of ventilation and extubation do not exist, patients should be evaluated daily to determine whether they still required mechanical ventilation. A spontaneous breathing trial as an extubation readiness test (Pressure support ventilation with PS 10 cm H_2O and PEEP 5 cm H_2O for 2 h) was associated with a reduction in the duration of mechanical ventilation by 24 h [299], though this requires further study before it can be universally recommended [300]. One should consider the following before termination of ventilation and extubation: evidence of recovery from the cause of respiratory failure, minimal O_2 or PEEP requirement (e.g. FiO_2 <0.4, PEEP <6 cmH_2O), absence of significant acidosis (e.g. pH >7.25), hemodynamic stability, good respiratory drive and ability to protect the airway.

Conclusion

Mechanical ventilation plays a pivotal role in the treatment of critically ill children. The knowledge of childhood physiology and ventilation techniques may be among the most important skills a physician practices in critical care. Over time, mechanical ventilators have become more sophisticated and new modes of ventilation have been introduced and monitoring techniques have undergone dramatic improvements. With the recognition of the complications associated with PPV and the advances in monitoring, it is possible that in the near future we will be able to tailor, in real-time, the modality of ventilation to a specific patient with a specific disease.

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Therapeutic Gases in the Pediatric ICU

9

Brian M. Varisco

Abstract

The principal function of our lungs is to absorb oxygen from the environment and expel carbon dioxide into it. One of the foremost duties of the pediatric intensivist is to ensure adequate tissue oxygen delivery and to aid in carbon dioxide elimination. This chapter first discusses the oxygen enrichment of inspired air and the delivery of this oxygen to the alveoli and tissues. Particular attention is given to the alveolar gas equation. The chapter then turns its attention to adjunctive gases used in the PICU. Some of these gases, such as nitric oxide are used pharmacologically, whereas others, such as helium, are used for their physical properties. Through an array of devices, the pediatric intensivist can deliver a variety gases to maintain adequate oxygen delivery and promote patient healing and recovery.

Keywords

Gases • Oxygen • Nitric oxide • Carbon dioxide • Helium

Introduction

Although imperceptible, the atmosphere of gas that surrounds us and its associated pressure is critical to nearly every biological process that occurs from a sub-cellular to an organismal level. At sea level, our atmosphere exerts a pressure of 760 mmHg on our bodies, and we inhale atmospheric gases by increasing our thoracic volume through diaphragmatic contraction and rib cage expansion, which reduces our transpulmonary gradient by several mmHg. This pressure gradient allows ingress of gas through a patent upper airway and inflation of our alveoli until a neutral transpulmonary gradient is again achieved. Our diaphragm then relaxes to allow the egress of gas through the elastic recoil of our lung parenchyma thus completing the respiratory cycle [1]. Respiratory care in the Pediatric Intensive Care Unit (PICU) largely consists of remedying limitations of gas flow in the conducting airways and impairments of gas exchange in the distal airspaces. The pediatric intensivist achieves this by physically or pharmacologically altering the airway, by altering the gas admixture entering the lungs, and by altering the pressure gradient by which gas enters the lungs.

Therapeutic Gases Used in the PICU

Gases used in the PICU can be classified as reactive or inert. Reactive gases are those that are used in the PICU due to their biological effects. Oxygen is the quintessential reactive gas used in the PICU and is crucial for the functioning of every cell in the body (except, paradoxically, red blood cells). Carbon dioxide results from cellular oxidative metabolism. It is critical for maintenance of intracellular and extracellular pH as carbonic anhydrase catalyzes its reaction with water to form bicarbonate anion. Carbon dioxide has rare therapeutic applications in the PICU. Carbon monoxide is a highly toxic free radical that may significantly impair oxygen delivery if inhaled in significant quantities. In lower quantities, however, it is a potent anti-inflammatory and is currently under

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investigation as a therapeutic agent. Nitric oxide is also a potent free radical but it is has roles as a neurotransmitter, vasodilator, and modulator of innate immune response. Its use in the PICU is now widespread with an evolving consensus on its appropriate use. Inhaled anesthetic gases such as isoflurane are commonly used in the operating room as anesthetic agents, but their bronchodilatory and antiepileptic properties make them potent, though rarely employed therapeutic gases.

Inert gases are those that confer no benefit apart from their physical properties. Helium is a noble gas that decreases the density of inhaled gas and reduces airflow turbulence. It is used to overcome obstruction of larger conducting airways. Nitrogen is a generally non-reactive gas that has clinical relevance under conditions of rapid depressurization such as a quick assent when deep-sea diving. Nitrogen is also used to create sub-atmospheric oxygen levels (i.e., $FiO_2 < 0.21$) for the manipulation of pulmonary vascular resistance during the management of critically ill children with congenital heart disease and pulmonary over-circulation. Radioisotopes such as xenon-133 may be used for nuclear medicine studies, but have no therapeutic uses.

Oxygen

Historical Perspective

Since ancient times, breath and life have been nearly synonymous. However, it was not until 1774 that scientists became aware that air might be a mixture of several different substances. In that year Joseph Priestly discovered *dephlogisticated air* through the performance of two key experiments. Both experiments involved the heating of mercuric oxide in an inverted glass container using a magnifying glass which released the *dephlogisticated air*. In the first experiment, smoldering wood splits burst into flame when placed in contact with it. In the second, a mouse lived several times longer than one in the in a similar container with ambient air [2].

We now know that oxidative phosphorylation is the principal mechanism by which all eukaryotic organisms derive the energy to perform necessary biological processes and that the saga of evolution is in large part built on increasingly complex and efficient mechanisms of oxygen delivery and utilization. Maintaining adequate oxygen delivery from alveolus to mitochondria is one of the principal goals of the pediatric intensivist. Here, we focus on the relevant physical and chemical properties of oxygen. The bulk flow of oxygen through the respiratory tree and its transport across the alveolar and capillary membranes are described elsewhere in this textbook.

The Physiology of Oxygen Delivery

One of the principal concerns of the pediatric intensivist is the delivery of oxygen. To achieve this, blood must both contain oxygen (arterial oxygen content) and be circulated to tissues (cardiac output). Thus oxygen delivery (DO_2) is equal to cardiac output (CO) times arterial oxygen content (C_aO_2).

$$DO_2 = C_aO_2 \times CO$$

The determinants of cardiac output are covered elsewhere, but may briefly be summarized as the amount of blood the heart ejects per cycle (stroke volume, SV) times the cycles per minute (heart rate, HR).

$$CO = SV \times HR$$

Alveolar Oxygen and Carbon Dioxide Tensions

To understand how oxygen gets from the alveolus to the blood, we must first understand how oxygen acts in the alveolus. By Dalton's law, the partial pressure of a gas (P_{gas}) is determined by the product of its fractional concentration multiplied by atmospheric pressure (P_{ATM}).

$$P_{gas} = Fractional\ Gas\ Concentration \times P_{ATM}$$

The ambient fractional concentration of oxygen is 0.21. Therefore, at sea level, the partial pressure of oxygen is

$$P_{ATM}O_2 = 0.21 \times 760\,mmHg = 160\,mmHg$$

The composition of inspired air changes between the atmosphere and the alveolus. First, air is humidified as it passes through the nasal passages and upper airway resulting in 100 % humidification by the time air reaches the alveolus. At 37 °C water has a partial pressure of 47 mmHg in the alveolus. Second, carbon dioxide reduces the partial pressure of oxygen in the alveolus. Alveolar carbon dioxide levels remain relatively consistent throughout the respiratory cycle for two reasons. One, carbon dioxide from the pulmonary microcirculation equilibrates quickly with alveolar gas; and two, during normal tidal breathing, a large percentage of alveolar gas is not exhaled (functional residual capacity). These two factors result in a relatively consistent partial pressure of carbon dioxide in the alveolus that is essentially equal to the arterial partial pressure of carbon dioxide. Thus, the partial pressures of two gases, carbon dioxide (P_ACO_2) and water (P_AH_2O), reduce alveolar oxygen tension (P_AO_2). However, oxygen and carbon dioxide may not be exchanged at the same rate in the alveolus. If less than one O_2 molecule is consumed for every CO_2 molecule created (i.e. more CO_2 is exhaled than O_2 consumed), then there will be a small increase in the partial pressure of carbon dioxide resulting in a slight decrease in alveolar O_2 content. This ratio of O_2

consumption to CO_2 production is referred to as the respiratory quotient (R).

$$R = \frac{CO_2\ Production}{O_2\ Consumption}$$

The degree of oxidation or reduction of a substrate determines its respiratory quotient. Highly oxidized organic compounds have a large percentage of carbon-oxygen bonds whereas highly reduced substances have a high percentage of carbon-hydrogen bonds. As demonstrated below, glucose has a respiratory quotient of one, palmitic acid 0.68, and glycine 0.75.

$$Glucose: C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O$$

$$Palmitic\ Acid: C_{16}H_{34}O_2 + 23\frac{1}{2}O_2 \rightarrow 16CO_2 + 17H_2O$$

$$Glycine: NC_2H_5O_2 + 1\frac{1}{2}O_2 \rightarrow NH_3 + 2CO_2 + H_2O$$

The respiratory quotient for a standard US diet is approximately 0.8. High fat diets decrease the respiratory quotient and high carbohydrate diets increase it. Under conditions of anaerobic metabolism, the respiratory quotient can be significantly greater than one.

In considering fractional oxygen content, water vapor partial pressure, carbon dioxide partial pressure, and respiratory quotient, we can calculate alveolar oxygen partial pressure as

$$P_AO_2 = F_iO_2\left(P_{ATM} - P_AH_2O\right) - \frac{P_ACO_2}{R}$$

This is the alveolar gas equation and is one of the fundamental equations of pediatric critical care. The equation has two important implications. First, by providing supplemental oxygen, the intensivist increases the partial pressure of oxygen in the alveolus. Although commonly employed, this maneuver can increase the gradient by which oxygen diffuses into the pulmonary capillaries and improve pulmonary venous oxygen saturation and systemic oxygen delivery. The second implication of the alveolar gas equation is that elevated levels of carbon dioxide reduce alveolar oxygen pressure. Therefore, in the absence of intrapulmonary or cardiac shunting, hypoventilation can reduce P_AO_2, P_aO_2 and arterial oxygen saturation. Under-appreciation of this fact and masking respiratory acidosis with low levels of supplemental oxygen can lead to severe clinical consequences. By means of demonstration, at sea level and under normal physiologic conditions, a P_aO_2 of 91 mmHg correlates to a saturation of 97 % and P_aO_2 of 62 correlates with an oxyhemoglobin saturation of 92 %. If P_AO_2 is equal to P_aO_2 (i.e. low Alveolar-arterial oxygen gradient), a respiratory quotient of 0.8 is assumed, and an elevation of P_ACO_2 is entirely to blame for reduced oxyhemoglobin saturation, then the P_ACO_2 must be 70 mmHg when the arterial oxygen saturation is 92 %. If the F_iO_2 is increased to 25 %, then a P_ACO_2 of 93 mmHg is required to see the same level of desaturation. These calculations do not account for the reduction in hemoglobin oxygen saturation attributable to respiratory acidosis which would further reduce oxygen saturation levels.

Oxygen Delivery

Once in the blood, there are three determinants of blood oxygen content: solubilized oxygen, hemoglobin concentration, and hemoglobin oxygen saturation. The solubility of oxygen in blood at 37 °C is 0.003 mL per deciliter of blood per mmHg. Adult hemoglobin can carry 1.34 mL of oxygen per gram of hemoglobin. Hemoglobin oxygen saturation is influenced by many factors detailed elsewhere in this textbook, though the principal determinant of hemoglobin saturation is arterial oxygen tension (P_aO_2). Arterial oxygen content (C_aO_2) is the sum of dissolved oxygen content and the product of the fractional hemoglobin oxygen saturation (S_aO_2) and hemoglobin concentration (g/dL).

$$C_aO_2 = 1.34 \times S_aO_2 \times Hb + 0.003 \times P_aO_2$$

Both the partial pressure of oxygen in the alveolus and arterial oxygen content have profound implications for the intensivist. Specifically, arterial oxygen content can be increased by increasing the fraction of oxyhemoglobin, increasing hemoglobin concentration, or increasing dissolved oxygen content. The patients described in Table 9.1 demonstrate how the intensivist can manipulate these variables to maximize oxygen delivery. Patient A is healthy and at sea level. Patient B is healthy and 5,280 ft above sea level with an atmospheric pressure of 640 mmHg. Patient C is a trauma patient at sea level before any medical intervention. Patient D is this same patient with administration of 100 % O_2 by a nonrebreather mask. Patient E has severe pneumonia and is breathing room air. Note that hemoglobin concentration is the principal determinant of arterial oxygen content. Also note that in severe anemia increasing dissolved oxygen content can substantially increase arterial oxygen content.

Oxygen Administration

An increase in fractional inspired O_2 can be achieved by several means.

Non-contact Devices and Techniques

The clinician needs to weigh the benefits and disadvantages of each modality of oxygen administration given clinical

Table 9.1 Clinical scenarios dealing with arterial oxygen content

	S_aO_2	Hb (g/dL)	P_aO_2 (mmHg)	C_aO_2 (mL/dL)
Patient A	0.97	12	91	11.9
Patient B	0.94	12	74	11.5
Patient C	0.97	5	91	5.1
Patient D	1	5	663	7.0
Patient E	0.75	12	41	9.1

Three factors determine arterial oxygen content (CaO_2). Patient A is a normal adult at sea level. Patient B is a normal adult at 5,280 ft above sea level. Note that despite a small significant drop of arterial oxygen tension (P_aO_2) oxygen saturation and arterial oxygen content are little affected. Patient C is a healthy adult trauma patient. Note that a decrease in hemoglobin concentration significantly reduces arterial oxygen content. Patient D is this same trauma patient after administration of 100 % oxygen by non-rebreathing mask. Note that an increase in the dissolved oxygen content in the blood increased oxygen carrying capacity by 37 % in this low-hemoglobin state. Patient E is an adult with severe pneumonia prior to treatment. Note that even with oxygen saturations of 75 %, the arterial oxygen content is still 76 % of Patient A

circumstances. For example, placing and keeping a nasal cannula on vigorous infants and toddlers can induce significant agitation, and oxygen administration by alternative means may be adequate (Fig. 9.1). Blow-by oxygen can be administered through several different devices such as corrugated tubing, an open face mask, or an anesthesia bag. This method provides for low increases in inspired O_2 concentration that are highly variable, but this technique induces less agitation than techniques that require application of masks or prongs to a patient's face. Oxygen tents are plastic enclosures into which oxygen is delivered providing an oxygen-enriched atmosphere for the infant. The tents can achieve F_iO_2 of 0.4–0.5 and have the disadvantage of preventing access to the infant without reducing this F_iO_2. Oxygen hoods are smaller than tents and form a relatively tight seal around the neck. Oxygen is introduced through a port in one of the side walls. Oxygen hoods can achieve F_iO_2 of up to 0.9 and have the advantage of allowing access to the infant's body. Size and patient movement are the principal limitations of this device.



Fig. 9.1 Non-threatening oxygen administration. Children should be allowed to remain in their position of comfort, as this will optimize gas exchange. Supplemental oxygen should be administered in a non-threatening manner (in some instances, a parent may need to administer supplemental oxygen) (Reprinted from George et al. [43]. With permission from Center for Pediatric Emergency Medicine)

Contact Devices and Techniques

A nasal cannula is a common device that uses two short prongs to deliver oxygen to the nasal passages. The fractional inspired oxygen depends on oxygen flow and tidal volume. As inspiratory air flow exceeds oxygen flow, room air is entrained and the maximal F_iO_2 that can be expected is 0.4. In the adult, an increase in F_iO_2 by 0.04 for every liter per minute flow increase can be expected. Even with mouth breathing, an increase in F_iO_2 is achieved due to the entraining of air from the oxygen-enriched nasopharyngeal space.

Several different face masks are available for use in the PICU, including simple masks, partial rebreathing masks, non-rebreathing masks, and Venturi masks. Simple face masks are loose fitting and cover the nose and mouth. They can be expected to achieve F_iO_2 levels of 0.35–0.65 with flow rates between 5 and 10 liters per minute. Flow rates of less than 5 liters per minute may not be sufficient to displace exhaled carbon dioxide and should be avoided.

Partial rebreathing masks are rarely used. This mask uses a plastic bag for a gas reservoir attached to the end of a loose-fitting plastic mask that goes over the nose and mouth. Unlike a non-rebreathing mask, it has no exhalation valve. Exhaled CO_2 is dissipated in the large volume of the bag and mask and exits around the mask during exhalation. As such, carbon dioxide rebreathing is trivial. Partial rebreathing masks can be expected to achieve F_iO_2 levels of 0.5–0.6. Non-rebreathing masks look similar to partial rebreathing masks except that they have an exhalation valve to minimize

carbon dioxide rebreathing and are tight-fitting. The plastic bag acts as an oxygen reservoir and prevents the entrainment of room air. F_iO_2 levels of near one can be achieved with non-rebreathing masks. Venturi masks utilize the Bernoulli principle to tightly control F_iO_2. A jet of oxygen is introduced into the mask at high velocity which entrains a consistent volume of room air. Higher flow rates generate lower F_iO_2 as the low pressure created by the jet increases. This mask allows the clinical to maintain constant gas composition independent of minute ventilation.

Bag Mask Ventilation

If the above devices cannot improve oxygen delivery sufficiently, positive pressure ventilation may be required. The clinician can provide this manually via bag mask ventilation. Two providers are preferred for this procedure; however, the intensivist should be proficient at performing bag mask ventilation independently. The mask provides the interface between the patient and the bag ventilation device. One of the most important considerations in bag mask ventilation is achieving a proper seal. The mask should fit snuggly over the bony bridge of the nose and the bony prominence of the chin. Pushing the mask down to achieve a better seal is generally ineffective and the provider should focus on bringing the face to the mask and on efforts to open the airway such as a chin lift, jaw thrust, or use of an artificial airway. Nasopharyngeal airways are effective in conscious patients while oropharyngeal airways should be reserved for obtunded or sedated patients. Neck over-extension should be avoided as this can lead to airway closure. Figures 9.2 and 9.3 demonstrate the proper application of the mask during bag mask ventilation for one and two provider bagging.

Two types of devices are commonly used for bag mask ventilation: self-inflating bags and anesthesia bags. The ventilation portion of self-inflating bags consists of an easily deformable soft plastic reservoir which quickly reinflates with ambient or oxygen enriched air when released. The delivered F_iO_2 with this device is variable when used without an oxygen reservoir due to air entrainment (0.3–0.8). When extended corrugated tubing or an oxygen reservoir bag us used F_iO_2 levels up to 0.95 can be achieved. Self-inflating bags contain an exhalation valve which prevents the redelivery of exhaled air, and they often contain manometer which allows the clinician to monitor delivered pressures. There is also a pressure release valve that will not permit delivery of pressures greater than approximately 35 cm of water; however, this valve can be disabled—usually with a metal clasp or plastic switch. The bag connects to the patient interface via a 90° elbow. In order to apply end expiratory pressure, a PEEP (positive end-expiratory pressure) device must be utilized. Most self-inflating bags have a loose fitting cap on non-bag side of the exhalation valve which can be replaced with a PEEP device. Figure 9.4 shows the different sizes of self-inflating bags available and a PEEP device. It is critical to recognize that self-inflating bags are not capable of continuous flow and that continuous positive airway pressure (CPAP) or continuous blow-by oxygen is not possible with these devices. Airflow can only be achieved with depression of the bag.

Anesthesia bags require a constant flow of gas to distend the balloon-like bag. They require a bit more experience to operate effectively than self-inflating bags, but they are preferred by many intensivists because they permit the clinician to "feel" the lung compliance, they allow for blow-by oxygen, and they allow for the application of CPAP. The bag is connected to a 90° elbow which connects to the patient interface. There is no exhalation valve so adequate flow is required for carbon dioxide removal. Most of these bags use an adjustable pressure relief valve that allows the provider to easily adjust the level of CPAP or PEEP applied and also monitor the pressure applied during bag mask ventilation. Figure 9.5 shows a self-inflating bag with manometer.

Carbon Dioxide

Carbon dioxide had previously been used in rare circumstances to increase pulmonary vascular resistance in patients with congenital heart disease and substantial pulmonary overcirculation. This particular technique is discussed elsewhere in the textbook. The most common use for carbon dioxide in the PICU is in extracorporeal membranous oxygenation (ECMO). The oxygenator of the ECMO circuit often is much more efficient at removing carbon dioxide than oxygenation and so at times, carbon dioxide needs to be administered with the oxygen admixture. An in depth discussion of this topic is beyond the scope of this chapter but the reader is referred to the ECMO Specialist Training Manual [3].

Carbon Monoxide

At higher concentrations, carbon monoxide binds hemoglobin with high affinity and reduces the effective arterial oxygen content. Studies conducted in the laboratory suggest that carbon monoxide may act as a potent anti-inflammatory agent to improve cellular adaptation to stress. Two enzymes, heme oxygenase 1 and 2 naturally synthesize carbon monoxide. Preclinical trials of use of carbon monoxide in lung injury [4–6], cardiopulmonary bypass [7], and sepsis [8] have suggested substantial benefit and carbon monoxide may be the next therapeutic gas to undergo trials in the PICU.

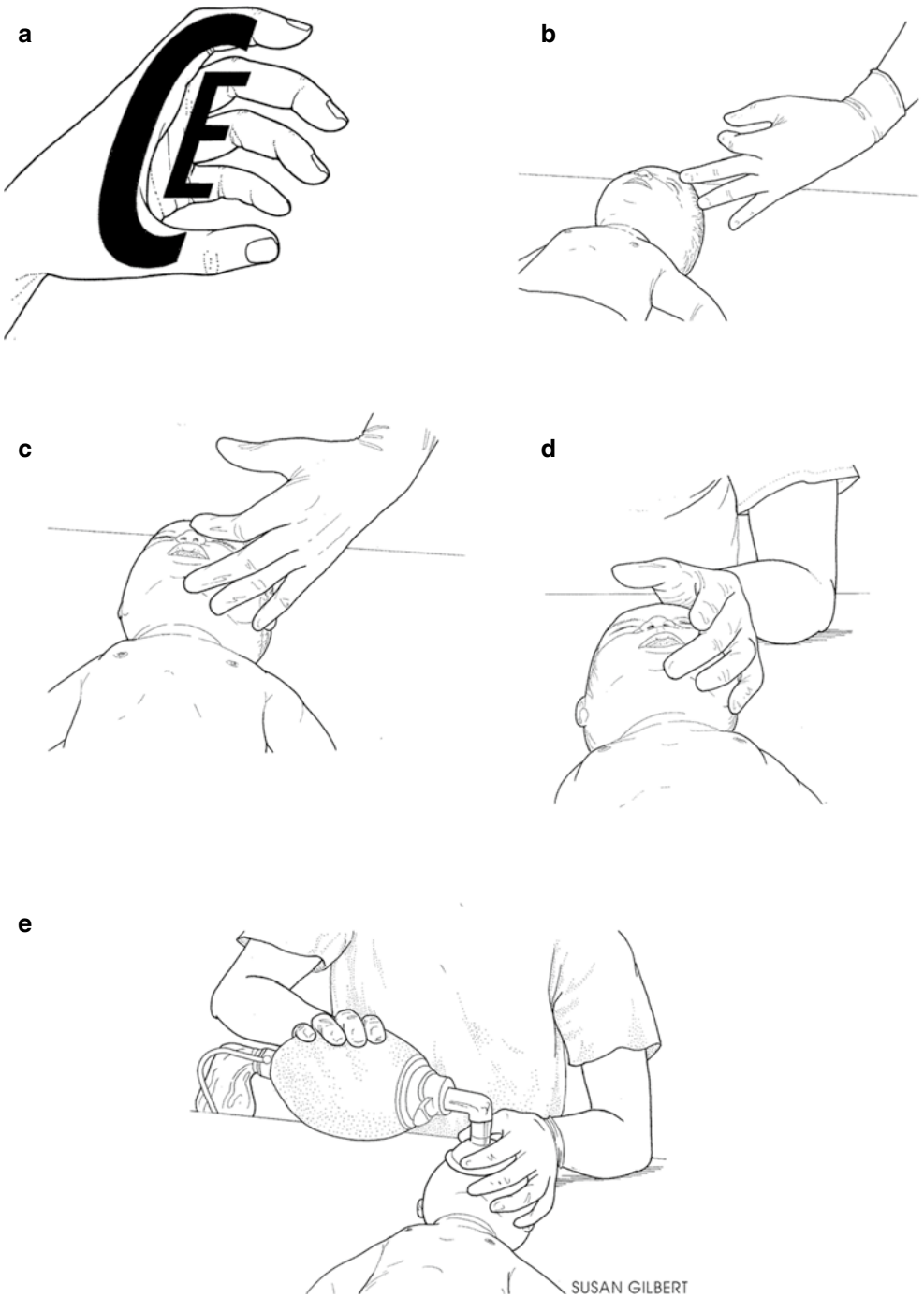


Fig. 9.2 Technique for one-provider bag mask ventilation. The E-C clamp technique achieves a good seal when placing a mask for assisted ventilation. The third, fourth, and fifth fingers are placed along the jaw to provide a chin lift (forming an E); and the thumb and index finger are placed to hold the mask on the child's face (forming a C). (**a**) Hand displaying E-C shape. (**b**) E formed with small, ring, and middle fingers; C formed with index finger and thumb. (**c**) E fingers resting on bony ridge of jaw. (**d**) C fingers positioned to hold mask. (**e**) Proper E-C clamp for assisted ventilation (Reprinted from George et al. [43]. With permission from Center for Pediatric Emergency Medicine)

Nitric Oxide

Background

Nitric oxide (NO) is a free radical synthesized endogenously by nitric oxide synthase-of which there are three isoforms. Inducible nitric oxide synthase (iNOS) is present in many cell types but most studied in macrophages where it is important in innate immune defense [9]. Endothelial nitric oxide synthase (eNOS) is present principally in endothelial cells and is activated by cellular stretch. eNOS produces nitric oxide which reduces vascular smooth muscle tone [10]. Figure 9.6 illustrates the key signaling pathways in nitric oxide-mediated pulmonary arterial vasodilatation. Neuronal nitric oxide synthase (nNOS) is expressed in neurons where NO acts as a neurotransmitter [11]. There is considerable overlap in the expression pattern of NOS isoforms and the reader is directed to several reviews for a more in depth discussion of nitric oxide signaling [12–14]. Inhaled nitric oxide (iNO) is rapidly inactivated by heme and NO serum concentrations are negligible before leaving the pulmonary circulation. Therefore, the vasodilatory effects of

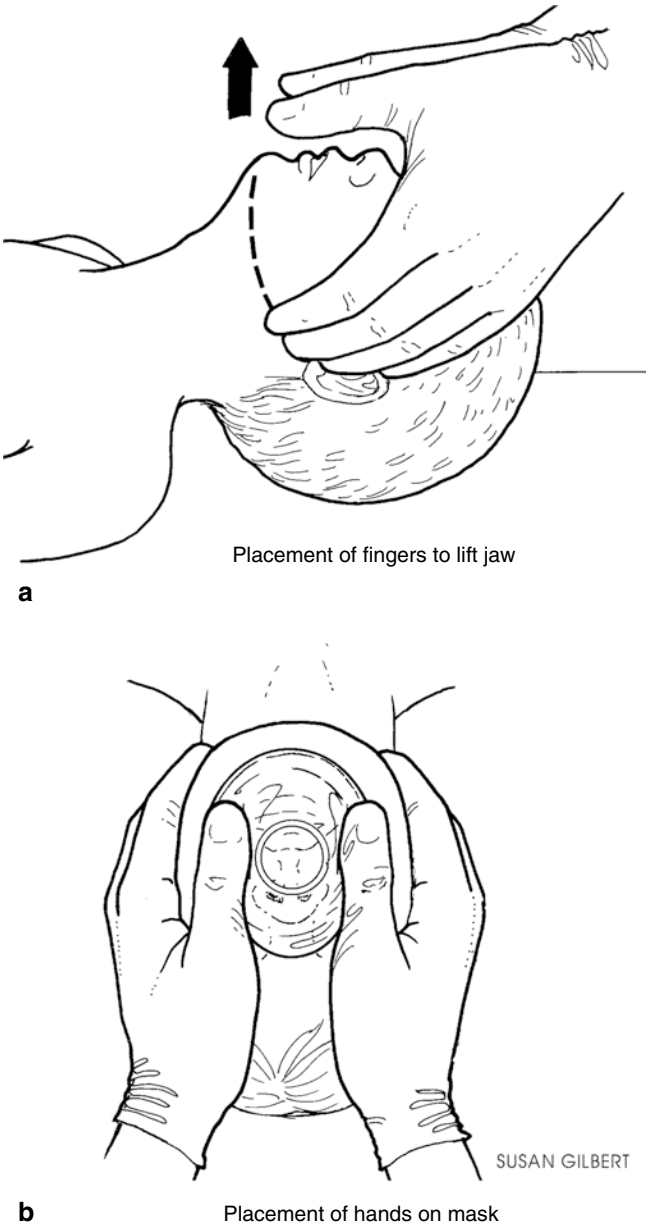


Fig. 9.3 Technique for two-provider bag mask ventilation. The triple airway maneuver (head tit, chin lift, jaw thrust) is an effective technique for maintaining airway patency during two-provider bag mask ventilation. First, the 3rd and 4th fingers are placed at the angle of the mandible. Then, the head is tilted, chin lifted, and jaw thrust applied simultaneously (**a**). The mask is applied with the thumbs (**b**) (Reprinted from George et al. [43]. With permission from Center for Pediatric Emergency Medicine)

iNO are entirely local. However, nitric oxide can also react with cysteine at its sulfur residue to nitrosylate the protein. S-nitrosylation alters the function of a host of proteins such as hemoglobin, hypoxia inducing factor-1α (alpha), matrix metalloproteinase 9, L-type calcium channels, cardiac sodium channels, insulin receptor-β (beta), and protein kinase B [15]. The clinical implications of S-nitrosylation are unclear at this time. While the use of nitric oxide in the PICU is becoming more widespread, there is a general consensus that indications for its use need to be more clearly defined. After addressing the administration of iNO, this section will then focus on the evidence based medicine supporting its clinical application.

Administration

Nitric oxide is generally administered at concentrations of 20 parts per million (ppm) or less bled in through the inspiratory limb of a conventional or oscillatory ventilator. When administered via nasal cannula, higher concentrations (60–80 ppm) may be used to compensate for the entrainment of ambient air. Nitric oxide is supplied in gas tanks and specialized equipment that continuously monitors nitric oxide concentration. The equipment also monitors concentrations of the toxic byproduct nitrogen dioxide.

Clinical Applications

Persistent Pulmonary Hypertension

In utero, the human fetus maintains a relatively low P_aO_2 at 30 mmHg and the fluid-filled lungs have an elevated pulmonary vascular resistance and receive a relatively low percentage of cardiac output with the majority of right ventricular cardiac output passing through the foramen ovale and across the ductus arteriosus. At birth, the lungs inflate, pulmonary vascular resistance decreases, pulmonary blood flow increases, and P_aO_2 rises [1]. Infants born prematurely may have persistence of this elevated pulmonary vascular resistance with continued right to left shunting and its associated right ventricular strain. This condition is termed persistent pulmonary hypertension of the newborn (PPHN). The United States Federal Drug Administration (FDA) has approved the use of inhaled nitric oxide for PPHN largely based on favorable outcomes in two studies. In 1992 Kinsella, et al. demonstrated that inhaled nitric oxide at 10–20 ppm resulted in an increase in systemic blood pressure in infants that were going onto ECMO for PPHN [16]. In a large, multicenter randomized trial published in 2000 (NINOS study), inhaled nitric oxide at 20 ppm was noted to reduce the use of ECMO for PPHN by half [17]. Currently, PPHN is the only FDA-approved indication for iNO and the only indication with Level I evidence.

Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) is a spectral disorder with diverse etiologies resulting in a similar clinical manifestation. Defining different subgroups of ARDS is the subject of much investigation. Ventilation-perfusion

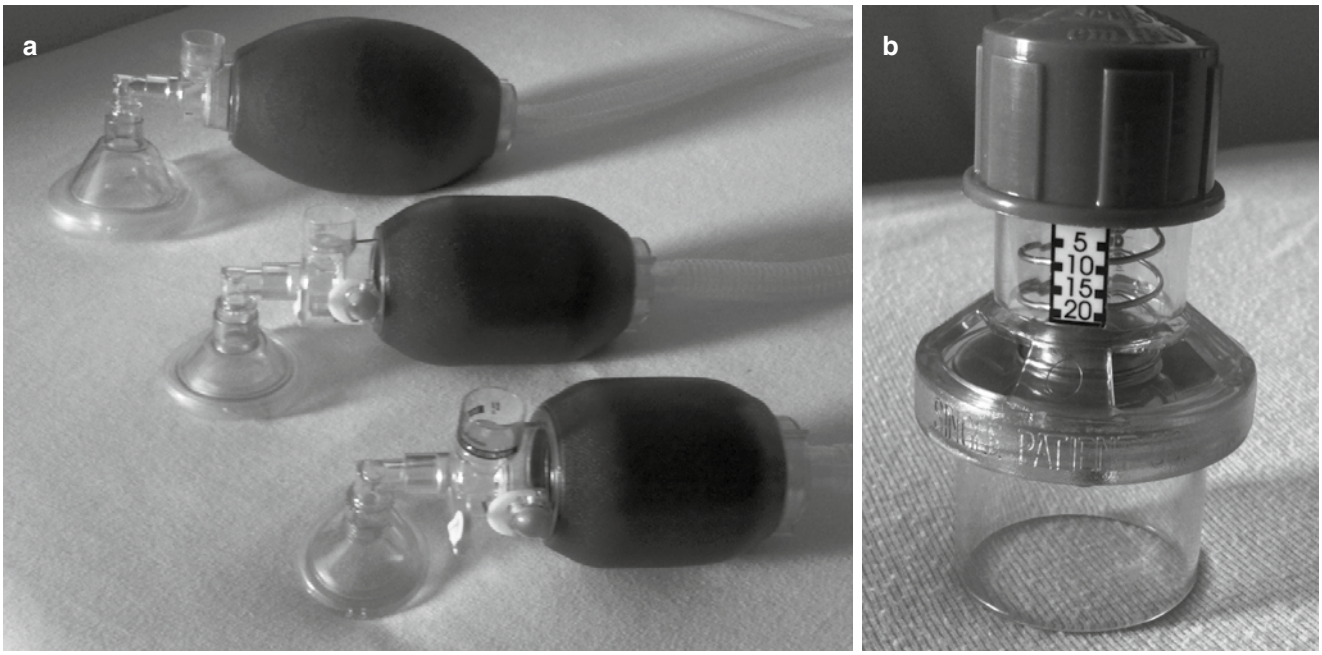


Fig. 9.4 Self-inflating bag equipment. (**a**) Several different sized self-inflating bags are available for different sized patients. (**b**) A PEEP device is required if application of PEEP is required during bag mask ventilation

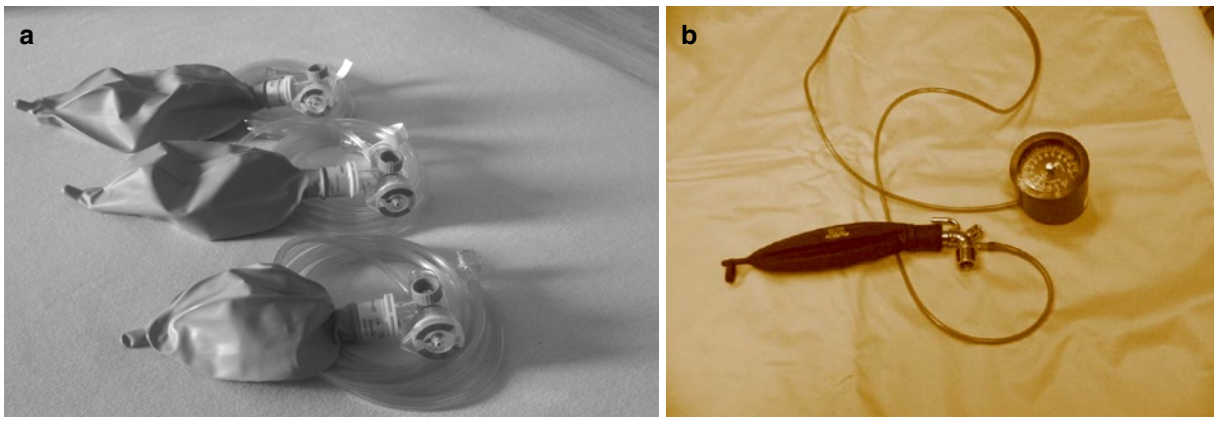


Fig. 9.5 Anesthesia bag. (**a**) Several different anesthesia bags are available for use. Most have a manometer attached. (**b**) Those bags without a manometer have a port into which an external manometer can be attached

mismatching is the primary reason for the reduced P_aO_2/F_iO_2 (or Sat-F_iO_2) [18] ratio required for the diagnosis of ARDS. Inhaled nitric oxide selectively vasodilates ventilated lung regions and reduces this ventilation-perfusion mismatch. There is clear evidence that inhaled nitric oxide improves oxygenation in ARDS [19, 20]; however; randomized control trials have also clearly demonstrated that inhaled nitric oxide does not improve outcome in adult [21, 22] pediatric [20] or neonatal [23] hypoxemic respiratory failure. Despite this data, use of inhaled nitric oxide in adult ICUs for ARDS is common [24] and is likely more prevalent in PICUs. Although randomized control trials do not support its general use for ARDS, in a given patient a trial of inhaled nitric oxide is reasonable if the improvement in oxygenation provided would allow the clinician to forgo a significant escalation of therapy.

Pulmonary Hypertension

Pulmonary hypertension is commonly seen in patients with variety of congenital heart lesions, particularly those with preexisting pulmonary over-circulation. The reduction of pulmonary vascular resistance afforded by inhaled nitric oxide can reduce right ventricular afterload and improve cardiac output in the immediate post-operative period, and the intensivist should anticipate those patient who may benefit

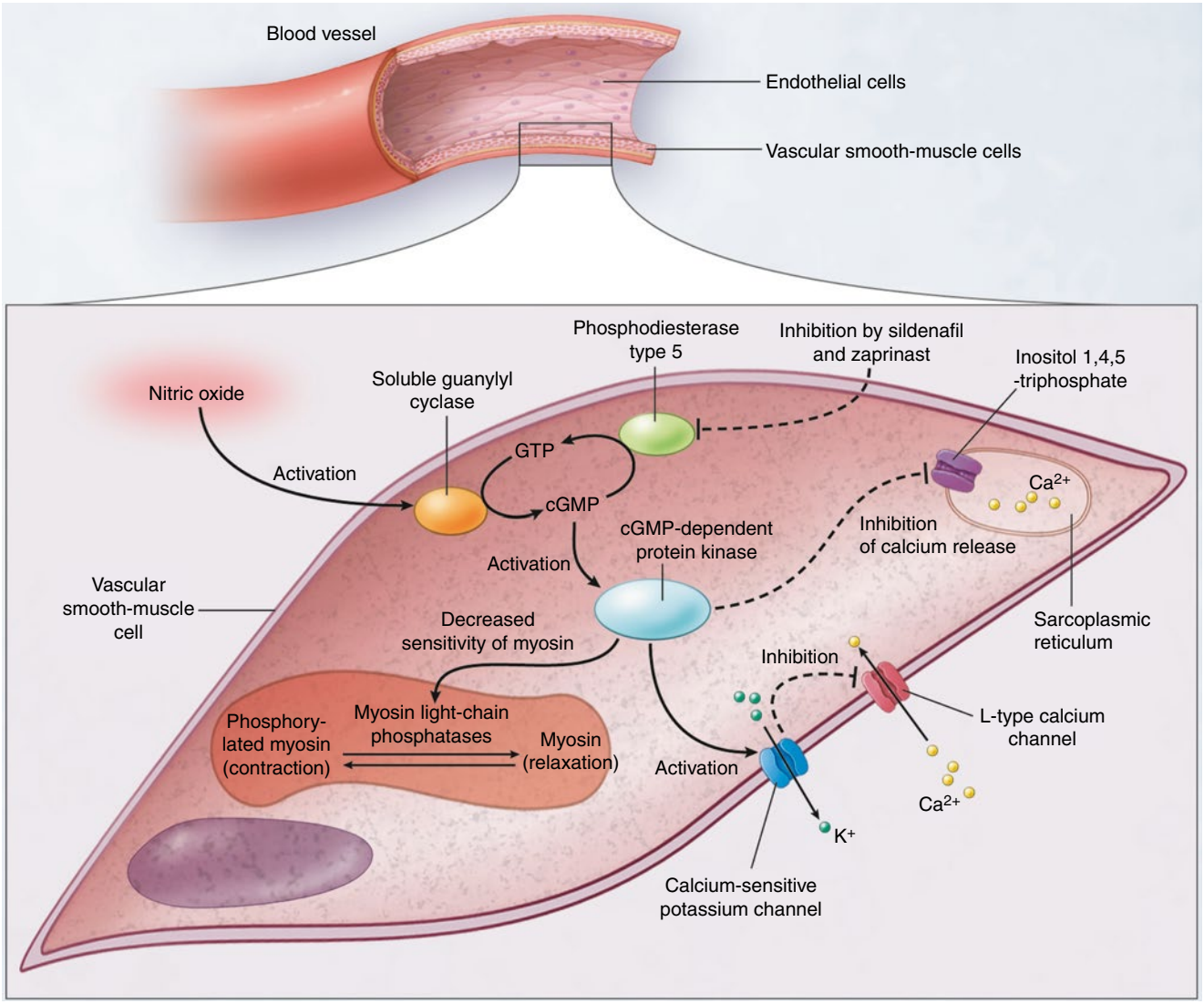


Fig. 9.6 Key signaling pathways in nitric oxide mediated vasodilatation. Nitric oxide is produced by endothelial cells via endothelial nitric oxide synthase and binds to soluble guanyl cyclase. Soluble guanyl cyclase converts guanyl triphosphate (GTP) to cyclic guanyl monophosphate (cGMP). GMP inhibits cGMP gated calcium channels and activates potassium channels inhibiting the influx of calcium and promoting the efflux of potassium. cGMP activates protein kinase G which phosphorylates calcium releasing proteins in the sarcoplasmic reticulum. The reduced calcium content of the cell reduces the activity of myosin light chain kinase which acts to reduce myosin activity and reduce the tension of the smooth muscle cell (Reprinted from Griffiths and Evans [12]. With permission from Massachusetts Medical Society)

from its use so that arrangements may be made prior to his or her post-operative arrival. A proactive approach to the management of post-operative pulmonary hypertension can mitigate against a cycle of poor cardiac output, hypotension, metabolic acidosis, and escalating vasopressor requirement with associated increased afterload. Nitric oxide improves myocardial function [25, 26] and pulmonary arterial pressures [27–33] following cardiopulmonary bypass. No study to date has demonstrated a significant mortality benefit. The clinician should be aware that pulmonary arterial hypertension secondary to pulmonary venous hypertension is not amenable to nitric oxide therapy.

Toxicity and Complications

Nitric oxide is an oxidizing agent that can oxidize heme iron from its ferric to ferrous state inducing methemoglobinemia. This is rare at concentrations of 20 ppm or less [34], but the astute clinician should be aware of this complication should difficulties with oxygen delivery develop.

Abrupt discontinuation of iNO can lead to rebound vasoconstriction [35] which can be clinical important in patients with impaired right ventricular function. The etiology of this phenomenon is unclear, but it is thought to be related to a down regulation of endogenous endothelial nitric oxide

synthase, soluble guanylate cyclase, and/or an increase in endothelin-1 expression [36–39]. For non-pulmonary hypertension indications, this rebound can typically be treated with a brief increase in F_iO_2.

Inhaled Anesthetic Gases

Apart from their anesthetic properties, the anesthetic gases isoflurane, sevoflurane, desflurane, and halothane are potent bronchodilatory and antiepileptic agents [40, 41]. These properties allow inhaled anesthetic agents to be used for status asthmaticus and status epilepticus in the PICU. Halothane has largely fallen out of favor due to its hepatoxicity.

Anesthetic gases must be administered through an anesthesia cart with a vaporizer specific to the agent being administered and a scavenging system. Indeed, the need for specialized equipment often precludes use of these gases in the PICU setting. The patient may be ventilated with the anesthesia cart as in the operating room; however, these carts generally do not have the same sophisticated software available on most conventional PICU ventilators. Gases may also be bled in through the inspiratory limb of a conventional ventilator; however, calculated volumes will be inaccurate and patients must often be ventilated in a pressure control mode. Pharmacologically, anesthetic gasses are very lipophilic which accounts for their quick transit across the blood-brain barrier. However, with sustained use they accumulate in adipose tissue which often leads to continued drug effect after discontinuation.

Helium

According to the Hagen-Poiseuille Law, resistance to flow through the airway is inversely proportional to the fourth power of airway diameter under conditions of laminar flow. Resistance is higher in turbulent flow but increases in a non-linear fashion [1]. In conditions where there is a reversible obstruction of airflow in the large conducting airways, the conversion of turbulent to laminar flow can significantly decrease work of breathing. Helium-oxygen mixtures are used for this purpose. The understanding of how this works rests in nineteenth century physics.

Although George Gabriel Stokes first described the mechanics of flow of fluid through a tube, the Reynolds Number is named for Osborne Reynolds who widely applied the principles described 50 years earlier [42]. The Reynolds Equation provides a value above which flow becomes turbulent

$$Re = \frac{\rho VD}{\mu}$$

Re represents Reynolds number, ρ represents the density of the fluid (kg/m^3), V is the velocity (meters/s), and D is the diameter of the tube (meters), and μ is the viscosity of the fluid (Pascals × s). Reynolds numbers of less than 2,000 result in laminar flow, 2,000–4,000 in transitional flow, and greater than 4,000 in turbulent flow [1].

Helium is a low density gas. By the Ideal Gas Law, molecules of a gas (moles, n) at a given temperature (T) and pressure (P) will disperse evenly within a given container (volume, V) as a function of the ideal gas constant (R).

$$PV = nRT$$

Therefore the density of a gas is directly proportional to its molecular weight, and only one element, hydrogen, has a lower molecular weight than helium. This also explains why helium:oxygen mixtures of less than 70:30 are generally ineffective. Heliox comes pre-mixed as 80:20 or 70:30 admixtures to prevent the dangerous situation of inadvertently administering 100 % helium, and consequently no oxygen to the patient. It can be delivered through nasal cannula or mask. Flow should be high enough to minimize entrainment of room air which lessens heliox efficacy. Heliox can also be administered through a conventional ventilator although with the reduced density of gas volume and pressure measurements will be inaccurate unless the ventilator is calibrated using the heliox admixture or an external calibration monitor is applied. Experience using heliox with oscillatory ventilation is lacking although several case reports exist.

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High Frequency Oscillatory Ventilation

10

Kathleen M. Ventre and John H. Arnold

Abstract

Forty years have elapsed since investigators first appreciated that tidal volumes measuring less than the physiologic dead space can produce reliable ventilation when delivered at high frequencies. Of all high frequency ventilation techniques, high frequency oscillatory ventilation (HFOV) is the most well studied and is the most commonly utilized in clinical practice today. In HFOV, small volume oscillatory vibrations are superimposed on continuous distending pressure in a manner that allows efficient CO_2 elimination during continuous alveolar recruitment. By preserving end-expiratory lung volume, minimizing cyclic stretch, and avoiding alveolar overdistension at end-inspiration, HFOV is uniquely capable of providing the ultimate "open lung" strategy of ventilation. Over the past decade, a growing evidence base implicating phasic alveolar stretch in the pathogenesis of acute and chronic lung injury in patients with respiratory failure has driven the iterative refinement of HFOV management protocols for infants, children, and adults. The next step toward applying HFOV in a manner that takes into account the heterogeneity of parenchymal involvement in diseases such as the acute respiratory distress syndrome will require the development of non-invasive bedside technologies capable of identifying regional changes in lung volume and lung mechanics. Electrical impedance tomography (EIT) is a promising technique that could play a supporting role in the conduct of future clinical trials seeking to identify HFOV strategies that are maximally lung protective.

Keywords

High frequency oscillatory ventilation • Diffuse alveolar disease • Congenital diaphragmatic hernia • Neonatal respiratory distress syndrome • Airleak • Acute lung injury • Acute respiratory distress syndrome • Respiratory impedance plethysmography • Electrical impedance tomography • High frequency percussive ventilation

Introduction

Evidence supporting the feasibility of high frequency oscillatory ventilation (HFOV) follows from the observation that delivering very small tidal volumes at high frequencies can overcome the need for adequate bulk gas flow in the lung. While it had been appreciated years earlier that pressure oscillations could enhance oxygen diffusion [1], the stage was fully set for the dawning of the HFOV era in the early 1970s, after several investigators independently reported that applying small volume oscillatory vibrations to the airway

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efficiently eliminated CO_2, even in the absence of chest wall excursion [2–5]. The discovery was made incidentally, during experiments designed to measure cardiac or lung impedance in large animals and humans. The investigators' fortuitous decision to monitor CO_2 clearance provided the proof that ventilation with sub-dead space tidal volumes was possible. Thereafter, HFOV was recognized as a highly promising supportive care strategy, and very quickly it went on to play a major role in the global paradigm shift toward "open lung" ventilation techniques. By 1980, a series of 12 patients ranging in age from 3 days to 74 years had been successfully supported for an hour at a time, using a prototype piston pump oscillator capable of delivering tidal volumes as low as 7.5 mL, at 15 Hz [6]. In early 1983, the first pilot trial of HFOV for neonatal respiratory distress syndrome (RDS) began enrolling infants [7].

The next 30 years in this story would witness the widespread use of HFOV in neonatal intensive care units, with subsequent dissemination to pediatric and adult intensive care units. Concurrently, evidence implicating phasic alveolar stretch in the pathogenesis of acute and chronic lung injury in patients with respiratory failure has driven the iterative refinement of HFOV protocols. As of now, a large body of evidence suggests that repetitive cycles of pulmonary recruitment and de-recruitment are associated with identifiable markers of lung injury, and experimental models of ventilatory support which avoid alveolar overdistention, reverse atelectasis, and limit phasic changes in lung volume appear to be less injurious [8–15]. Chief among the major clinical trials that support this concept is the ARDS Network (ARDSNet) trial published in 2000. The ARDSNet investigators demonstrated that adults with acute lung injury or the acute respiratory distress syndrome (ARDS) who were randomized to receive a tidal volume of 6 mL/kg (predicted body weight) with plateau pressure limitation to $\leq$30 cm H_2O had a mortality reduction of 22 % relative to those ventilated with 12 mL/kg tidal volumes and allowable plateau pressures up to 50 cm H_2O [16]. This study is also one of several that would demonstrate a greater reduction in plasma levels of proinflammatory cytokines among patients who are ventilated with lower tidal volumes [10, 17, 18]. Together these studies suggest that reducing the magnitude of phasic stretch during mechanical ventilation attenuates the systemic inflammatory response and can potentially reduce the incidence of nonpulmonary organ dysfunction in patients with respiratory failure.

The long documented benefits of tidal volume reduction compel the expectation that high-frequency ventilation should have an important role in the clinical arena because of its unique ability to ventilate using subphysiologic tidal volumes and continuous alveolar recruitment. In theory, high-frequency ventilation is capable of providing the ultimate *open-lung* strategy of ventilation: preserving end-expiratory lung volume, minimizing cyclic stretch, and avoiding parenchymal overdistension at end-inspiration by limiting tidal volume and transpulmonary pressure [8–11].

Modalities of High Frequency Ventilation

The major modalities of high frequency ventilation include high frequency flow interruption (HFFI), high frequency positive pressure ventilation (HFPPV), high frequency jet ventilation (HFJV), high frequency percussive ventilation (HFPV), and high frequency oscillatory ventilation (HFOV). HFOV remains the most widely used form of high frequency ventilation in clinical practice today. In HFOV, lung recruitment and oxygenation are maintained by the application of relatively high mean airway pressure (Paw), while ventilation is achieved by superimposed sinusoidal pressure oscillations (ΔP) that are delivered by an electromagnetically driven piston-diaphragm at a frequency of 3–15 Hz [11, 19]. HFOV is the only form of high frequency ventilation in which expiration is an "active" process. This means that CO_2 egress is facilitated by pressure gradients produced with each retrograde movement of the ventilator's piston, rather than requiring lung recoil or involvement of skeletal musculature. As a result, alveolar ventilation can be achieved during HFOV using tidal volumes in the range of 1–3 mL/kg, even in the most poorly compliant lungs [19].

Gas Transport and Control of Gas Exchange in HFOV

Many years of detailed study in the laboratory have produced an accounting of the gas transport mechanisms at work during HFOV. While direct bulk flow can be enough to ventilate proximal alveolar units during HFOV, the key advantage of high frequency techniques in facilitating gas transport throughout the lung has to do with its ability to markedly accelerate the movement of gas molecules [20]. The added velocity alters the dynamics of gas distribution in ways that facilitate gas exchange. First, during HFOV efficient gas mixing is believed to occur through radial diffusion taking place along the parabolic inspiratory gas front as it advances down the airways [20–22]. Second, shear flows created by the advancing gas front spread concentration gradients over a broad axial area, a phenomenon called "Taylor dispersion", which further facilitates diffusion. Third, "*Pendelluft*", or mixing of gases among alveolar units with varying time constants, also contributes significantly to gas exchange at high frequencies [20–23]. Finally, axial asymmetry of inspiratory and expiratory gas flow profiles creates separation of fresh gas and exhaled gas so that inspiratory gas flow travels down

the central axis of the airway, while expiratory flow is distributed along the airway wall [20–22].

In HFOV, ΔP, frequency, Paw, and I:E are all directly controlled by the operator. Experiments performed in healthy rabbits have shown that CO_2 elimination during HFOV is a function of frequency and the square of the tidal volume ($V_{CO2}=f\times Vt^2$) [24]. In HFOV, tidal volume varies directly with the amplitude of oscillation (ΔP), and varies *inversely* with the frequency (Hz) [25]. Reducing the frequency effectively lengthens the overall cycle time, which enhances CO_2 elimination at the expense of a longer inspiratory time and a higher stroke (tidal) volume. Although much of the foundational research on HFOV involved the use of higher frequency ranges, satisfactory CO_2 elimination can probably occur at many potential combinations of *f* and Vt, with higher frequency ranges providing conditions of lowest lung impedance and consequently, a lower pressure cost of ventilation [26, 27].

Alveolar recruitment during HFOV is directly related to both Paw and the ratio of inspiratory time to expiratory time (I:E) [28]. While this relationship also holds true for conventional ventilation, an important distinction between the two modalities is that HFOV delivers the Paw as a continuous distending pressure, which maximizes the alveolar surface area available for gas exchange throughout the respiratory cycle. In the injured lung, HFOV produces better oxygenation and higher mean lung volume than conventional ventilation at an equivalent Paw, *provided that the Paw is set above the lung's opening pressure* (Fig. 10.1) [29]. If HFOV is initiated early enough in the disease process that pressure-volume hysteresis is preserved, a preceding recruitment maneuver can position the lung on the deflation limb of the volume-pressure curve, where lung volume (and oxygenation) is maintained at a lower Paw. Carefully adjusting the Paw setting downward, letting it hover just above the lung's closing pressure, will exploit pulmonary hysteresis, allowing satisfactory oxygenation at the lowest possible pressure cost (Fig. 10.2). In practice, this corresponds to the lowest Paw value that maintains the oxygenation gains from the recruitment maneuver. HFOV's superior ability to capitalize on pressure-volume hysteresis is a key part of the rationale for its use in the management of diffuse alveolar disease and airleak syndromes.

Presently available high frequency ventilators vary with respect to pressure waveforms, consistency of the I:E ratio over a range of frequencies, and the relationship between displayed mean airway pressure and the actual mean alveolar pressure [25, 30, 31]. Most of the clinical experience with HFOV involves the SensorMedics 3100A (CareFusion Corporation, Yorba Linda CA), which was approved for use in neonates in 1991 and for older infants and children in 1995. More recently, the SensorMedics 3100B high-frequency oscillatory ventilator (CareFusion, Yorba Linda, CA) became available for use in larger pediatric patients (>35 kg) and adult patients. The 3100B model was approved for use outside of the US in 1998 and within the US in 2001, addressing concerns arising from large animal experiments that adequate alveolar ventilation for larger patients might not be achievable using the 3100A model [32, 33]. The 3100B differs from the 3100A model by having a more powerful electromagnet, which produces faster acceleration to maximal oscillatory pressure (ΔP). It also allows a higher maximal bias flow, which makes it possible to deliver higher mean airway pressures [34]. Many pediatric intensive care units now use the 3100A and 3100B oscillators interchangeably for older children, although operating each machine using a particular combination of settings may not produce exactly the same results in an individual patient. The automated piston centering mechanism on the current generation of 3100B oscillators was designed to counteract retrograde piston displacement when maintenance Paw is set in the range of 40–45 cm H_2O [31]. At least one group of investigators has observed that operating the 3100B using an I:E of 1:2 and a lower Paw (30 cm H_2O) can cause the piston position to shift in a way that truncates the pressure waveform, reducing tidal volume delivery below what the 3100A model would deliver at the same settings [31]. Clinicians can compensate for this phenomenon by adjusting settings as appropriate to achieve therapeutic objectives.

Years of experience gained in laboratory and clinical settings have provided clinicians with a fairly detailed understanding of each device's other important performance characteristics. Multiple lines of evidence using a variety of experimental models confirm that the endotracheal tube both distorts and dramatically attenuates oscillatory pressure waves (Fig. 10.3) and that the I:E ratio is an important determinant of how much pressure (and tidal volume) is ultimately transmitted to the alveoli [28, 31, 35–39]. Preclinical data have consistently shown that limitation of expiratory time using an I:E ratio of 1:1 promotes alveolar gas trapping. In fact, under certain conditions mean alveolar pressure can actually exceed the Paw displayed on the ventilator console [28, 30, 40–42]. This observation prompted the suggestion that HFOV be applied in the clinical setting using an I:E ratio no greater than 1:2.

Strategies for Initiating HFOV: Diffuse Alveolar Disease and Airleak

Many neonatal intensive care units now use HFOV preferentially over conventional ventilation to support the most vulnerable preterm infants with moderate to severe lung disease [43]. In older infants and children, typical indications for initiating HFOV include (1) diffuse alveolar disease without evidence of severe airflow obstruction or intracranial

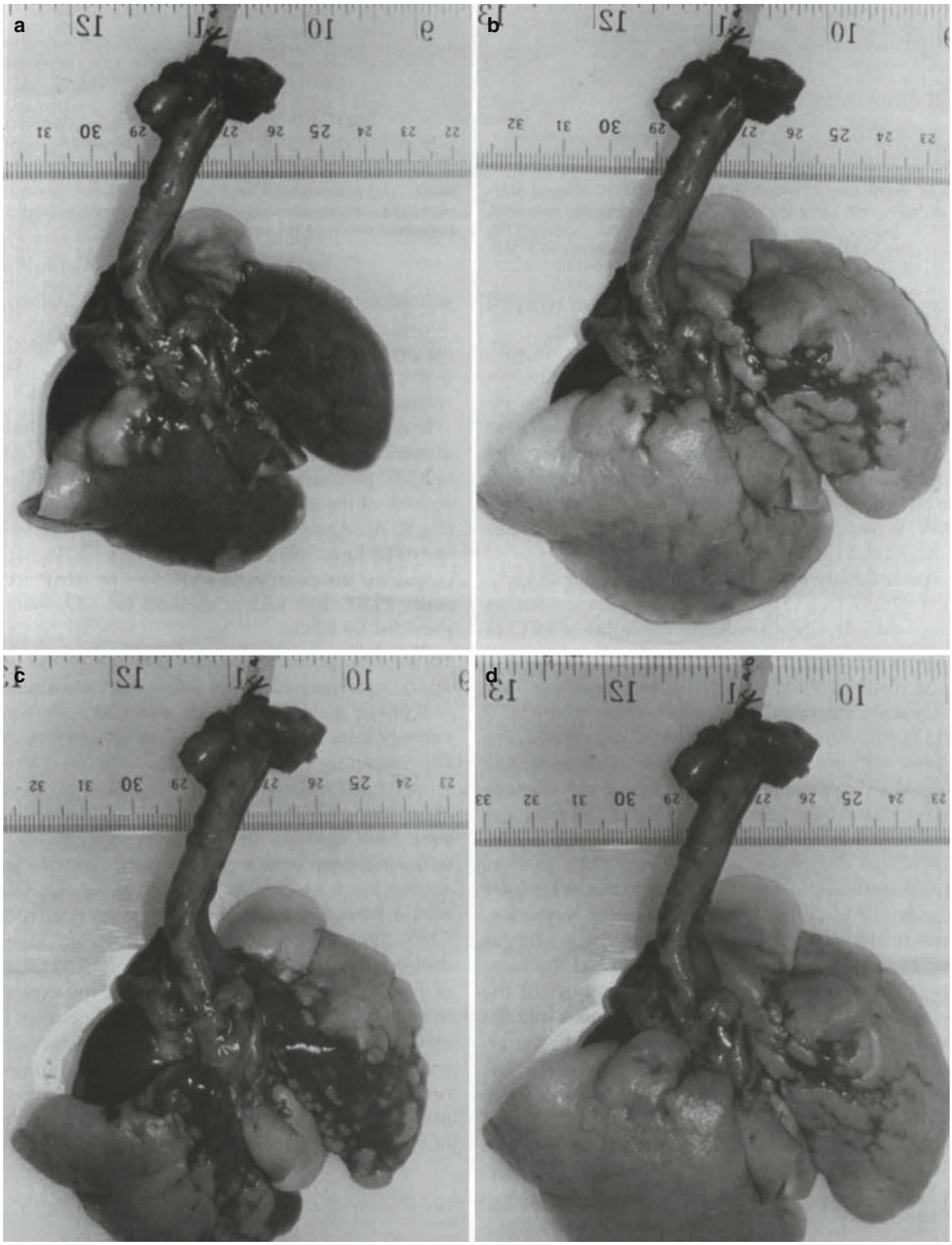


Fig. 10.1 (**a**–**d**): Lung volume during conventional ventilation (Panels **a**, **b**) compared to HFOV (Panels **c**, **d**), at equivalent mean airway pressure. Excised lungs from a rabbit lung lavage model are shown. Panel (**a**) depicts marked atelectasis at end-expiration (PEEP 9 cm H_2O). Panel (**b**) shows the lung at end inspiration; tidal volume is adjusted to produce eucapnea. Panels (**c**, **d**) depict the same lung during HFOV, using a mean airway pressure equivalent to the one represented in Panels (**a**, **b**). Panel (**c**) shows the lung during HFOV without a preceding recruitment maneuver; residual atelectasis remains apparent. Panel (**d**) shows the lung during HFOV with a preceding recruitment maneuver (Reprinted from Kolton et al. [29]. With permission from Wolter Kluwers Health)

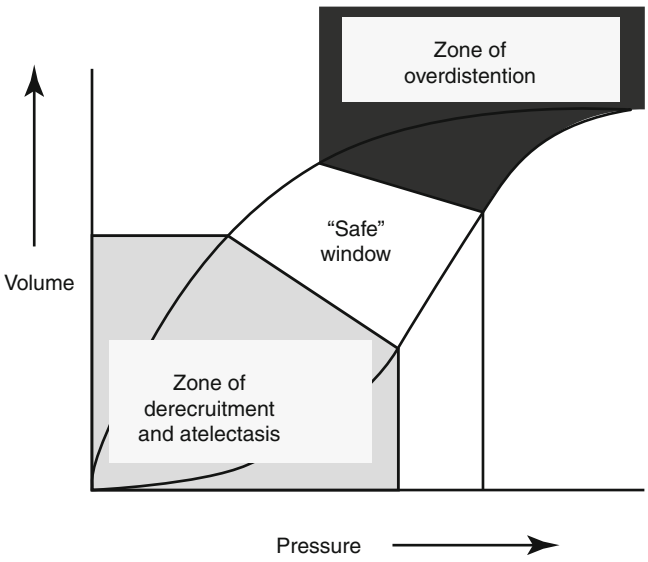


Fig. 10.2 Pressure-volume relationships in acute lung injury. High end-expiratory pressures and small tidal volumes minimize the potential for derecruitment (*lower left*) and overdistension (*upper right*). The critical opening pressure of the lung corresponds to the lower inflection point on the inspiratory limb of the volume-pressure curve. The closing pressure of the lung corresponds to the lower inflection point on the expiratory limb of the curve (Reprinted from Froese [129]. With permission from Wolter Kluwers Health)

hypertension; and (2) oxygenation failure (FiO_2 ≥0.7 and mean airway pressure ≥15 cm H_2O on conventional ventilation); or (3) ventilation failure (pH <7.25 with tidal volume ≥6 mL/kg predicted body weight and plateau pressure ≥30–35 cm H_2O) [44]. When transitioning the patient from conventional (phasic) ventilation to HFOV, the Paw on HFOV is typically set up to 5 cm H_2O above the Paw last used on the conventional ventilator, in order to maintain recruitment in the face of pressure attenuation by the endotracheal tube. Amplitude (ΔP) is set by adjusting the Power control, which controls the amount of current that is delivered to the motor driving the ventilator piston. The frequency is initially set between 10 and 15 Hz for small infants. However, when initiating HFOV in children and adults, a lower frequency setting is usually necessary in order to achieve adequate ventilation. Strict age-based ranges have historically determined where clinicians set the frequency, partly out of concern that the present generation of high frequency ventilators would not be capable of generating enough volume displacement to adequately ventilate larger patients unless the frequency was drastically reduced. However, recent studies in test lung models [30], large animal models [38], and adult humans [30] have confirmed that frequency reductions have a greater impact on tidal volume delivery than amplitude increases, and tidal volumes approaching those generated

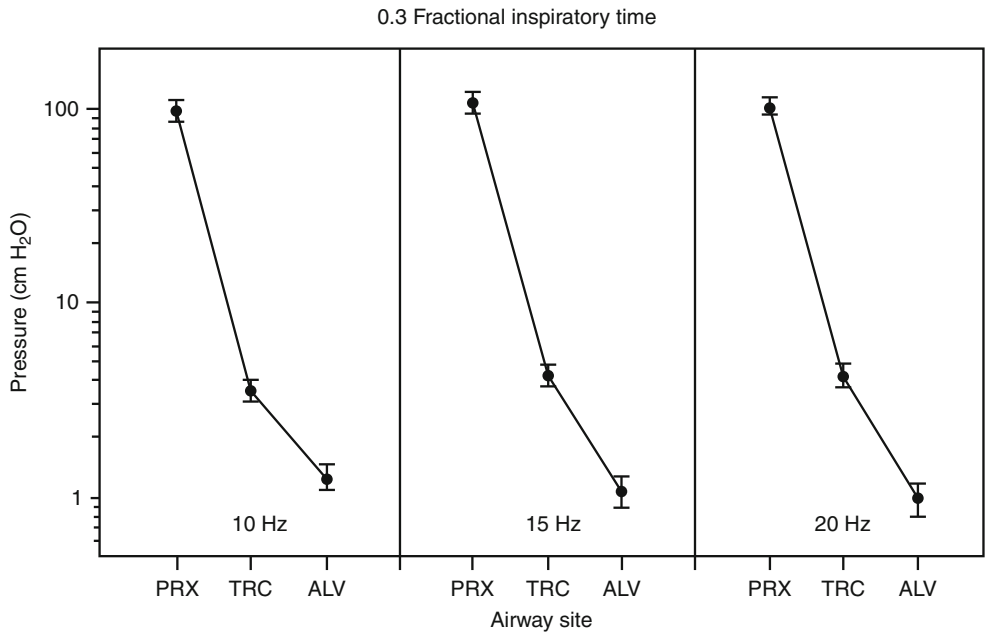


Fig. 10.3 Amplitude attenuation on HFOV, in open-chested rabbits (without lung injury): The relationship between proximal, tracheal, and alveolar amplitudes are shown at 10, 15, and 20 Hz, and %I:E 0.3 (*plotted values* represent mean peak-to-trough pressure ± SEM). Proximal pressures are measured at the airway opening. Tracheal pressures are measured 2 cm below the distal opening of the 3.0 mm (outer diameter) endotracheal tube. Alveolar pressures are measured using a pressure transducer attached to a low mass capsule mounted on the pleural surface. Panels depict significant, progressive amplitude attenuation across the endotracheal tube, from airway opening ("*PRX*") to trachea ("*TRC*") and down to the alveolus ("*ALV*") ($p<0.0001$) (Reprinted from Gerstmann et al. [35]. With permission from Nature Publishing Group)

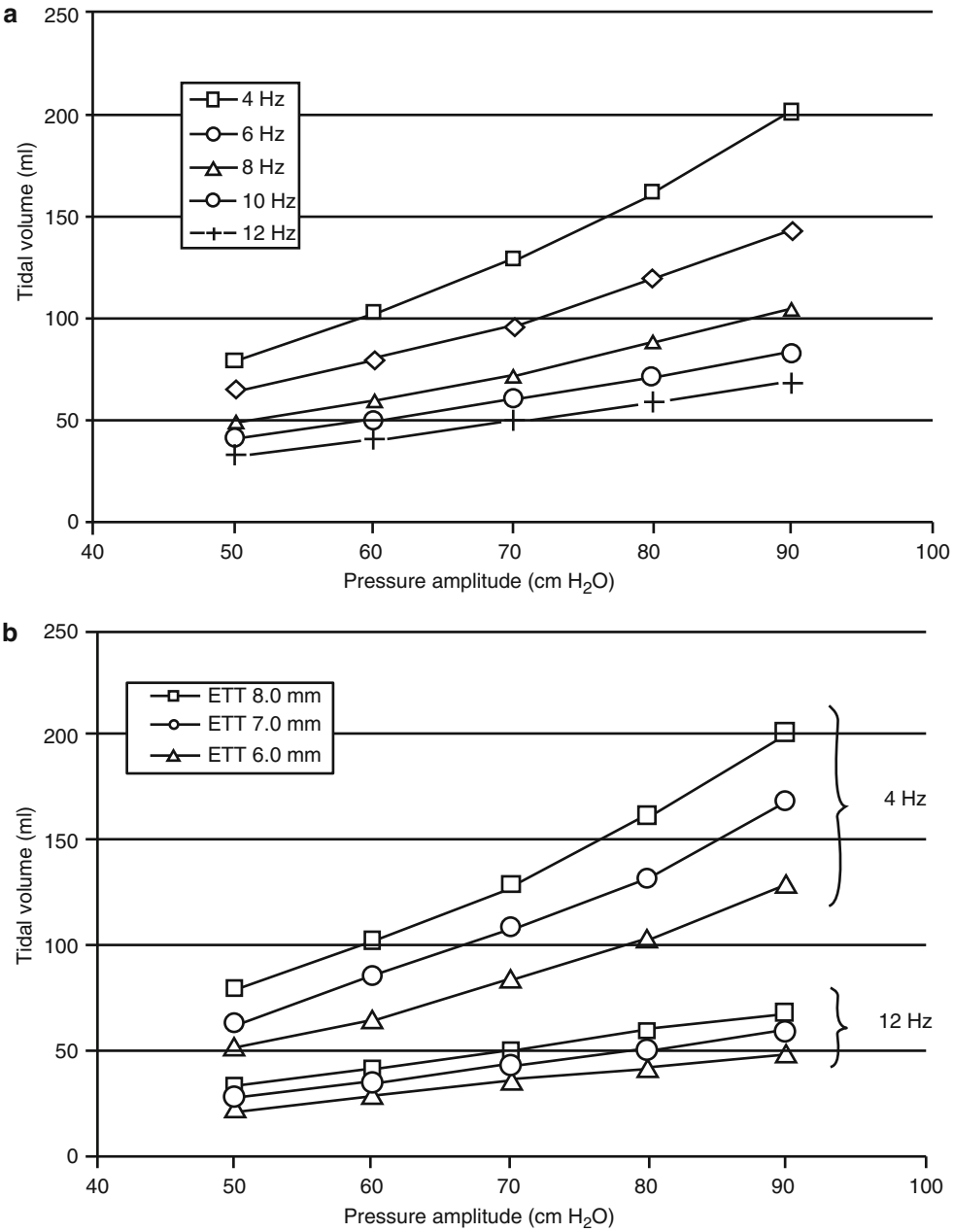


Fig. 10.4 Effect of frequency, amplitude, and ETT diameter on tidal volume delivery during HFOV. Data shown in this figure were collected during ventilation of a test lung (MI Instruments, Grand Rapids, MI) with a 3100B oscillator. In these experiments, bias flow is constant at 30 L/min, compliance is constant at 30 mL/cm H_2O, and I:E is constant at 1:2. Tidal volume is measured using an adult hot wire anemometer. Panel (**a**) depicts the relationship between tidal volume and pressure amplitude at a range of frequencies (4–12 Hz), using an 8 mm (inner diameter) endotracheal tube (*ETT*). Increasing frequency by 2 Hz reduces tidal volume by an average of 21.3 ± 4.1 %. A similar frequency-tidal volume relationship was confirmed by the investigators in a series of adult patients with ARDS, intubated with an 8 mm ETT. In these patients, increasing amplitude by 10 cm H_2O produced an average tidal volume increase of only 5.6 ± 4.5 %. Panel (**b**) depicts the effect of ETT diameter on the relationship between tidal volume and pressure amplitude, at 4 and 12 Hz (Reprinted from Hager et al. [30]. With permission Wolters Kluwer Health)

during conventional ventilation can be delivered when "low frequency HFOV" is used (Fig. 10.4). Small animal models of lung injury appear to confirm that low frequency ventilation (5 Hz) produces histologic evidence of more severe ventilator-associated injury than high frequency ventilation (15 Hz), although studies differ on the magnitude of this difference [45, 46]. In accordance with these data, contemporary HFOV management protocols suggest maintaining the frequency at the highest level that will provide adequate ventilation [30, 43, 44, 47, 48] (Fig. 10.5). For patients with lower airways disease or for small infants who achieve adequate recruitment on low mean airway pressures, some experts advocate modest reductions in maintenance frequency in order to counter the tendency for lower airways collapse and air trapping in these situations [42].

If employing an "*open lung*" ventilation strategy for diffuse alveolar disease (Fig. 10.5), a static recruitment maneuver is performed, and Paw is adjusted relative to the initial setting (in 1–2 cm H_2O increments) until the arterial saturation stabilizes at ≥90 %. The next step in confirming that the patient has achieved a satisfactory degree of alveolar recruitment is to titrate the FiO_2 downward, with the goal of arriving at a Paw that will allow arterial saturations to stabilize at ≥88–90 % (PaO_2 55–80 Torr) using an FiO_2 of ≤0.6, without evidence of hyperinflation or decreased cardiac output. Patients with any degree of intravascular volume depletion

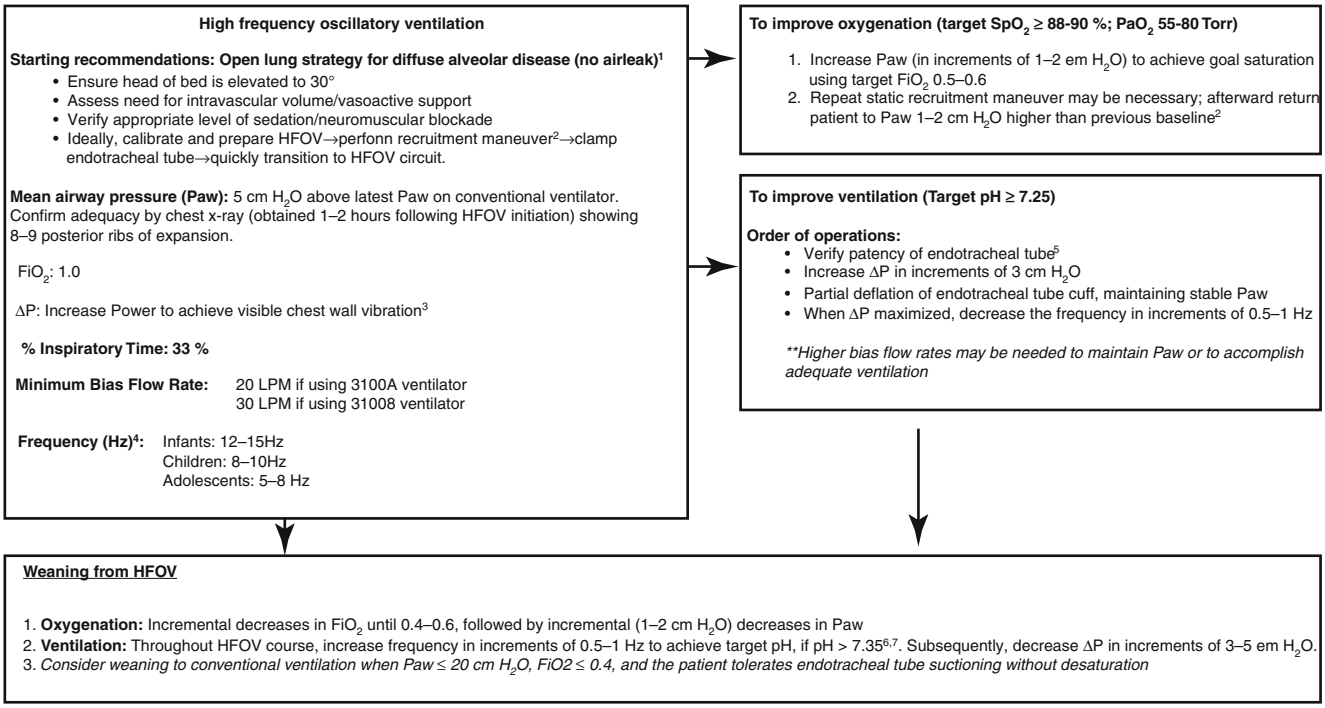


Fig. 10.5 Transitioning the critically ill child from conventional mechanical ventilatory support to HFOV HFOV initiation, maintenance, and weaning parameters. *1* See text for airleak strategy modifications, *2* Recruitment maneuvers can precipitate acute hemodynamic compromise and should not be routinely performed in patients with hypotension or active airleak. Careful hemodynamic monitoring is advised, and recruitment maneuvers should cease if hypotension occurs [44], *3* Magnitude and extent of chest wall vibrations will vary according to chest wall and/or abdominal compartment compliance, *4* To maximize the lung protective effects of HFOV, the maintenance frequency setting should target the upper limit of each age-based range, *5* Suctioning the poorly compliant lung can result in rapid desaturation. Preoxygenation is recommended, *6* This protocol presumes permissive hypercapnea with target pH ≥ 7.25. This approach is not recommended if there are clear contraindications to permissive hypercapnea (e.g., increased intracranial pressure), *7* Increasing frequency can affect oxygenation by reducing the % inspiratory time. Monitor oxygenation carefully as frequency is adjusted upward (Adapted from Ventre and Arnold [130]. With permission from Elsevier)

will often require volume expansion during the recruitment phase of HFOV initiation because under these conditions, alveolar pressure can quickly exceed the perfusing pressure of the adjacent pulmonary vasculature, creating an increase in alveolar dead space and hemodynamic deterioration [49, 50]. The final step in verifying the adequacy of lung recruitment following HFOV initiation, and an important mechanism for monitoring it thereafter, is to ensure that both hemidiaphragms are displaced to the level of the 8th or 9th posterior rib on chest x-ray [19]. When the patient demonstrates an ability to maintain target saturations on FiO_2 of 0.5–0.6 for a period of time, he or she will generally begin to tolerate slow downward titrations of Paw in increments of 1–2 cm H_2O, provided saturations remain stable. Once compliance begins to improve, surface forces will normalize, rendering the lung less prone to closure, and thus allowing lung volume to be maintained as Paw is decreased [51]. Until this occurs, suctioning should be minimized and unnecessary circuit disconnections should be avoided.

A typical sequence of steps for addressing hypercarbia after verifying the patency of the endotracheal tube and an appropriate degree of lung inflation includes (i) increasing the ΔP in increments of 3 cm H_2O until Power is maximized, (ii) subsequently decreasing the frequency in increments of 0.5–1 Hz, and (iii) partially deflating the endotracheal tube cuff, if present, to allow additional egress of CO_2 (Fig. 10.5) [34, 52, 53]. In the latter case, any decrement in Paw should be corrected by further restricting the circuit pressure control valve (turning the "mean pressure adjust" knob clockwise) or by increasing the bias flow of fresh gas as necessary to maintain a stable level of distending pressure [34, 53]. In the event that very high pressure amplitudes are required to provide adequate ventilation, typical maintenance bias flow settings may be inadequate to ensure CO_2 clearance from the circuit. In this setting, the bias flow should be augmented to counter potential increases in the circuit's effective dead space [30, 39].

If employing an HFOV strategy targeted at managing active air leak, the lung is initially recruited using stepwise increases in Paw to achieve an SaO_2 ≥88–90 % (PaO_2 55–80 Torr) using an $FiO_2 \leq 0.6$. Ideally, Paw and ΔP are then slowly lowered to a point just below the "*leak pressure*", the

value at which air is no longer seen draining from the thoracostomy tube, if there is one in place. From this point, hypoxia should be addressed by preferentially increasing FiO_2 to 0.8 before increasing the Paw. In patients with airleak, routine recruitment maneuvers should be avoided following initiation of HFOV, if possible. Ventilation should be provided using the highest frequency that will allow adequate CO_2 clearance, a technique which will minimize both inspiratory time and tidal volume [44]. Maintenance of a controlled modest respiratory acidosis with $pH \geq 7.25$, is preferred unless clear clinical contraindications preclude this approach [23, 54–56]. Once chest radiographs indicate that the airleak has sealed for 24–48 h, many patients will tolerate a transition to a typical HFOV strategy for diffuse alveolar disease, as outlined above.

HFOV in the Neonate and Infant

Neonatal Respiratory Distress Syndrome

High chest wall compliance, surfactant deficiency, and unstable end expiratory lung volume all interact to potentiate repetitive cycles of derecruitment and reinflation that make the preterm neonatal lung particularly well-suited to an open lung strategy of ventilation. Over 20 years ago, a preclinical study exposing surfactant-deficient premature baboons to either HFOV or conventional ventilation demonstrated that early use of HFOV appeared to protect the animals from developing mechanical, biochemical, and histologic evidence of hyaline membrane disease [57]. A follow up study published in 2000 exposed surfactant-deficient premature baboons to exogenous surfactant plus either early HFOV or "lung sparing" conventional ventilation with tidal volumes reduced to 4–6 mL/kg [58]. HFOV was initiated using a Paw 2 cm H_2O above what was required to stabilize the animal on the conventional ventilator. Target blood gas tensions in each group were identical ($PaCO_2$ 45–55 Torr; PaO_2 55–80 Torr), and high supplemental oxygen fractions were avoided through preferential increases in mean airway pressure or PEEP. Remarkably, the animals received supportive care for 1–2 months, allowing the investigators to sequentially examine an array of mechanical, cellular, and biochemical parameters as they sought to determine whether HFOV could mitigate the development of chronic lung disease over time. Animals supported with HFOV demonstrated significantly better pulmonary mechanics for nearly every one of the 8 time points at which they were evaluated between 12 h and 28 days ($p<0.05$). Although between-groups differences for tracheal cytokine concentrations were less consistent across the study period, conventionally ventilated animals demonstrated significantly higher macrophage/monocyte, eosinophil, and lymphocyte infiltration by 10 days ($p<0.05$). Finally, while both groups of animals demonstrated histopathologic findings consistent with chronic lung disease on *post mortem* examination, HFOV supported animals showed significantly better lung inflation patterns by panel of standards analysis ($p<0.001$). Together these studies are representative of a remarkable two decades of scientific inquiry, which established that ventilator-associated injury amplifies the inflammatory response to the primary parenchymal insult experienced by patients with respiratory failure. Thus, the magnitude of acute lung injury, and the incidence and extent of chronic lung injury, are modifiable through the use of more protective ventilation strategies.

Despite HFOV's sound physiologic rationale and the large body of preliminary evidence affirming its potential advantages [2, 6, 7, 29, 59–61], larger scale efforts to evaluate the efficacy of HFOV versus conventional ventilation for human hyaline membrane disease (i.e., neonatal respiratory distress syndrome or RDS) had a disappointing start. The first large randomized, controlled trial in premature infants comparing high-frequency ventilation using a piston oscillator with conventional mechanical ventilation was published during the pre-surfactant era by the *HIFI Study Group* [62]. This crossover trial was designed to evaluate the impact of HFOV on the incidence of chronic lung disease of prematurity and included 673 infants weighing 750–2,000 g who had been supported less than 12 h on conventional ventilation for respiratory failure in the first 24 h of life. Infants randomized to receive HFOV were administered a Paw and FiO_2 equal to those administered on conventional ventilation. Infants assigned to the HFOV arm who had not already been tracheally intubated at the time of randomization were supported using an FiO_2 equal to what they received before intubation, and a Paw of 8–10 cm H_2O. In each arm of the trial, hypoxemia was first addressed by increasing the FiO_2, and then by increasing the Paw [62]. Significantly more infants in the HFOV group crossed over to the conventional arm of the trial after they were judged to have failed therapy with the assigned ventilator (26 % vs 17 %; $p=0.01$). All infants were analyzed as part of the study group to which they were assigned. Ultimately the study was unable to show a significant difference in the incidence of chronic lung disease or in 28-day mortality between the two groups. Despite the fact that the HIFI investigators made efforts to limit maintenance mean airway pressures and indeed did not incorporate alveolar recruitment into the HFOV strategy, infants in the HFOV arm experienced a significantly higher incidence of airleak (3 % vs 1 %; $p=0.05$). They also experienced a significantly higher incidence of periventricular leukomalacia and high-grade intraventricular hemorrhage, unanticipated developments that contributed to the trial's early closure [3, 62].

A decade later, two large multicenter trials were published in an effort to clarify the role of high-frequency ventilation in the management of the infant respiratory distress syndrome [63, 64]. By this time, many centers had accumulated a great deal of experience using the 3100A high

frequency oscillator in neonates. Each of these trials emphasized alveolar recruitment as part of the HFOV strategy. In their remarkably well-controlled study, Courtney and colleagues randomized 500 preterm infants to receive either conventional ventilation targeting a tidal volume of 5–6 mL per kg body weight, or HFOV using a frequency of 10–15 Hz [63]. Eligible infants were less than 4 h of age, had received one dose of surfactant, and required mechanical ventilation using a mean airway pressure >6 and an $FiO_2 \geq 0.25$. These investigators were able to show that infants randomized to receive high-frequency oscillatory ventilation successfully separated from mechanical ventilation earlier than those assigned to a lung-sparing strategy of conventional ventilation. Those assigned to high-frequency ventilation also demonstrated a significant reduction in the need for supplemental oxygen at 36 weeks postmenstrual age [63]. By defining a disease threshold in the study infants, adhering to lung-protective protocols for mechanical ventilation, and extubating from the assigned ventilator according to specific criteria, this study identified a set of circumstances in which HFOV may be used with clear benefit in preterm infants with RDS [63]. In contrast, the companion trial by Johnson and colleagues included healthier patients, used fewer defined protocols, and pursued more aggressive ventilator strategies. In both study arms, Johnson and colleagues targeted a $PaCO_2$ of 34–53 Torr, while Courtney and colleagues allowed more permissive levels of hypercapnea [63]. For those infants who were supported on HFOV, Johnson and colleagues initiated therapy at a frequency of 10 Hz, and if maximizing amplitude (ΔP) did not achieve adequate CO_2 clearance, the frequency was subsequently reduced [64]. Finally, Johnson's group transitioned the majority of study infants to conventional ventilation for weaning after a median time on HFOV of 3 days, a relatively small proportion of the total time on mechanical ventilation [64]. This trial found no difference between groups in its composite primary outcome, death or chronic lung disease at 36 weeks postmenstrual age.

It is important to emphasize that neither of these studies was able to duplicate the findings of the HIFI group with respect to linking the use of HFOV with the development of airleak or brain injury. However, the difference in outcomes between the two trials is intriguing. It is possible that the rigorously controlled conditions in the Courtney study isolate the effect of HFOV with greater clarity. Their data suggest that only 11 infants need be supported with HFOV in order to prevent one occurrence of chronic lung disease at 36 weeks postmenstrual age [63]. Johnson's data suggest the number of infants needed to support on HFOV in order to prevent one occurrence of chronic lung disease is 50 [64]. Although the study design used by Johnson and colleagues may better represent actual practice, the outcomes indicate that exposure to aggressive conventional ventilation practices may ultimately counter the benefits of HFOV.

Congenital Diaphragmatic Hernia

Infants with congenital diaphragmatic hernia (CDH) commonly demonstrate complex pulmonary pathophysiology, deriving principally from alveolar and pulmonary vascular hypoplasia [65]. Over 15 years ago, consistent identification of ventilator-induced lung injury on histopathology specimens recovered from CDH patients [66, 67] began to focus attention on the possibility that aggressive ventilator strategies seeking to manipulate pulmonary vascular resistance through hyperventilation actually produce excess morbidity and mortality in this population. The Hospital for Sick Children in Toronto and Children's Hospital Boston published tandem articles in 1997 in which they reviewed their CDH outcomes over a 14 year time span (1981–1994) [66, 67]. In each paper, outcomes were stratified by time periods in which the prevailing management strategy was different than the one that the institution had used before. While overall survival for CDH was similar at each institution, both saw improved survival rates after instituting a strategy of permissive hypercapnea. In Boston, this difference achieved statistical significance (69 % survival vs 44 %; $p = 0.007$) [68]. In Toronto, where clinicians tended to use HFOV more commonly for CDH than their Boston colleagues, the use of HFOV was not independently associated with improved survival [66]. By now a variety of centers have published case series in which infants with CDH demonstrate dramatic short term reductions in $PaCO_2$ and improvements in oxygenation when managed with HFOV [69, 70]. Some of these reports appear to confirm the Toronto experience that the use of HFOV may in fact be associated with an improvement in survival in this population [69–71].

Overall the role of HFOV in the management of infants with CDH is still evolving. For those clinicians who opt to use HFOV for this population, it is essential to recognize that infants with CDH do not have inherently recruitable lungs. In this setting, attempts to improve gas exchange by applying high levels of mean airway pressure can actually increase the dead space fraction and may result in acute inflammatory injury, alveolar or airway rupture, or potentially dangerous elevations in pulmonary vascular resistance. For this reason, experienced centers often recommend limiting the mean airway pressure to 16 cm H_2O or less [72]. The Hospital for Sick Children in Toronto has developed an HFOV protocol that emphasizes maintaining preductal SaO_2 above 85 %, tolerating hypercarbia provided the pH is compensated, and initiation of HFOV when the peak inspiratory pressure on conventional (phasic) ventilation exceeds 25 cm H_2O. This institution has reported significantly increased survival among CDH infants since implementing this set of guidelines in 1995 [72].

Persistent Pulmonary Hypertension of the Newborn

Several investigators have tested the hypothesis that sustained alveolar recruitment using HFOV could enhance the delivery of therapeutic gases to patients with respiratory failure from a variety of causes. In one large multicenter trial, therapy with HFOV was coupled with inhaled nitric oxide (iNO) in an effort to identify the relative contribution of each therapy to outcomes in patients with persistent pulmonary hypertension of the newborn (PPHN). The investigators randomized 200 neonates with severe hypoxic respiratory failure and PPHN to receive therapy with either HFOV alone or conventional ventilation combined with iNO [73]. Crossover as a result of treatment failure resulted in combined therapy with HFOV and iNO. The study found that patients demonstrated significant short-term improvements in PaO_2 during combined treatment with HFOV and iNO, after failing either therapy when it was delivered alone [73]. Combining HFOV and iNO was particularly effective among patients with severe parenchymal disease attributable to RDS and meconium aspiration [73]. The suggestion that iNO efficacy depends upon the adequacy of alveolar recruitment is also supported by a retrospective analysis of data from older children who were enrolled in a multicenter randomized trial of the use of iNO in the treatment of acute hypoxic respiratory failure[74].

Air Leak Syndromes

Given the expectation that satisfactory gas exchange occurs at a lower pressure cost during HFOV, it is not surprising that this therapy has been applied with success in severe air leak syndromes. In one case series, 27 low birth weight infants (mean birthweight 1.2 kg) who developed pulmonary interstitial emphysema on conventional ventilation were transitioned to HFOV. All demonstrated early improvement on HFOV, and survivors demonstrated sustained improvements in oxygenation and ventilation, allowing for lower Paw, FiO_2, and ultimate resolution of air leak. Overall survival among non-septic patients was 80 % [75].

Bronchiolitis

Despite concerns that ventilation at high frequencies may exacerbate dynamic air trapping in diseases of the lower airways, HFOV has been used in the management of bronchiolitis due to respiratory syncytial virus [76, 77]. A couple of small case series have reported the successful application of HFOV using an open lung strategy in young infants with bronchiolitis [76, 77]. Applying a relatively high Paw in this clinical context follows the observation that lower Paw may promote worsening hyperinflation by creating *choke points* that impede expiratory flow [42]. The investigators used a frequency of 10–11 Hz and I:E of 0.33, with initial pressure amplitude (ΔP) in the 35–50 cm H_20 range. All patients survived without development of pneumothoraces attributable to HFOV and without need for ECMO [76, 77].

HFOV in the Child

Diffuse Alveolar Disease

Much of the data on the application of HFOV outside of the neonatal period comes from case series in which this therapy was applied to children with acute severe respiratory failure attributable to diffuse alveolar disease and/or air leak syndromes. In the early 1990s, two centers reported the use of HFOV in pediatric patients with these conditions who had been managed on conventional ventilation for varying periods of time [55, 78]. In general, each concluded that HFOV may be applied safely as rescue therapy in pediatric patients with severe hypoxic lung injury, and that its use is associated with improvement in physiologic endpoints such as $PaCO_2$ and oxygenation index ($OI = [(Paw \times FiO_2)/PaO_2)] \times 100$). In addition, there were no reports of worsening air leak [55, 78]. Each of these studies initiated HFOV after recruiting the lung, but one of them [55] modified the HFOV protocol for patients with active air leak by dropping the Paw below the leak pressure following recruitment, raising the FiO_2 as necessary to maintain adequate oxygenation, and tolerating hypercarbia as long as the arterial pH remained above 7.25.

The first and largest multicenter randomized trial evaluating the effect of HFOV on respiratory outcomes in pediatric patients is a crossover study that enrolled patients with diffuse alveolar disease and/or air leak [54]. The investigators randomized 70 patients to receive conventional ventilation using a strategy to limit peak inspiratory pressure, or HFOV at a frequency of 5–10 Hz, using an open-lung strategy in which the lung volume at which optimal oxygenation occurred was defined ($SaO_2 \geq 90$ % and $FiO_2 < 0.6$), and in patients with air leak, airway pressure was then limited while preferentially increasing in FiO_2 to achieve saturations of ≥85 % and pH ≥7.25 until it resolved [54]. The study found no difference in survival or duration of mechanical ventilatory support between the two groups. However, significantly fewer patients randomized to receive HFOV remained dependent on supplemental oxygen at 30 days, compared to those who were randomized to receive conventional ventilation, despite the use of significantly higher Paw in the HFOV group [54]. The OI, used often in the pediatric literature to quantify oxygenation failure, was shown in this study to discriminate between survivors and non-survivors after 24 h of

therapy. In addition, the time at which changes in OI were noted to occur influenced the likelihood of survival: an OI ≥42 at 24 h predicted mortality with an odds ratio of 20.8, sensitivity of 62 %, and specificity of 93 % [54]. *Post hoc* analysis revealed that outcome benefits were not as great among patients that crossed over to the HFOV arm [54], supporting the suggestion by numerous studies that HFOV is most efficacious if employed early in the course of disease, using a strategy that emphasizes alveolar recruitment [13, 57, 78–80].

Other Conditions

Published reports on the use of HFOV for treatment of lower airways disease in older pediatric patients are few. In one interesting case report, HFOV was successfully applied to a toddler with status asthmaticus [81]. The authors achieved optimal CO_2 clearance using an *open lung* strategy with Paw 20 cm H_2O, low frequency (6 Hz), I:E 0.33, and relatively high ΔP (65–75 cm H_2O in the first 24 h of therapy) without apparent air leak [81]; however, the use of HFOV in obstructive lung diseases must be considered carefully.

HFOV in the Adolescent and Adult

Early experience with the use of HFOV on adolescent and adult patients with hypoxic respiratory failure is summarized in several case series [34, 82]. In each, low frequency (maximum 5–6 Hz) HFOV using a strategy of volume recruitment was used as rescue therapy in patients with ARDS who were failing conventional ventilation. These studies included patients with severe disease, including mean values for PaO_2/FiO_2 in the 60 range at the time of enrollment [34, 82]. Although neither study was powered to measure significant differences in outcomes such as mortality, the majority of patients in the two studies demonstrated an improvement in short-term physiologic variables such as FiO_2, PaO_2/FiO_2 ratio, and OI [34, 82]. Non-survivors in each of these studies were exposed to significantly longer periods of conventional ventilation, suggesting once again the importance of instituting HFOV early in the course of disease.

The first multicenter prospective, randomized controlled trial designed to evaluate the safety and efficacy of HFOV as compared to conventional ventilation in the management of early ARDS ($PaO_2/FiO_2 \leq 200$ while on PEEP 10 cm H_2O) in adult patients was published in 2002 [53]. Treatment strategies for both arms of the study included a volume recruitment strategy and were directed at achieving SaO_2 ≥88 % on FiO_2 ≤60 %. Patients in the conventional arm were managed in a pressure-limited mode, targeting a delivered tidal volume of 6–10 mL/kg actual body weight, without specific attention to plateau pressures. Patients in the HFOV arm were ventilated at frequencies of 3–5 Hz, and were transitioned back to conventional ventilation when FiO_2 ≤0.5 and Paw ≤24 cm H_2O with SaO_2 ≥88 %. After the transition, conventional ventilation was reinstituted using a Paw equivalent to the last setting on HFOV [53]. With regard to short-term physiologic measures, these investigators also reported a significantly higher Paw and significant early increases in PaO_2/FiO_2 among patients on HFOV [53]. Post-study multivariate analysis also revealed that the trend in OI was the most significant post-treatment predictor of survival, regardless of treatment group. Survivors showed a significant improvement in OI over the first 72 h of the study period, while non-survivors did not [53]. Although the OI is not a measure traditionally reported in the adult literature, it has been reported by some investigators as predictive of mortality in adult ARDS [82]. This trial was not powered to evaluate differences in mortality between the two groups, but there was a clear trend toward increased 30-day mortality among the patients randomized to receive conventional ventilation versus those who received HFOV (52 % vs. 37 %) [53].

Since the publication of that first clinical trial, experience with adult HFOV has been documented in six subsequent randomized controlled trials comparing HFOV to conventional ventilation in patients with acute hypoxic respiratory failure [83–88]. The largest of these enrolled 61 patients [85]. All of these studies maintained HFOV at a frequency of 5 Hz or less, a practice now believed to generate tidal volumes approaching what would be delivered during conventional ventilation [44, 89]. In 2007, Fessler and colleagues issued a consensus document in 2007 recommending that HFOV protocols for adult ARDS combine high amplitudes with the highest oscillatory frequency that will produce a target pH of 7.25–7.35 (Fig. 10.5) [44]. The large-scale, multicenter **Oscil**lation for **A**RDS **T**reated **E**arly ("OSCILLATE") trial was the first to prospectively test this approach [90]. This trial was designed to evaluate the impact of high-amplitude, maximal frequency HFOV against an "open lung", low tidal volume conventional ventilation strategy on all-cause hospital mortality for adults with ARDS. The investigators randomized 548 adults ≥16 years of age with acute hypoxic respiratory failure (PaO_2/FiO_2 ≤200 on standardized ventilator settings) and diffuse alveolar disease to receive either phasic ventilation targeting a tidal volume of 6 mL/kg and plateau pressure ≤35 cm H_2O -or HFOV using the Sensormedics 3100B (CareFusion Corporation, Yorba Linda CA), oscillating at the highest possible frequency that would allow maintenance of an arterial pH >7.25. Both ventilator protocols targeted a PaO_2 55–80 Torr, guided by a standardized PEEP (or Paw)-FiO_2 grid, and both included recruitment maneuvers. Transition from HFOV to phasic ventilation and weaning from mechanical ventilatory support

were strictly protocolized. Ultimately the steering committee terminated the OSCILLATE trial well short of its goal of enrolling 1,200 patients, after three consecutive interim analyses suggested an increase in mortality with HFOV. In the final analysis, the HFOV group had an in-hospital mortality of 47 % compared to 35 % in the control group (RR for death with HFOV 1.33; 95 % CI 1.09–1.64, p = 0.005). This new and perhaps surprising development in the history of HFOV trials has several intriguing implications. As the OSCILLATE trial investigators suggest, it is possible that the theoretical benefits of maximal frequency (i.e., "low stretch") HFOV may be countered by deleterious effects from the high mean airway pressures that are typically required when using such a strategy [90]. The OSCILLATE trial outcomes may also compel clinicians to consider the possibility that HFOV may be a technique better suited to patients with diffuse alveolar disease and increased chest wall compliance—conditions that often coexist in infants and young children with acute lung injury and ARDS.

Adjuncts to HFOV: Non-invasive Assessment of Lung Volume

One of the difficulties facing intensive care clinicians is that evaluation of the adequacy of recruitment after initiating HFOV and in response to changes in ventilator settings must be guided by indirect measures such as peripheral oxygen saturations, fractional inspired oxygen concentration, blood gas tensions, AP chest radiographs, and a visual assessment of chest wall vibration. Global measures of alveolar plateau pressure, tidal volume, and pulmonary mechanics that are available from breath to breath when using conventional ventilation are not provided on the high frequency ventilator console. The operator must often use intuition when adjusting ventilator settings, risking sudden and clinically significant de-recruitment or alveolar over-distension. In recent years, respiratory impedance plethysmography (RIP) and electrical impedance tomography (EIT) have emerged as two promising means by which pulmonary mechanics and alveolar recruitment can be assessed non-invasively at the bedside of patients receiving HFOV.

Respiratory impedance plethysmography is a monitoring technique that is capable of quantifying global lung volume by relating it to measurable changes in the cross-sectional area of the chest wall and the abdominal compartment. In RIP, two elastic bands with Teflon-coated wires embedded in a zig-zag distribution along their circumference are applied to the patient. One is typically placed around the chest, 3 cm above the xyphoid process, and the other is typically placed around the abdomen. Each of these two bands produces an independent signal and the sum of the two signals is calibrated against a known volume of gas. Use of this technique in association with HFOV has been validated in animal models [91, 92]. In a large animal model of acute lung injury managed with HFOV, Brazelton and colleagues have demonstrated that RIP-derived lung volumes correlated well with those that were obtained using a supersyringe ($r^2 = 0.78$), and that RIP is capable of tracking global changes in lung volume and creating a pressure-volume curve during HFOV[91]. In a newborn animal model, Weber and colleagues were able to demonstrate that RIP is capable of detecting relative changes in pulmonary compliance that were induced by saline lavage [92]. Experience with RIP in human subjects is limited to investigations of its application during conventional ventilation. One study in adult patients [93] and another in pediatric patients [94] have utilized RIP to quantify the relative degree of de-recruitment that is associated with closed, *in-line* techniques for endotracheal tube suctioning, as compared to open suctioning techniques. Each study was able to demonstrate a potential role for RIP in tracking global changes in lung volume at the bedside.

Applying HFOV in a way that harmonizes with what computed tomography has revealed about the heterogeneity of parenchymal involvement in ARDS [95] will ultimately depend on developing non-invasive bedside technologies that are capable of identifying regional changes in lung volume and pulmonary mechanics. CT images of the lung in ARDS patients have demonstrated that during a prolonged inspiratory maneuver, alveolar recruitment occurs all the way to total lung capacity, according to the specific time constants of individual lung units [95, 96] (Figs. 10.1 and 10.6). Therefore, *ideal* settings on HFOV would be those that achieve ventilation above the lower inflection point on the regional pressure-volume curves for the majority of lung units, while avoiding over-distension in the most compliant alveoli.

Electrical impedance tomography (EIT) is one technology that may be best suited to detecting regional heterogeneity at the bedside of the patient with diffuse alveolar disease. In EIT, a series of electrodes is applied circumferentially to the patient's chest. The electrodes sequentially emit a small amount of electrical current which is received and processed by the other electrodes in the array. Receiving electrodes determine a local change in impedance based on the voltage differential calculated between the transmitting electrode and the receiving electrode. Well-aerated areas, which conduct current poorly, are associated with high impedance, while fluid and solid phases (including atelectatic or consolidated lung) would be associated with lower impedance [97]. The impedance values that are generated are referenced to a baseline measurement, and represent relative rather than absolute changes in electrical properties [96]. This process creates a tomogram that depicts the distribution of tissue electrical properties in a cross-sectional image (Fig. 10.7), and the thickness of the slice of thorax that is represented in

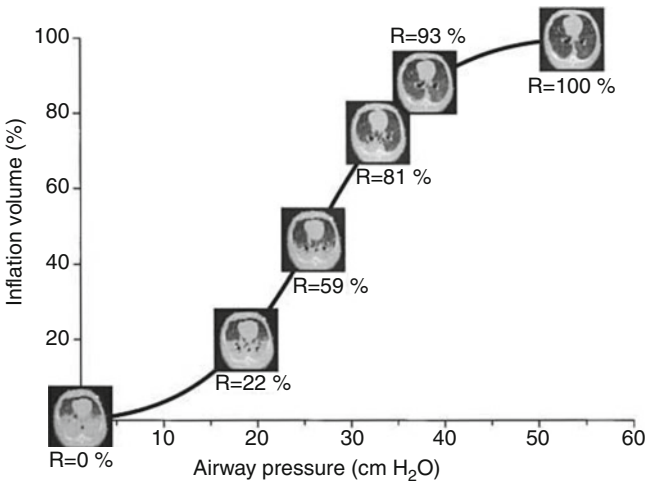


Fig. 10.6 Alveolar recruitment along the pressure-volume curve in ARDS: Data shown are from a large animal, oleic acid lung injury model. As lung volume increases toward total lung capacity, aeration of dependent lung units increases substantially, but at a very high airway pressure cost. At high airway pressures, non-dependent lung units may be vulnerable to overdistension. "*R*" indicates the percentage of total lung recruitment at each corresponding airway pressure (Reprinted with permission of the American Thoracic Society. Copyright (c) 2013 American Thoracic Society. Gattinoni et al. [95]. Official Journal of the American Thoracic Society)

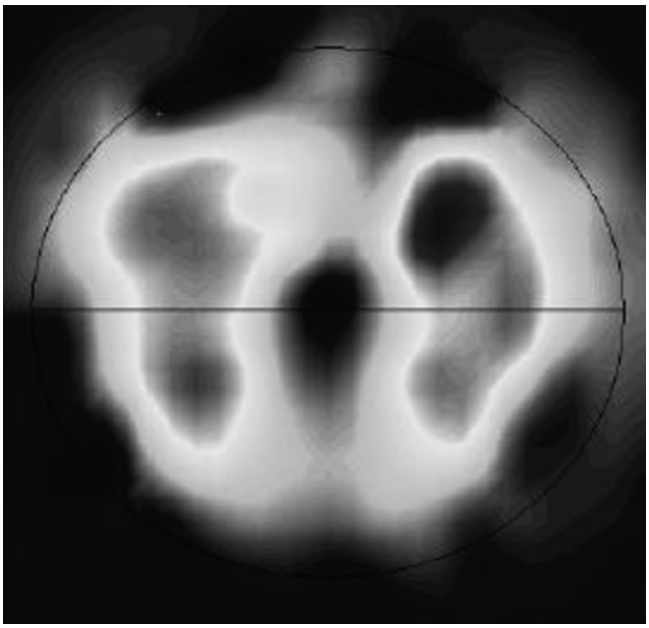


Fig. 10.7 EIT image of the lung. The orientation is the same as for a CT image. Both lung fields show equal impedance change during spontaneous breathing (Adapted from Wolf and Arnold [96]. With permission from Springer Science + Business Media)

the image varies between approximately 15 and 20 cm, depending on the circumference of the chest [96, 98]. Of the presently available EIT systems, the Goe MF II (University of Goettingen, Germany; distributed by Viasys, USA) seems to have the most favorable signal to noise ratio, and it is also capable of dynamic measurements at low lung volumes [96, 99]. This system scans at a rate of 13–44 scans/s (Hz), generating up to 44 cross-sectional images per second [96].

In the laboratory, EIT has been used in conjunction with both conventional ventilation and HFOV to describe regional lung characteristics. Investigations using conventional ventilation in large animal models of lung injury have validated EIT against supersyringe methods for the determination of regional pressure-volume (or *pressure-impedance*) curves [96, 100], and have demonstrated good correlation between EIT-derived regional changes in lung impedance and CT-derived regional variations in aeration [96, 101]. Using EIT to track regional lung mechanics in a large animal model of acute lung injury managed with HFOV, van Genderingen and colleagues were able to demonstrate that regional pressure-volume curves constructed using maneuvers on HFOV show less variation along the gravitational axis compared with pressure-volume curves that are obtained using a supersyringe method, suggesting that recruitment is more uniformly distributed between dependent and non-dependent areas during HFOV [102]. Published experience with EIT in human subjects with acute lung injury or ARDS has correlated regional impedance changes induced by slow inflation maneuvers using the DAS-01P EIT system (Sheffield, UK) with regional lung density measurements obtained by CT scanning [103]. A group of investigators at Children's Hospital Boston recently utilized EIT to detect regional changes in lung volume during a standardized suctioning maneuver in children with acute lung injury or ARDS who were supported on HFOV. These data demonstrate considerable regional heterogeneity in volume changes during a derecruitment maneuver (Fig. 10.8) [104] . The same investigators went on to correlate regional impedance changes with regional overdistension during HFOV in an animal model of acute lung injury, a finding bringing EIT research a step closer to identifying a precise role for this technology in the management of patients on HFOV [105].

It is tempting to expect that EIT will soon facilitate the development of more strategic HFOV protocols. Theoretically, this technology can create opportunities for therapeutic intervention by dynamically tracking the regional differences in alveolar recruitment that make portions of the lung highly susceptible to ventilator-induced lung injury (VILI). However, there are important limitations to the presently available technology. For instance, substantial bias may be introduced into the EIT image because of the tendency for electrical current to follow the path of lowest impedance, rather than the path of shortest distance between the transmitting and receiving electrodes [97]. This phenomenon may account in large part for the variation between EIT measures of regional lung impedance and CT measures of regional lung density [103]. In addition, because EIT

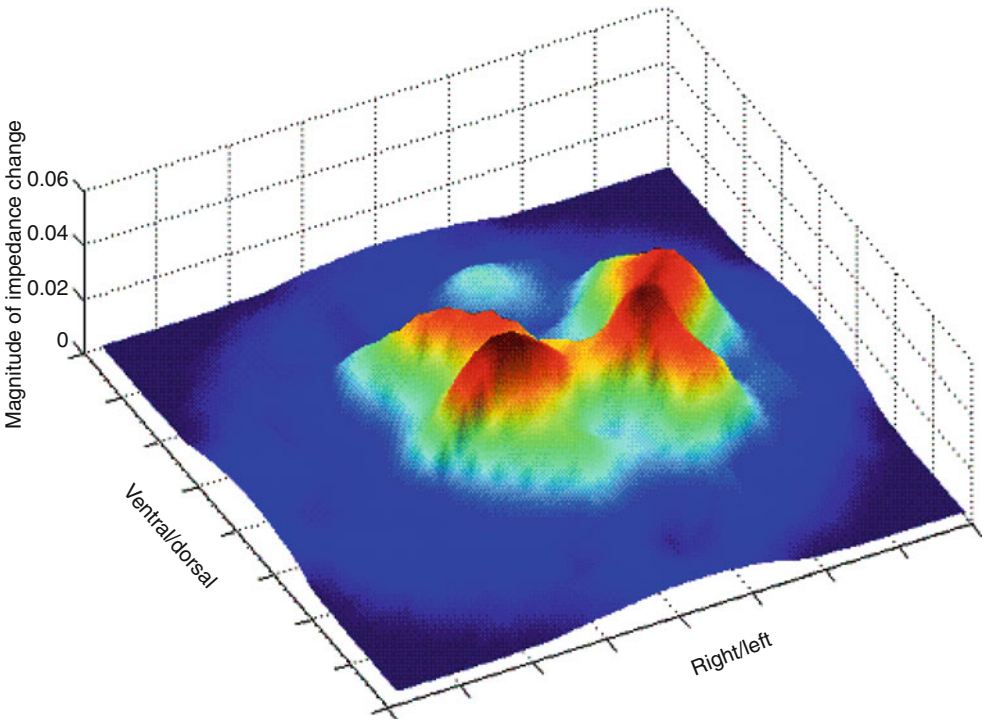


Fig. 10.8 Three dimensional depiction of recruitment after suctioning on HFOV. The standard deviation of impedance change after reconnection to the ventilator is displayed (Reprinted from Wolf and Arnold [104]. With permission from Wolter Kluwers Health)

measures impedance changes that are relative to baseline values, changes in baseline regional intrathoracic impedance resulting from sources other than alterations in gas volume and distribution could lead to errors in the interpretation of EIT-derived data. Despite these limitations, several investigators have reported that EIT reliably detects regional alterations in pulmonary blood flow [106] and extravascular lung water [107]. In summary, identifying a useful role for EIT as an adjunct to HFOV at the bedside will depend on additional technical modifications to make it suitable for reliably detecting very small regional tidal volumes at high frequency in the electrically hostile environment of the intensive care unit.

Weaning from HFOV

Numerous studies have suggested that limiting exposure to potentially injurious strategies on conventional ventilation may enhance outcome benefits attributable to HFOV among patients with severe lung injury. Large trials in the neonatal and pediatric populations have demonstrated favorable outcomes when HFOV is initiated early in disease, and it seems logical to expect that timing the transition back to conventional ventilation may be of substantial importance as well.

Weaning a patient from HFOV may be considered when the clinician determines that gas exchange and pulmonary mechanics are suitable for transition to acceptable settings on conventional ventilation. Some investigators have reported successfully extubating infants directly from HFOV [63, 64, 79], but this is difficult to accomplish in the older pediatric and adult patient, who may be less likely to tolerate a plane of sedation that would allow spontaneous respiration while on HFOV, and in whom spontaneous breathing may significantly depressurize the circuit, resulting in recurrent alveolar derecruitment. In general, when clinical improvement occurs to the point that Paw may be reduced to $\leq$20 cm H_2O, FiO_2 is reduced to $\leq$0.4, and the patient tolerates endotracheal suctioning without significant desaturation, it is appropriate to undertake a more detailed evaluation of the patient's response to phasic ventilation provided by conventional means [23]. This may be done by hand ventilating (with the aid of an in-line pneumotachometer, if necessary) while noting the pressures, tidal volume, and inspiratory to expiratory time ratio necessary to sustain satisfactory oxygen saturation. It is common to find on transition to conventional ventilation that the patient will demonstrate satisfactory gas exchange on a mean airway pressure several cm H_2O below the last Paw on HFOV.

Other Developments: Revisiting High Frequency Percussive Ventilation

Since the mid 1980s, reports have occasionally appeared in the literature examining the role of high frequency percussive ventilation (HFPV) in the management of neonates, children, and adults with lung injury from a variety of causes. HFPV is a form of high frequency ventilation in which a single ventilator (Percussionaire Corporation, Sandpoint ID) coordinates the set parameters of both conventional ventilation and HFOV

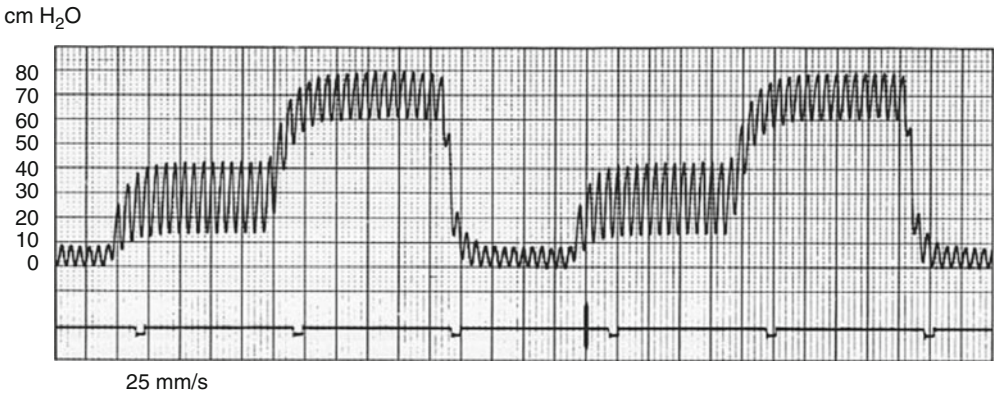


Fig. 10.9 Pressure-time waveform during HFPV ("convective pressure rise" feature engaged): stepwise progression to end inspiratory pressure is depicted. At the beginning of inspiration, oscillatory pressures reach an initial plateau. A "convective pressure rise" carries the breath toward the peak equilibrium pressure, which is then released at the end of inspiration toward the baseline PEEP (CPAP). In this tracing, oscillations are activated during both the inspiratory and the expiratory phase (From The VDR-4 Manual of Understanding [109], used with permission granted by Dr. Forrest Bird)

to deliver time-cycled, oscillatory, subphysiologic tidal volumes at approximately 3 Hz to at least 15 Hz. These are superimposed on time-cycled, pressure-limited tidal volumes (10–15/min) whose magnitude is determined by peak inspiratory pressure (PIP) and PEEP (CPAP) [108]. Oscillations during HFPV are created by a pneumatic "Phasitron®" (piston) positioned near the airway opening, which acts as both an inspiratory and expiratory valve and generates progressive, accumulative high velocity percussive waves that conduct into the lung. The net effect is a multiphasic oscillatory pattern that hits its maximum pressure during inspiration and its minimum pressure during expiration, when the lung recoils to the set PEEP (CPAP) level (Fig. 10.9) [108, 109]. The overall architecture of the respiratory cycle during HFPV is perhaps responsible for the observation that many patients can tolerate it without the need for neuromuscular blockade [108, 110]. During HFPV, the operator controls PIP, PEEP (CPAP), inspiratory time, expiratory time, percussive rate, and "conventional" rate [108].

Proponents of HFPV contend that it enhances tidal convective CO_2 clearance while augmenting oxygen diffusion through high velocity flow, in the manner common to all high frequency techniques [108, 109]. In addition, percussive waves are believed to promote the clearance of airway secretions and debris, a process that is further potentiated by periodic lung recoil [108, 111]. This is the rationale underlying the use of HFPV in patients with inhalational lung injury, although published studies examining the impact of HFPV on the incidence of pulmonary infection have shown conflicting results [112–115]. A variety of reports ranging from small case series [116–123] to case control studies [112, 113] and small-scale prospective randomized trials [114–116, 124–128], have documented improved CO_2 clearance and oxygenation efficiency at lower PIPs, when comparing HFPV to "traditional", high tidal volume conventional ventilation in neonates, children, and adults. There is a single published trial examining the efficacy of HFPV relative to lung protective ventilation using a modified version of the ARDSnet protocol [16, 115]. The incidence of ventilator-associated pneumonia, diagnosed by contemporary consensus criteria, was examined as a secondary outcome measure in this trial. The investigators randomized 62 burned adult patients with acute respiratory failure to either HFPV or conventional ventilation using tidal volumes of 6 mL/kg predicted body weight and plateau pressure limitation to ≤30 cm H_2O. Only a portion (37 %) of the study population had documented inhalational injury. In the HFPV cohort, the investigators reported significant reductions in PIP up to 5 days following randomization. However, this did not translate to an overall difference in the study's primary outcome measure, ventilator-free days in the first 28 days of the trial [115]. Significantly more patients in the conventional ventilation arm of this trial experienced new airleak or otherwise unexplained pneumatocele (13 % vs 0 %; $p=0.04$). There was a trend toward reduced incidence of ventilator-associated pneumonia in the HFPV arm, but this difference did not achieve statistical significance (32 % vs 52 % $p=0.12$). There was no difference in plasma cytokine levels between study groups. Significantly more patients in the conventional ventilation arm required a rescue mode of ventilation for failure to meet predetermined ventilation and/or oxygenation goals (29 % vs 6 %; $p=0.02$), a finding which closed the trial short of its goal of enrolling 170 patients. Thus, the available evidence suggests that HFPV is associated with short-term improvements in the efficiency of gas exchange among lung injured patients, but clinical trials have not yet confirmed a clear advantage of this modality over current best practices for either conventional ventilation or HFOV. In particular, the impact of the larger, low frequency tidal volumes on the inflammatory response and overall course of lung injured

patients managed with HFPV has yet to be fully elucidated [110]. Additional study will be needed before more widespread use of this modality outside of a controlled investigational setting would be justified.

Conclusions

In spite of compelling laboratory data supporting a physiologic rationale for HFOV in the treatment of diffuse alveolar disease, evidence of its superiority to conventional ventilation with regard to clinically important outcomes beyond the neonatal period is scant. The difficulty in proving significant clinical outcome benefit in pediatric and adult patients may be due in large part to the diverse potential etiologies of respiratory failure in these populations as well as a wide range of approaches to their medical management applied over a relatively long period of mechanical ventilatory support. It is also possible that low frequency HFOV as traditionally used in larger patients may not be as protective as the higher frequency strategies that have been used with success in small animal models and human infants.

HFOV remains a therapeutic option in the intensive care unit that is worthy of further study because it is a safe and practical way to provide a "low stretch" form of ventilation that is less likely to produce ventilator-induced lung injury [8, 10–13] Applying this concept with greater precision in the clinical arena will depend on developing bedside technologies capable of both identifying the critical opening pressure in a majority of lung units, and tracking regional changes in lung volume that follow changes in HFOV settings. Electrical impedance tomography is a promising technology that may ultimately be incorporated into the design of future trials that are powered to evaluate the benefits of specific HFOV protocols.

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Surfactant Therapy

11

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Abstract

Pulmonary surfactant is the evolutionary solution to the problem of surface tension and air breathing. Without surfactant, each breath would require inordinate energy expenditure to expose the huge intrapulmonary surface to inspired air, and life on land, at least as we know it, would be virtually impossible. Pulmonary surfactant exists in the alveolar hypophase in a complex microstructure of phospholipid-rich aggregates with incorporated four distinct surfactant proteins, each with their own function. Pulmonary surfactant serves two primary functions in the lungs. It is first and foremost a surface-active agent that lowers and varies surface tension to reduce the work of breathing, stabilize alveoli against collapse and overdistension, and lessen the hydrostatic driving force for edema fluid to transudate into the interstitium and alveoli. In addition, the specific apoprotein components of lung surfactant have been found to play an important role in the lung's innate immune response.

The crucial physiological importance of lung surfactant in respiration is demonstrated by the fact that a lack of this material in premature infants contributes to the development neonatal respiratory distress syndrome, a potentially fatal disease process. Exogenous surfactant replacement is now standard of care in the treatment of premature infants, and can be argued as being the most important discovery in pediatric medicine in the past 30 years. Despite this breakthrough in the treatment of neonatal lung disease, it is clear that the pathophysiology of acute pulmonary injury outside of the neonatal period is much different, and multifactorial, including inflammation, surfactant dysfunction, vascular dysfunction, edema, oxidant injury, ventilation/perfusion mismatching, and injury to alveolar, capillary, and other pulmonary cells. Clinical studies of multiple surfactant preparations in multiple target populations have resulted in unequivocal results. Therefore, the use of exogenous surfactants for the treatment of acute lung disease outside of the neonatal period is much more uncertain and complex, and remains the subject of on-going research.

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Overview of Lung Surfactant and Exogenous Surfactant Therapy

Pulmonary surfactant is the evolutionary solution to the problem of surface tension and air breathing. Without surfactant, each breath would require inordinate energy expenditure to expose the huge intrapulmonary surface (70 m^2, which is approximately the size of a badminton court) to inspired air, and life on land, at least as we know it, would be virtually impossible. One of the first insights into the existence of surface tension forces in the lungs came from the study of von Neergaard in 1929 [1]. Von Neergaard observed that it took nearly twice as much pressure to inflate excised animal lungs with air as it did with fluid. He speculated that since inflating the lungs with an aqueous solution eliminated the air/liquid interface in the alveoli, the additional work required to inflate the lungs with air must be incurred in overcoming surface tension forces at that interface. Von Neergaard's work was supported several decades later in studies by Gruenwald [2] and Mead [3], which further documented the importance of surface tension forces in respiration. Moreover, additional studies indicated that surface tension forces were moderated in the normal lungs by the action of surface-active agents (i.e., surfactants). Work by Pattle [4] in 1955 suggested that the stability of bubbles in the foam expressed from the lungs was related to surfactants that acted to *abolish the tension of the alveolar surface*. Clements [5], Brown [6], and Pattle [7] subsequently confirmed the existence of surfactants in the lungs by further surface tension and biochemical studies.

The crucial physiological importance of lung surfactant in respiration was demonstrated by the early finding that a lack of this material in premature infants contributed to the development of hyaline membrane disease (HMD, later called the neonatal respiratory distress syndrome or RDS) [7, 8]. This finding spurred further research into the function and composition of surfactant. However, clinical interest was significantly dampened by initial unsuccessful attempts by Robillard et al. [9] and Chu et al. [10, 11] in the 1960's to use aerosolized dipalmitoyl phosphatidylcholine (DPPC), the major phospholipid component of pulmonary surfactant, to treat HMD in premature infants. This lack of success was misunderstood as indicating that HMD was not due to surfactant deficiency and, consequently, that surfactant replacement was not an efficacious treatment [11]. Fifteen years of biophysical, biochemical, and animal research was required to reverse this clinical misconception, and establish a firm scientific basis for exogenous surfactant therapy (see Notter [12] for detailed review). Basic science research made it clear that DPPC alone is not a biologically active lung surfactant, and that the aerosolization techniques used by Robillard et al. [9] and Chu et al. [11] were ineffective for alveolar delivery. In 1980, Fujiwara et al. [13] reported the first successful use of exogenous surfactant therapy in premature infants with RDS, although it was another decade before FDA-licensed surfactant drugs were available in the United States. Exogenous surfactant therapy is now a standard of care for the treatment and prevention of RDS in premature infants, but the utility of this treatment approach in other conditions such as clinical acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) is less certain and remains the subject of on-going research as detailed later.

Pulmonary Surfactant and Its Functions

Pulmonary surfactant serves two primary functions in the lungs. It is first and foremost a *surface active agent* that lowers and varies surface tension to reduce the work of breathing, stabilize alveoli against collapse and over-distension, and lessen the hydrostatic driving force for edema fluid to transudate into the interstitium and alveoli. In addition, specific apoprotein components of lung surfactant have been found to play an important role in the lung's innate immune response.

Surface Tension and Surfactants

Molecules at the interface between two phases (solid, liquid, or gas) are subjected to specialized conditions that generate associated forces, which manifest as *interfacial tension*. Surface tension is the common name given to the interfacial tension at a liquid-gas interface. In biological systems, the most prevalent liquid-gas interface involves a water-based fluid layer contacting air, as occurs in the alveoli of mammals. In the absence of lung surfactant, surface tension at the alveolar interface would be quite high – on the order of 50 mN/m for tissue fluid that contains non-specific soluble proteins and other endogenous solutes [12]. The surface tension of aqueous fluids is high because water is a strongly polar substance with significant intermolecular attractive forces. Liquid (water) molecules at the interface have a strong attraction toward the bulk of the liquid with no equivalent attractive

forces above the surface since molecules in the gas (air) are so dilute. These unbalanced forces cause the surface to minimize its area, giving rise to surface tension. In a construct such as a spherical bubble, surface tension forces necessitate a pressure drop to maintain the interface at equilibrium against collapse. As described by Laplace in the eighteenth century for a spherical bubble, this pressure drop (ΔP) is directly proportional to the surface tension (γ) and inversely proportional to the radius of curvature (R), i.e., $\Delta P = 2\gamma/R$.

Surfactants are molecules that have an energetic preference for the interface. Molecules that are surface active at an air-water interface all share the characteristic of being amphipathic, that is, possessing both polar and non-polar regions in their structure. Pulmonary surfactant is largely composed of phospholipids that are molecules with polar phosphate *headgroups* and non-polar fatty chains or *tails*. This structure gives phospholipids an energetic preference for the interface in that they can orient with the polar headgroup in the aqueous hypophase and the non-polar hydrocarbon moieties in the air. Lung surfactant also contains essential proteins that have regions of polar and non-polar structure, and these proteins interdigitate with phospholipid molecules in the interfacial film and in bilayers/lamellae in the aqueous phase. A surfactant film at an air-water interface acts to lower surface tension because the attractive forces between surfactant molecules and water molecules are less than those of water molecules for each other (if this were not true, and the surfactant molecules had a stronger attraction for water, they would necessarily go into solution rather than being at the interface). The presence of a surfactant film thus reduces the net attractive force between interfacial region and bulk liquid molecules, lowering surface tension as a function of surfactant concentration. In the lungs, the surfactant film at the alveolar interface has powerful consequences for pressure-volume (P-V) mechanics and respiratory function.

Effects of Lung Surfactant on Respiratory Physiology

Pulmonary surfactant exists in the alveolar hypophase in a complex microstructure of phospholipid-rich aggregates with incorporated surfactant proteins (apoproteins). Surfactant material in the hypophase adsorbs to the air-water interface, which is energetically preferred as described above. The resulting interfacial surfactant film is compressed and expanded during breathing, and lowers and varies surface tension in a dynamic fashion. As alveolar size decreases during exhalation, the surfactant film is compressed and surface tension reaches very low values (<1 mN/m as compared to 70 mN/m for pure water at 37 °C). As alveolar size increases with inspiration, the surfactant film is expanded and surface tension proportionately increases. This dynamic variation of surface tension with area allows alveoli of different sizes to coexist stably at fixed pressure during respiration (Fig. 11.1). Small alveoli resist collapse at end-expiration because their surface tension is low. Consequently alveolar inflation is better distributed during inhalation since the ratio of surface tension to area is more uniform in different sized alveoli. Moreover, by reducing surface tension throughout the lungs, surfactant decreases the pressures (work) needed for pulmonary inflation. There is a direct connection between the surface activity of lung surfactant and pulmonary pressure-volume (P-V) mechanics. The physiological consequences of surfactant deficiency or dysfunction are profound, as seen in the diffuse atelectasis, uneven inflation, and severe ventilation/perfusion mismatching present in the lungs of preterm infants with RDS. The physiological roles of lung surfactant, and the surface properties that generate them as described above, are summarized in Table 11.1.

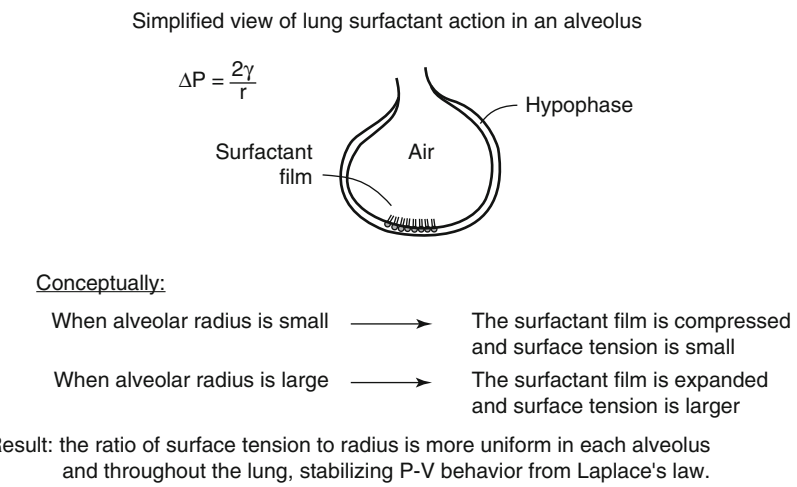


Fig. 11.1 Schematic showing the effects of lung surfactant on pulmonary pressure-volume behavior based on the Laplace equation. The pressure drop (ΔP) necessary to maintain alveoli at equilibrium is proportional to surface tension (γ) and inversely proportional to radius (r), i.e., $\Delta P = 2\gamma/r$ (Laplace's Law for a sphere). By lowering and varying local surface tension as a function of alveolar size (radius), lung surfactant acts to stabilize pulmonary P-V mechanics as shown schematically in the figure. Surfactant also greatly decreases the overall work of breathing by a generalized lowering of average surface tension throughout the alveolar network. See text for details

Table 11.1 Physiological actions and surface properties of functional lung surfactant

Physiological actions of functional surfactant
Reduces the work of breathing (increases lung compliance)
Increases alveolar stability against collapse during expiration
Improves alveolar inflation uniformity
Reduces the hydrostatic driving force for edema formation
Biophysical (surface) properties of functional surfactant
Adsorbs rapidly to the air-water interface
Reaches very low minimum surface tensions during dynamic compression
Varies surface tension with area during dynamic cycling
Respreads from surface collapse phases and other film-associated structures during cycling

Based on data from Notter [12]
See text for discussion

Table 11.2 Average mass composition of lung surfactant lipids and proteins

Phospholipids	88–90 %
Phosphatidylcholine (PC)	80 %
Saturated PCs	55–65 %
Unsaturated PCs	35–45 %
Anionic phospholipids (PG, PI, PS)	15 %
Other phospholipids	5 %
Neutral lipids	3–6 %
Cholesterol, cholesterol esters, glycerides	
Surfactant protein[a]	6–9 %
SP-A, SP-B, SP-C	

Based on data from Notter [12]
Weight percents shown are averages for alveolar surfactant obtained by bronchoalveolar lavage (BAL) in multiple studies. In practice, specific lung surfactant composition varies with animal species, age, and the size-distribution of aggregate fractions isolated from BAL (not shown)
Phospholipid abbreviations: *PC* phosphatidylcholine, *PG* phosphatidylglycerol, *PI* phosphatidylinositol, *PS* phosphatidylserine
[a]Tabulated protein content includes only the biophysically-active surfactant proteins (SP-A, SP-B, SP-C)

Biophysically-Functional Composition of Lung Surfactant

The surface behavior of lung surfactant results from molecular interactions between its lipid and protein components. An average mass composition of lung surfactant is given in Table 11.2. Functional surfactant contains primarily phospholipids and three active surfactant proteins (SP)-A, B, and C. A fourth protein (SP-D) that does not participate in surfactant biophysics but is important in host-defense along with SP-A (see below) also exists. Phosphatidylcholines (PCs) are the major phospholipid class in lung surfactant, including DPPC as the most prevalent single component. DPPC and other disaturated phospholipids form rigid, tightly-packed surface films capable of reducing surface tension to very low values under dynamic compression (<1 mN/m as noted earlier). Lung surfactant also contains fluid unsaturated PCs as well as a range of other phospholipid classes with a mix of saturated and unsaturated compounds. Fluid phospholipids increase the respreading of lung surfactant films so that material ejected from the interface during compression re-enters the film during expansion and remains available for subsequent respiratory cycles. Neutral lipids in lung surfactant also may help increase film respreading. Surfactant proteins have crucial biophysical actions in facilitating the adsorption of phospholipids into the air-water interface, and SP-B and SP-C also act within the surface film itself to refine its composition, to increase respreading, and to optimize surface tension lowering during dynamic cycling.

A summary of the molecular characteristics and activities of the lung surfactant proteins is given in Table 11.3. The two small hydrophobic surfactant proteins SP-B and SP-C are found in approximately equal amounts in endogenous surfactant (together totaling about 1.5–2 % by weight relative to lipid), and are vital to surface activity. SP-B, which is the most active of the two in increasing adsorption and overall dynamic surface activity [12, 15–19], is a particularly important component of functional surfactant. The presence or absence of these hydrophobic proteins in exogenous lung surfactants is a crucial factor in their efficacy as pharmaceutical agents as described later. Genetic deficiency of SP-B is associated with fatal respiratory distress in infancy [20–23], and infants with hereditary SP-B deficiency do not survive beyond the first days of life without surfactant replacement and ultimately lung transplantation [20, 24–26]. Conditional knockout studies have also shown that adult mice rendered acutely deficient in SP-B develop severe respiratory distress, with evidence of surfactant dysfunction and pulmonary inflammation despite maintaining normal levels of SP-C [27]. Mice that are left SP-B deficient die with pathology resembling ARDS, but abnormalities are reversed and mice survive if SP-B synthesis is restored [27]. Although SP-C is less physiologically crucial than SP-B based on such studies, mutations in SP-C in humans have been associated with diffuse interstitial pneumonitis and the early development of emphysema [28].

Surfactant Proteins and Innate Immune Function

Pulmonary surfactant is also important in innate (non-adaptive) pulmonary host defense. The epithelial lining of the lungs is critically positioned to participate in the neutralization and clearance of inhaled microorganisms and other particles. Two of the surfactant proteins (SP-A and SP-D) are members of a family of proteins called collectins that play a vital role in the innate host defense of the lung

Table 11.3 Molecular characteristics and activities of lung surfactant proteins

Surfactant protein (SP)	Selected characteristics and functions
SP-A	MW 26–38 kDa (monomer), 228 AA in humans
	Most abundant surfactant protein, relatively hydrophilic
	Acidic glycoprotein with multiple post-translational isoforms
	C-type lectin and member of the collectin family of host defense proteins
	Forms an active octadecamer (six triplet monomers)
	Aggregates and orders phospholipids (Ca^{++}-dependent)
	Necessary for tubular myelin formation (along with SP-B, Ca^{++})
	Enhances ability of lung surfactant to resist biophysical inhibition
	Has biological importance in host-defense and in helping to regulate surfactant reuptake/recycling/metabolism
SP-B	MW 8.5–9 kDa (monomer), 79 AA in humans (active peptide)
	Most essential SP for increasing adsorption and overall dynamic surface activity
	Contains both hydrophobic residues and charged residues (10 Arg/Lys and 2 Glu/Asp)
	Secondary structure has 4–5 amphipathic helices plus turn/bend and β-sheet regions
	Has significant biophysical interactions with both lipid headgroups and fatty chains
	Necessary for tubular myelin formation (along with SP-A, Ca^{++})
	Can form functional dimers and other oligomers in addition to acting as a monomer
	Fuses/disrupts lipid bilayers, promotes lipid insertion/adsorption into the interface, and enhances lipid mixing and spreading in surface films
SP-C	MW 4.2 kDa (monomer), 35 AA in humans (active peptide)
	Most hydrophobic SP, with only two charged residues (Arg/Lys)
	Contains two palmitoylated cysteine residues in humans
	Monomer is primarily α-helical in structure, with a length that spans a lipid bilayer
	Can form dimers/oligomers, but also detrimental non-specific beta (amyloid-like) forms
	Primary functional biophysical interactions are with hydrophobic phospholipid chains
	Disrupts and fuses lipid bilayers, promotes lipid adsorption, and enhances film spreading
SP-D	MW 39–46 kDa (monomer), 355 AA in humans
	Has significant structural similarity to SP-A
	C-type lectin and member of the collectin family of host defense proteins
	Oligomerizes to a dodecamer (four triplet monomers)
	Not implicated in lung surfactant biophysics, but facilitates host defense and may also participate in surfactant metabolism

Adapted from [12, 14]

MW molecular weight, *AA* amino acids

([29–32] for review). SP-A and SP-D are synthesized and secreted by alveolar type II cells and also by non-ciliated bronchiolar cells (Clara cells) in the airways [29, 30].

As a class, collectins are large multimeric proteins composed of an N-terminal cysteine-rich region, a collagen-like region, an alpha helical coiled *neck* region, and a carbohydrate recognition domain (CRD) [29–31]. The basic collectin structure is a trimer of the polypeptide chain, but different collectins have different degrees of higher order oligomerization [31]. SP-A forms octadecamers (6 trimers), while SP-D preferentially accumulates as dodecamers (4 trimers). The carboxy-terminal domains of SP-A and SP-D are responsible for their lectin (carbohydrate binding) activity, and trimeric clusters of the peptide chains are required for high-affinity binding to multivalent ligands. Both proteins bind to the mannose or glucose sugars present in most microbial ligands, although SP-A preferentially binds to the dimannose repeating unit in gram-positive capsular polysaccharides and SP-D to the glucose-containing core oligosaccharides of gram-negative lipopolysacharide (LPS) [29]. Both can also interact with lipids; SP-A with phospholipids and the lipid A domain of gram-negative LPS, and SP-D with the lipid and inositol moieties of phosphatidylinositol.

SP-A and SP-D can bind, agglutinate, and opsonize a variety of pathogens as well as induce chemotaxis, phagocytosis, and provoke killing by phagocytic cells. Table 11.4 lists selected organisms bound by SP-A and/or SP-D. While no specific diseases associated with deficiencies of these proteins in humans have been described, murine knockout models have elucidated their role in host defense. SP-A deficient mice have normal surfactant homeostasis and respiratory function, but enhanced susceptibility to a number of different bacteria, viruses, and parasites [29, 33, 34]. The phenotype of SP-D deficient mice is somewhat confusing in that these animals develop a lipoproteinosis-like disease that

makes effects on innate immunity difficult to separate from lung injury-induced inhibitory changes in surfactant function [35]. Nonetheless, SP-D can be shown to similarly bind, agglutinate, and opsonize a variety of pathogens [29, 36, 37].

Surfactant Metabolism and Recycling

Much is known regarding the complex metabolism of pulmonary surfactant ([12, 38–46] for review). Lung surfactant is synthesized, packaged, stored, secreted and recycled in type II epithelial cells in the alveolar lining. The phospholipid components are synthesized in the endoplasmic reticulum and transported through the Golgi apparatus to the lamellar bodies, while surfactant proteins are translated in the usual fashion and then undergo extensive post-translational processing. SP-A, SP-B and SP-C [47–51], but not SP-D [52, 53], are found in lamellar bodies.

Lamellar bodies are subcellular organelles, and their contents are composed of tightly packed membrane-like structures that are effectively identical in composition to surfactant obtained from the alveolar space. Lamellar bodies make their way to the cell surface where their contents are extruded into the alveolar hypophase and unwind into a lattice-like construction called tubular myelin [54–56] (Fig. 11.2). Tubular myelin is a regularly spaced lattice of phospholipid bilayers studded with regularly spaced particles thought to be SP-A. SP-B and calcium are also required for tubular myelin formation [56, 57] and are present in its lattice structure. In addition to tubular myelin, a variety of other size-distributed surfactant aggregate forms (lamellar, vesicular, and non-specific) exist in the alveolar hypophase [12]. Lung surfactant adsorbs from tubular myelin and other active aggregates to form a complex mixed lipid/protein film at the alveolar hypophase-air interface as described earlier.

Lung surfactant has a finite life span in the alveoli and then is cleared from the alveolar space. As much as 90 % of the surfactant cleared from the alveolar space is taken up and recycled by type II pneumocytes, with the highest uptake percentages found in newborn compared to adult or premature animals ([12, 38, 58, 59] for review). Alveolar macrophages are responsible for only about 10–15 % of surfactant clearance, and a smaller percentage (<5 %) is cleared via the airways. Studies using labeled surfactant introduced into the airways have demonstrated direct uptake by type II pneumocytes, repackaging in lamellar bodies, and eventual re-secretion [60]. The half-life for turnover of human surfactant is variable, and has been reported to range from 1 to 24 h in

Table 11.4 Interactions of lung surfactant collectins with bacterial ligands

	Bacterial ligand	Collectin
Gram-negative bacteria		
Pseudomonas aeruginosa	LPS?	SP-A, SP-D
Klebsiella pneumoniae	LPS core (cap-phenotype)	SP-D
	Capsule (di-mannose)	SP-A
Escherichia coli	LPS core	SP-D
	Not defined	SP-A
H. influenzae, type A	P2 outer membrane protein	SP-A
Gram-positive bacteria		
Group B Streptococci	Not defined	SP-A
Staphylococcus aureus		
Cowan I strain	Not defined	SP-A
Clinical isolate	Not defined	SP-A
Streptococcus pneumoniae	Not defined	SP-A

Based on data from Crouch and Wright [29]

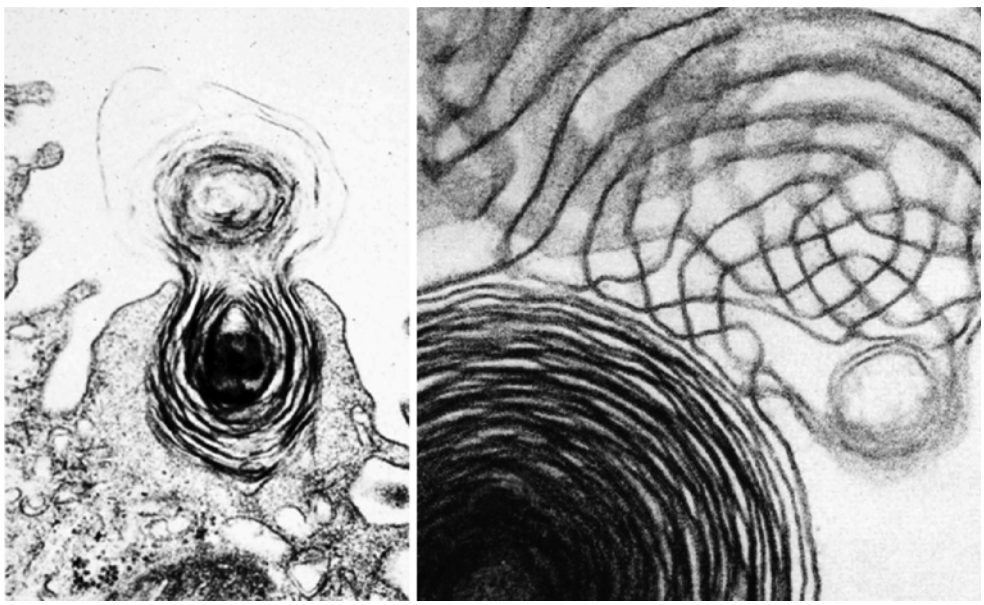


Fig. 11.2 Lung surfactant secreted from a lamellar body and resulting tubular myelin. Lamellar body contents being extruded from a type II pneumocyte (*left image*), which subsequently "unwind" into tubular myelin in the alveolar hypophase (*right image*). Formation of tubular myelin requires phospholipids, SP-A, SP-B, and calcium. Alveolar surfactant also exists in a variety of other large and small aggregate microstructural forms in addition to tubular myelin (Reprinted from Williams [54]. © 1977 Rockefeller University Press)

animals [12, 38, 58]. SP-A has been found to enhance the uptake of surfactant phospholipids into type II pneumocytes [61–63], and SP-B/C may also influence phospholipid uptake in type II cells [64, 65]. The uptake of exogenously administered surfactants as substrate is thought to be an important factor in the indirect (non-surface active) benefits of surfactant therapy, particularly for relatively inactive preparations with a high DPPC content such as Exosurf® and ALEC® (pharmaceutical surfactants are described in more detail later).

Acute Lung Injury/Acute Respiratory Distress Syndrome (ALI/ARDS)

The pathophysiology of acute lung injury is multifactorial and includes inflammation, surfactant dysfunction, vascular dysfunction, edema, oxidant injury, ventilation/perfusion mismatching, and injury to alveolar, capillary, and other pulmonary cells. This pathophysiology is described in detail elsewhere in this text. A common aspect of acute pulmonary injury is damage to the cells of the alveolar-capillary membrane (type I and type II alveolar epithelial cells and capillary endothelial cells) with a loss of barrier integrity leading to interstitial and alveolar edema. Another common feature is inflammation. The innate pulmonary inflammatory response is complex, involving the recruitment and activation of circulating leukocytes as well as participation by resident lung cells. A large number of inflammatory mediators and transduction and regulatory pathways are involved in acute pulmonary inflammation and injury (e.g., [66, 67] for review).

ALI/ARDS is a prevalent and potentially lethal condition in adults and children following direct or indirect pulmonary injury from multiple etiologies [67–70]. Common direct causes of acute pulmonary injury include respiratory infection, gastric or toxic liquid aspiration, pulmonary contusion, thoracic radiation, hyperoxia, and noxious gas inhalation, among others. Common indirect (systemic) causes of acute pulmonary injury include sepsis, hypovolemic shock, burn injury, pancreatitis, fat emboli, and generalized body trauma. Acute pulmonary injury also affects infants in addition to older patients. In term infants, while not generally labeled ALI/ARDS, common causes of lung-injury induced respiratory failure include meconium aspiration, pulmonary infection, and sepsis. In preterm infants, acute respiratory failure is most commonly initiated by surfactant deficiency (i.e., RDS), but secondary lung injury and surfactant dysfunction can arise in association with hyperoxia, mechanical ventilation, infection, edema from patent ductus arteriosus, and other factors. In addition to acute respiratory failure, ALI/ARDS can also progress to a fibroproliferative phase that leads to chronic lung injury with tissue remodeling and the initiation of fibrosis. However, surfactant dysfunction is most prominent in the acute phase of ALI/ARDS.

Surfactant Dysfunction in ALI/ARDS

In their original descriptions of ARDS (initially termed "adult" instead of "acute" respiratory distress syndrome), Ashbaugh et al. [71] and Petty and Ashbaugh [72] commented on its similarity to infantile RDS, and Petty et al. [73] reported abnormalities in surfactant function. However, as described earlier, respiratory failure in RDS is initiated by a quantitative deficiency in surfactant that leads to progressive atelectasis and overdistension with decreased lung compliance. Although an element of surfactant deficiency can be present in ALI/ARDS, surfactant dysfunction (inhibition, inactivation) as a consequence of inflammatory injury and edema is generally much more prominent. Extensive basic research has identified many of the mechanisms contributing to surfactant dysfunction in lung injury (for detailed review of lung surfactant inhibition and mechanisms of dysfunction see [12, 18, 74]). Irrespective of whether the initiating event is direct injury from the alveolar side or indirect pulmonary injury from the vascular side, surfactant dysfunction may arise by multiple pathways that include the following (Table 11.5):

1. *Physicochemical interactions with inhibitory or reactive substances*: A prevalent cause of surfactant dysfunction in lung injury is through biophysical or chemical interactions with substances that gain access to the alveolar space following damage to the alveolar-capillary membrane. Albumin, hemoglobin, fibrin, fibrinogen, and

Table 11.5 Pathways and processes that can contribute to surfactant abnormalities in acute inflammatory lung injury

Lung surfactant dysfunction/inactivation
Biophysical inactivation by inhibitory substances in edema or the inflammatory response
Chemical degradation by lytic enzymes or reactive oxygen/nitrogen species
Depletion or detrimental alteration of active large aggregate surfactant subtypes
Alveolar epithelial cell damage or alteration
Type I cell injury and death leading to increased permeability of the alveolar epithelial barrier
Type II cell injury and/or hyperplasia causing altered surfactant synthesis, secretion, recycling
Inflammation and microvascular dysfunction
Capillary endothelial injury with increased microvascular permeability, resulting in interstitial or alveolar edema containing surfactant inhibitors
Inflammatory mediators and products produced by leukocytes and lung cells that exacerbate lung injury or interact chemically/physically with functional surfactant components.

See text for discussion. Surfactant dysfunction and its mechanisms in ALI/ARDS are reviewed in detail by Notter [12] and Wang et al. [74]

Table 11.6 Examples of endogenous compounds that inhibit lung surfactant activity by direct physical or chemical interactions

Biophysical inhibitors
Plasma and blood proteins (e.g., albumin, hemoglobin, fibrinogen, fibrin monomer)
Fluid cell membrane lipids
Lysophospholipids
Fluid free fatty acids
Glycolipids and sphingolipids
Meconium
Chemically-acting inhibitors
Lytic inflammatory enzymes (proteases, phospholipases)
Reactive oxygen and nitrogen species

Adapted from [12, 18, 74]
Tabulated inhibitors are examples only. See text for discussion

other blood or serum proteins have been shown in vitro to impair the surface tension lowering of lung surfactant by competing with the adsorption of its active components into the air-water interface, thus compromising film formation [75, 76]. Other biophysical inhibitors include cell membrane lipids, lysophospholipids, or fatty acids that mix into the interfacial film itself to compromise surface tension lowering during dynamic compression [76–79]. Additional biophysical inhibitors are listed in Table 11.6, which also includes chemically-acting inhibitors such as phospholipases or proteases that can degrade essential surfactant lipids or proteins to impair surface activity [80–82]. Lung surfactant can also be chemically altered by interactions with reactive oxygen and nitrogen species [74]. Fortunately, although surfactant can be inhibited by these physicochemical processes, it has been well-documented, at least in vitro, that dysfunction can be overcome by increasing the concentration of active surfactant even if inhibitors are still present [12, 18, 74].

2. *Altered surfactant aggregates and metabolism*: Another pathway by which surfactant activity can be reduced during lung injury is by depletion or alteration of active large aggregates. As noted earlier, surfactant exists in the alveolar hypophase in a size-distributed microstructure of aggregates, the largest of which typically have the greatest surface activity and the highest apoprotein content [83–90]. The percentage of large aggregates and their content of SP-A and SP-B are reduced in bronchoalveolar lavage from patients with ALI/ARDS [91–93]. Surfactant phospholipid composition can also be altered in patients with ALI/ARDS [93, 94]. Animal models of ALI/ARDS demonstrate that large surfactant aggregates can be depleted or reduced in activity by physicochemical interactions with inhibitors or by changes in surfactant metabolism [86, 95–98]. Although large aggregates can be detrimentally affected in ALI/ARDS, information on total surfactant pools is inconsistent, with both decreased [99–101] and unchanged amounts [94, 102] reported.

In assessing surfactant dysfunction in ALI/ARDS, it is important to realize that the pathology is not static. The contribution of surfactant dysfunction to ALI/ARDS is dependent on the stage of injury, which commences with an exudative phase involving alveolar-capillary membrane damage and acute inflammation, but may evolve to include elements of fibroproliferation and fibrosis. The superimposition of iatrogenic factors such as ventilator-induced lung injury and hyperoxic injury during intensive care further confounds pathology, as does the multi-organ disease that is frequently present in patients with ALI/ARDS. The multifaceted pathology of lung injury is an important issue when evaluating the potential efficacy of exogenous surfactant therapy in ALI/ARDS.

Surfactant Therapy in ALI/ARDS

The existence of surfactant dysfunction in ALI/ARDS provides a conceptual rationale for therapy with exogenous surfactant, but the use of surfactant preparations having the greatest surface activity and ability to resist inhibition is clearly required. Moreover, to be effective in ALI/ARDS, exogenous surfactant must be delivered and distributed to injured alveoli in the necessary amounts, despite the presence of edema and inflammation. In analogy with initial attempts to treat RDS in premature infants, the first large controlled trial of surfactant replacement in ARDS using the aerosolized protein-free synthetic surfactant Exosurf® was an unequivocal failure [103]. This failure at least partly can be explained by similar reasons to the initial failed neonatal trial, i.e., the use of a surfactant with inadequate activity and an ineffective delivery method. However, surfactant therapy in ALI/ARDS faces more complex challenges than in the case of neonatal RDS, and this therapy remains investigational as detailed below.

Pharmaceutical Surfactants

Although the composition of endogenous pulmonary surfactant is similar throughout mammalian species, this is not true of exogenous surfactant drugs. The degree of resemblance of pharmaceutical surfactants to native surfactant is highly variable, and this has direct consequences for surface and physiological activity. Pharmaceutical surfactants can be divided into three functionally relevant groups: (i) organic solvent extracts of lavaged lung surfactant from animals; (ii) organic solvent extracts of processed animal lung tissue with or without additional synthetic additives; and (iii) synthetic preparations not containing surfactant material from animal lungs (Table 11.7).

Table 11.7 Clinical exogenous surfactant drugs used to treat lung diseases involving surfactant deficiency/dysfunction

I. Organic solvent extracts of lavaged animal lung surfactant
Infasurf® (CLSE, calfactant)
bLES®
Alveofact®
II. Supplemented or unsupplemented organic solvent extracts of processed animal lung tissue
Survanta®
Surfactant-TA®
Curosurf®
III. Synthetic exogenous lung surfactants
Exosurf®
ALEC®
Surfaxin® (lucinactant, KL4)
Venticute® (Recombinant SP-C surfactant)

Adapted from [12, 104]
Infasurf® (ONY, Inc and Forest Laboratories), Survanta® (Abbott/Ross Laboratories), and Curosurf® (Chesi Farmaceutici and Dey Laboratories) are currently FDA-approved in the U.S. for neonatal administration, and Surfaxin® is under active FDA evaluation. Exosurf® (Glaxo-Wellcome) is also FDA-approved, but is no longer used clinically. Details on the composition, activity, and efficacy of these exogenous surfactants in neonatal RDS are reviewed elsewhere (e.g., Refs. [12, 105–109]). The use of these surfactants in ALI/ARDS is discussed in the text, along with the development of new synthetic lipid/peptide exogenous surfactants in current research

Organic solvent extracts of lavaged alveolar surfactant (Category I) contain all of the hydrophobic lipid and protein components of endogenous surfactant, although specific compositional details can vary depending on preparative methodology. Extracts of minced or homogenized lung tissue (Category II) necessarily contain some non-surfactant components, and require more extensive processing that can further alter composition compared to native surfactant. The synthetic surfactants in Category III that have been most widely studied are the early protein-free preparations Exosurf® and ALEC® (artificial lung expanding compound). Exosurf is a mixture of DPPC:hexadecanol:tyloxapol (1:0.11:0.075 by weight) and ALEC is a mixture of 7:3 DPPC:egg PG. These two preparations are no longer in active clinical use because they have been found to have inferior activity compared to animal-derived surfactants [12, 110–115]. Two additional newer synthetic surfactants, KL4 (Surfaxin®, lucinactant) and recombinant SP-C surfactant (Venticute®), are currently undergoing clinical evaluation.

The composition and activity of the animal-derived and synthetic exogenous surfactants in Table 11.7 are discussed in detail by Notter [12], and their efficacy in preventing or treating RDS in clinical trials in premature infants is extensively reviewed elsewhere (e.g., [12, 105–109, 116, 117]). The three animal-derived exogenous surfactant preparations that are currently licensed and used for treating or preventing RDS in preterm infants in the United States are: Infasurf®, Survanta®, and Curosurf®. Infasurf® is a direct chloroform: methanol extract of large aggregate surfactant obtained by bronchoalveolar lavage from calf lungs [12, 19]. Survanta® is made from an extract of minced bovine lung tissue to which dipalmitoylphosphatidylcholine (DPPC), tripalmitin, and palmitic acid are added [12, 19]. Curosurf® is prepared from minced porcine lung tissue by a combination of washing, chloroform: methanol extraction, and liquid-gel chromatography [117]. Surfaxin®, which has recently gained FDA-approval, contains a 21 amino acid peptide (KL4) that has repeating units of one leucine (K) and four lysine (L) residues. This peptide is combined at 3 % by weight with a 3:1 mixture of DPPC and palmitoyl-oleoyl phosphatidylglycerol (POPG) plus 15 % palmitic acid [12]. Venticute® contains synthetic lipids and palmitic acid plus a 34 AA modified human recombinant SP-C that has substitutions of phenylalanine for cysteine at two positions and isoleucine for methionine at another [12].

Relative Activity and Inhibition Resistance of Exogenous Surfactant Drugs

The relative activity and efficacy of surfactant drugs are crucial for evaluating and optimizing therapy. As noted above, direct clinical comparison trials in premature infants and retrospective meta analyses have indicated that current animal-derived surfactants are more efficacious in treating preterm infants than protein-free synthetic surfactants such as Exosurf® (e.g., [12, 109, 112–116]). Differences in clinical activity between surfactants can in many cases be directly linked to their composition. The fact that surfactants derived from animal lungs (Categories I and II, Table 11.7) have greater efficacy than protein-free synthetic surfactants like Exosurf® reflects a lack of synthetic components to adequately replace the highly active hydrophobic surfactant proteins SP-B/C. The surface and physiological activity of Exosurf® is significantly increased by the addition of purified bovine SP-B/SP-C, demonstrating that its synthetic components are not functionally effective in substituting for these active proteins [110]. Animal-derived clinical surfactants themselves also vary markedly in surface activity and ability to resist inhibitor-induced dysfunction based on their apoprotein content and other compositional differences. Laboratory research indicates that the surface and physiological activity of direct extracts of lavaged surfactant (Category I surfactant drugs, Table 11.7) are typically greater than those of other clinical surfactants (Figs. 11.3, 11.4, and 11.5). As an example, the activity and inhibition resistance of Infasurf® are substantially greater than Survanta® in basic biophysical and animal studies [19, 110, 111, 118] (Figs. 11.3, 11.4, and 11.5), and these differences correlate directly with the content of SP-B in the two preparations

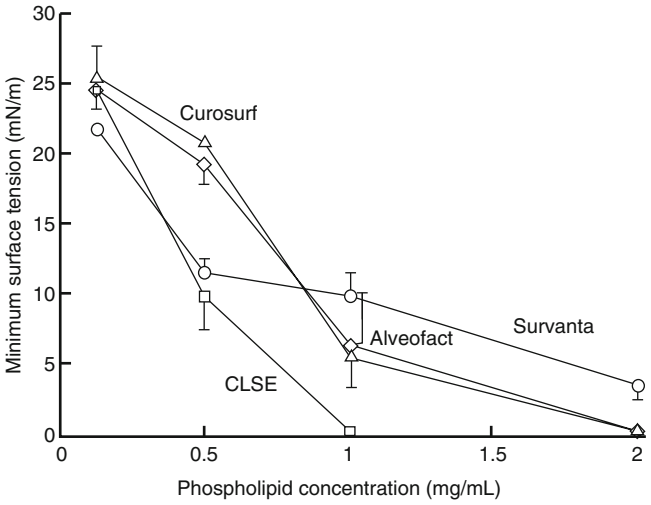


Fig. 11.3 Overall surface tension lowering ability of clinical exogenous surfactants. Minimum surface tension after 5 min of pulsation in a bubble surfactometer (37° C, 20 cycles/min, 50 % area compression) is plotted as a function of surfactant phospholipid concentration for several clinical surfactants. More active surfactants reduce surface tension to lower values at lower concentrations. The surfactants shown vary widely in overall surface tension lowering ability, with the most active being CLSE (Infasurf®, Category I, Table 11.7) (Reprinted from Seeger et al. [111]. With permission from European Respiratory Society)

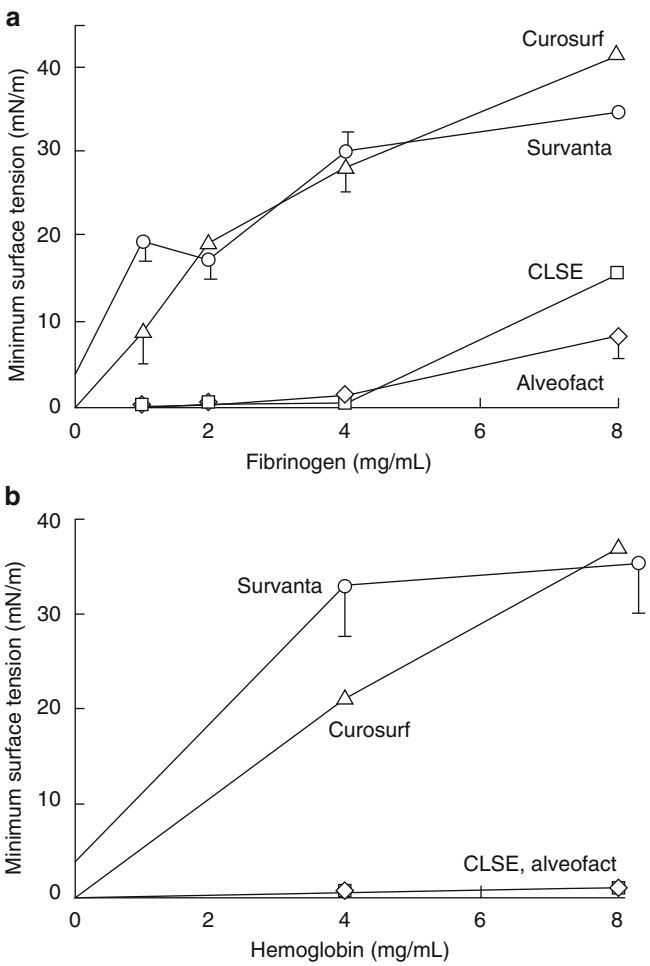


Fig. 11.4 Resistance of clinical surfactants to inhibition by blood proteins. Minimum surface tension of clinical surfactants after 5 min of pulsation in a bubble surfactometer (37° C, 20 cycles/min, and 50 % area compression) is plotted against the concentration of added inhibitory blood proteins (fibrinogen and hemoglobin). Exogenous surfactants that most closely mimic natural surfactant (Category I drugs from Table 11.7) are best able to resist inhibition and reach low surface tension despite high levels of inhibitory proteins. Surfactant phospholipid concentration was constant at 2 mg/ml (Reprinted from Seeger et al. [111]. With permission from European Respiratory Society)

[19, 24, 118]. Survanta® contains only 0.044 % SP-B by weight relative to phospholipid due to losses during processing of lung tissue [19]. In contrast, Infasurf® has a specific SP-B content of 0.9 % by weight (and a total hydrophobic protein content of 1.7 % by weight) equivalent to lavaged calf lung surfactant [19]. As described earlier, SP-B is the most active of the hydrophobic surfactant proteins in enhancing the adsorption and overall dynamic surface activity of phospholipids [15–17, 19, 119, 120]. The addition of SP-B or synthetic SP-B peptides to Survanta® significantly improves its activity towards that of natural surfactant [19, 118, 121] (Fig. 11.5), indicating that the lack of SP-B in this exogenous surfactant is functionally important. Even without SP-B, however, Survanta® still has significantly better activity compared to protein-free surfactants like Exosurf® because of its content of SP-C and other ingredients [12].

New Synthetic Lung Surfactant Development

Recent advances in molecular bioengineering and peptide chemistry provide the potential to design new even more active synthetic lung surfactants than those in Table 11.7, and several approaches are currently being studied ([122–125] for review). One important approach involves synthetic surfactants bioengineered to contain lipids combined with active SP-B peptides that incorporate functionally crucial structural regions of the human protein. Two significant examples of highly active SP-B peptides are the 34 residue Mini-B peptide [126, 127] and the 41 residue Super Mini-B peptide [128]. Mini-B and Super Mini-B both incorporate active N- and C-terminal amphipathic helices from human SP-B, as well as its functional Saposin bend character and key intramolecular connectivities. In addition, Super Mini-B includes an N-terminal lipophilic sequence from human SP-B. Super Mini-B and Mini-B peptides have very high surface and physiological activity when combined with lipids in synthetic surfactants [126, 128]. Synthetic exogenous surfactants containing an SP-B peptide like Super Mini-B or Mini-B can also be bioengineered to contain a second peptide component based on

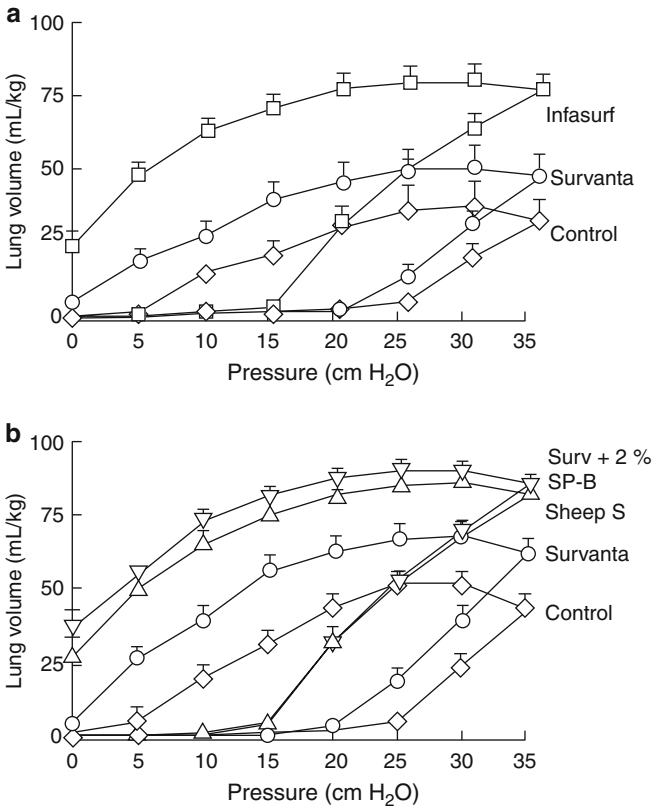


Fig. 11.5 Effects on physiological activity from the addition of purified SP-B to Survanta®. (**a**) Premature rabbit fetuses (27 days gestation) treated with Survanta® or Infasurf®, and untreated controls; (**b**) Premature rabbit fetuses treated with Survanta®, Survanta®+SP-B (2 % by weight by ELISA), natural surfactant from adult sheep (Sheep S), or untreated controls. Infasurf® improved lung mechanics more than Survanta® (**a**), and the importance of SP-B in this behavior is demonstrated by the increased activity of Survanta®+SP-B compared to Survanta® alone (**b**). Surfactants were instilled intratracheally at a dose of 100 mg/kg body weight, and quasistatic pressure-volume curves were measured following 15 min of mechanical ventilation (Reprinted from Mizuno et al. [118]. With permission from Nature Publishing Group)

human SP-C, but designed to be more stable and resistant to amyloid formation that can detrimentally impact the activity of native SP-C. Synthetic surfactants containing SP-B/C peptides can also incorporate novel synthetic phospholipid analog components that are designed to have high surface activity plus beneficial chemical properties like phospholipase-resistance. One particularly active synthetic lipid analog of this kind is DEPN-8, a phospholipase-resistant diether lipid analog of DPPC developed by Notter and co-workers [122, 126, 129–131]. Synthetic surfactants containing DEPN-8 or other phospholipase-resistant lipids plus active SP-B peptides have the potential for particular utility in ALI/ARDS [82, 122, 126, 128, 131–134], where these lytic enzymes can be elaborated in high concentrations during the inflammatory response in injured lungs [135–141].

Animal Studies of Surfactant Therapy in ALI/ARDS

Animal models of ALI/ARDS in which exogenous surfactant therapy has been found to improve respiratory function or mechanics include acid aspiration [142–144], meconium aspiration [145–148], anti-lung serum [149], bacterial or endotoxin injury [150–155], vagotomy [156], hyperoxia [157–161], *in vivo* lavage [121, 162–166], N-nitroso-N-methylurethane (NNNMU) injury [167–169], lung contusion [170], and viral pneumonia [171, 172]. In addition to demonstrating that surfactant therapy has potential benefit in ALI/ARDS, animal studies are also important in comparing surfactant activity under reproducible conditions, as well as in examining other variables of interest for clinical therapy. These variables include the method of surfactant delivery (instillation versus aerosolization), the timing of administration, the effects of different modes of ventilation, the effects of dose, and so forth. For example, animal studies indicate that direct airway instillation is more effective than current aerosol techniques in delivering exogenous surfactant to the alveoli. In addition, these studies demonstrate that early therapy is preferable to later therapy in terms of distributing surfactant to injured lungs ([12] for review). However, despite their utility for assessing the acute effects of exogenous surfactants and comparing preparations and delivery methods, animal models offer limited insight into longer-term morbidity or mortality. For that, one must ultimately turn to human studies.

Human Studies of Surfactant Replacement Therapy in ALI/ARDS

Multiple clinical studies have reported respiratory benefits following the instillation of exogenous surfactants to term infants, children, or adults with ALI/ARDS or related acute respiratory failure [173–192] (Table 11.8). However, many of these were pilot treatment studies or small controlled trials that reported only improvements in acute lung function (oxygenation). Results in sizeable randomized controlled trials of surfactant therapy in ALI/ARDS are more equivocal, particularly in adults.

Infant Investigations

The best-studied application of surfactant therapy in term infants with acute pulmonary injury is in meconium aspiration syndrome [186–190]. Meconium obstructs and injures the lungs when aspirated and is known to cause surfactant dysfunction [194, 195]. Auten et al [186], Khammash et al. [189], and Findlay et al. [190] have all reported significant improvement from surfactant administration in infants with meconium aspiration. The randomized study of Findlay et al.

Table 11.8 Selected clinical studies reporting benefits of exogenous surfactant therapy in acute respiratory failure (ALI/ARDS)

Study	Patients (N)	Disease or syndrome	Surfactant	Outcomes
Günther et al. [173]	Adults (27)	ARDS	Alveofact	Improved oxygenation Improved surfactant function
Walmrath et al. [174]	Adults (10)	ARDS from sepsis	Alveofact	Improved oxygenation
Spragg et al. [175]	Adults (6)	ARDS from multiple causes	Curosurf	Improved oxygenation and biophysical function
Wiswell et al. [178]	Adults (12)	ARDS from multiple causes	Surfaxin	Improved oxygenation
Spragg et al. [176]	Adults (40)	ARDS, multiple causes	Venticute	Improved oxygenation, decreased IL-6 in BAL
Amital et al. [177]	Adults (42)	Lung transplant	Infasurf	Improved oxygenation, better graft function
Willson et al. [179, 180]	Children (29 & 42)	ARDS from multiple causes	Infasurf	Improved oxygenation
Willson et al. [181]	Children (152)	ARDS from multiple causes	Infasurf	Improved survival
Lopez-Herce et al. [182]	Children (20)	ARDS + post-op cardiac	Curosurf	Improved oxygenation
Hermon et al. [183]	Children (19)	ARDS + post-op cardiac	Curosurf or alveofact	Improved oxygenation
Herting et al. [184]	Children (8)	Pneumonia	Curosurf	Improved oxygenation
Moller et al. [185]	Children (35)	ARDS, multiple causes	Alveofact	Improved oxygenation
Auten et al. [186]	Infants (14)	Meconium aspiration or pneumonia	Infasurf (CLSE)	Improved oxygenation
Lotze et al. [187, 188]	Infants (28 & 328)	ECMO, multiple indications	Survanta	Improved oxygenation, decreased ECMO
Khammash et al. [189]	Infants (20)	Meconium aspiration	bLES	Improved oxygenation
Findlay et al. [190]	Infants (40)	Meconium aspiration	Survanta	Improved oxygenation, decreased pneumothorax and mechanical ventilation
Luchetti et al. [191, 192]	Infants (20 & 40)	RSV bronchiolitis	Curosurf	Improved oxygenation

The tabulated studies of Willson et al. [180, 181], Findlay et al. [190], Moller et al. [185], Lotze et al. [187, 188], Luchetti et al. [191, 192] and Amital et al. [177] were controlled trials, while the remaining studies were uncontrolled treatment trials. See text for details, plus Refs. [67, 68, 104, 193] for added reviews of exogenous surfactant therapy in ALI/ARDS

[190] found reductions in the incidence of pneumothorax, duration of mechanical ventilation and oxygen therapy, time of hospitalization, and requirements for ECMO in 20 term infants treated with Survanta® compared to controls. Lotze et al. [187, 188] also reported favorable results using Survanta® in a controlled trial in term infants referred for ECMO due to severe respiratory failure (meconium aspiration was a prevalent diagnosis in both studies). Twenty-eight infants treated with four doses of Survanta® (150 mg/kg) had improved pulmonary mechanics, decreased duration of ECMO treatment, and a lower incidence of complications after ECMO compared to control infants [187]. A subsequent multicenter controlled trial in 328 term infants also reported significant improvements in respiratory status and the need for ECMO following surfactant treatment [188]. Exogenous surfactant is now used in many institutions to treat respiratory failure in term infants with meconium aspiration or pneumonia, although fewer controlled studies are available for the latter condition. Surfactant therapy has also been studied in infants with congenital diaphragmatic hernia, but its use remains somewhat controversial in this context [196, 197].

Pediatric and Adult Investigations

Surfactant therapy in children and adults with ALI/ARDS has met with mixed success. Improvements in acute respiratory function following exogenous surfactant therapy have been shown in a number of studies in adults and children with ALI/ARDS [173–185] (Table 11.8). However, findings in substantive randomized prospective studies are less positive, particularly in adults. The first large prospective, controlled study of surfactant therapy in adults with ARDS was definitively negative. Anzueto et al. [103] administered nebulized Exosurf® vs. placebo to 725 adults with ARDS secondary to sepsis and found no improvement in any measure of oxygenation and no effect on morbidity or mortality. As described earlier, Exosurf® is no longer used clinically in the United States because of its lower activity compared to animal-derived surfactants, and aerosolization is currently not as effective as airway instillation in delivering surfactant to the distal lung fields. Gregory et al. [198] reported small benefits in oxygenation in a controlled trial in adults with ARDS who received four 100 mg/kg doses of Survanta®, but with no overall advantage in survival in the 43 surfactant-treated patients studied. A study by Spragg et al. [176] using recombinant SP-C surfactant (Venticute®) in adults with ARDS showed immediate improvements in oxygenation, but no longer-term improvement in duration of mechanical ventilation, lengths of stay, or mortality. *Post-hoc* analysis suggested, however, that the response in the subgroup of patients with ARDS due to direct lung injury was strongly positive.

This encouraging result led to a recent follow-up study aimed at determining the impact of Venticute® in adults with direct lung injury, which demonstrated no clinical benefit [199]. However, interpretation of this disappointing finding is complicated by questions raised about the specific surface activity of the newer drug suspension administered in the follow-up investigation [199].

Controlled studies of surfactant therapy in children with ALI/ARDS have been more encouraging than those in adults. A randomized but unblinded trial by Willson et al. [180] in 42 children at eight centers with ALI/ARDS showed that those receiving Infasurf® (70 mg/kg) had immediate improvement in oxygenation and fewer ventilator days and days in intensive care. This trial followed an initial open label trial by the same group demonstrating improved oxygenation in 29 children (0.1–16 years) treated with instilled Infasurf® [179]. Luchetti et al. [191, 192] have reported two small controlled studies showing that treatment with porcine surfactant (Curosurf®, 50 mg/kg) led to improved gas exchange as well as reduced time on mechanical ventilation and in intensive care for infants with bronchiolitis. A study by Moller et al. [185] reported that children with ARDS had immediate improvement in oxygenation and a lesser need for rescue therapy following treatment with the bovine surfactant Alveofact®, but was underpowered for assessment of more definitive outcomes. A substantial blinded controlled study by Willson et al. [181] in 2005 yielded very positive results in pediatric patients with ALI/ARDS, demonstrating both immediate benefits with regard to oxygenation as well as a significant survival advantage for patients receiving calfactant (Infasurf®) relative to placebo (Table 11.9), particularly in the direct lung injury cohort. The clinically significant results of this study generated a further combined pediatric and adult controlled study of calfactant in patients with direct lung injury. This adult/pediatric study was halted recently due to a lack of efficacy, but interpretations of this negative finding are complicated by questions about the effectiveness of surfactant delivery for the modified clinical drug suspension and administration methods used in the trial (Willson, personal communication). Another recent study involved the testing of the synthetic surfactant Surfaxin® (lucinactant) in a phase 2 study in infants less than 2 years of age with acute hypoxemic respiratory failure (AHRF) [200]. In this study, treatment with lucinactant appeared to be generally safe, and was associated with an improvement in oxygenation and a significantly reduced requirement for retreatment. These findings suggest that lucinactant might improve lung function in infants with AHRF [200], although more data will be required before this can be adequately determined.

None of the above studies showed any significant adverse long-term effects from surfactant administration, although transient hypoxia and some hemodynamic instability surrounding instillation appear common. Transmission of infectious agents or allergic reactions has also not been reported with any of the surfactants currently licensed in the United States.

Table 11.9 Clinical outcomes from a controlled study using exogenous surfactant (Infasurf; calfactant) in pediatric patients with ALI/ARDS

	Calfactant (n = 77)	Placebo (n = 75)	P Value
Mortality			
Died (in hospital)	15 (19 %)	27 (36 %)	0.03
Died w/o extubation	12 (16 %)	24 (32 %)	0.02
Failed CMV[a]	13 (21 %)	26 (42 %)	0.02
ECMO	3	3	–
Use of nitric oxide	9	10	0.80
HFOV after entry	7	15	0.07
Secondary outcomes			
PICU LOS	15.2 ± 13.3	13.6 ± 11.6	0.85
Hospital LOS	26.8 ± 26	25.3 ± 32.2	0.91
Days O_2 therapy	17.3 ± 16	18.5 ± 31	0.93
Hospital charges[b]	$205 ± 220	$213 ± 226	0.83
Hospital charges/day[b]	$7.5 ± 7.6	$7.9 ± 7.5	0.74

Based on data from Willson et al. [181]
In addition to improving mortality and reducing the percentage of patients that failed CMV as reported in the table, instilled calfactant also significantly improved oxygenation index compared to placebo (P = 0.01, data not shown)
Abbreviations: *CMV* conventional mechanical ventilation, *ECMO* extracorporeal membrane oxygenation, *HFOV* high frequency oscillatory ventilation, *iNO* inhaled nitric oxide
[a]Some patients that failed CMV had more than one non-conventional therapy (ECMO, iNO, or HFOV)
[b]Costs are given in thousands of dollars

The Future of Surfactant Therapy and Related Combination Therapies in ALI/ARDS

As described in this chapter, surfactant replacement therapy is standard care in the prevention and treatment of RDS in premature infants, and there is basic science and clinical evidence supporting its use in some forms of lung injury-associated respiratory failure. Data suggest that surfactant therapy in ALI/ARDS should be targeted to direct forms of lung injury where it is likely to be most effective (e.g., pneumonia, aspiration, etc.) as opposed to indirect lung injury (sepsis, systemic inflammatory response syndrome, etc.) [176, 181]. Clinical evidence showing the efficacy of surfactant therapy in term infants with meconium aspiration is sufficiently strong that this approach is now frequently used in neonatal intensive care units, and it is also being applied to other forms of neonatal respiratory failure like pneumonia. Clinical data also indicate that surfactant therapy can generate acute improvements in respiratory function in children with direct pulmonary forms of ALI/ARDS. At the same time, a sufficient consensus of controlled clinical trial data

does *not* exist for surfactant administration to be considered a standard therapy in the pediatric intensive care unit for children with ALI/ARDS. It may be argued that well-established basic science evidence of surfactant dysfunction in ALI/ARDS, along with favorable results for surfactant treatment in multiple animal models coupled with respiratory benefits in humans without significant adverse effects, makes a strong rationale for considering surfactant therapy in pediatric patients with direct lung injury and severe acute respiratory failure. From this perspective, the major downside of the therapy is its considerable expense in the context of limited data documenting broadly-improved long-term outcomes in controlled studies.

As emphasized in this chapter, some exogenous surfactants are more active and have better inhibition resistance than others. The severe pathology of lung injury makes it essential that only the most active and inhibition-resistant surfactant drugs be used for meaningful evaluations of the efficacy of this treatment approach. The ability to deliver active exogenous surfactant in adequate amounts to injured lungs is also a crucial factor in achieving efficacy. Currently, tracheal or bronchoscopic instillation as opposed to aerosolization are the standard delivery techniques used clinically. Future work perfecting more efficient aerosol delivery methods would be very valuable in facilitating the clinical use of exogenous surfactant in patients with compromised respiration. In addition, the delivery of instilled exogenous surfactants to injured lungs can possibly be improved by the use of specific administration methods or particular modes/strategies of mechanical ventilation, such as the use of positioning and recruitment maneuvers as were explored in the most successful human surfactant trials. For example, studies have suggested that the distribution and/or efficacy of instilled exogenous surfactant can be improved by jet ventilation [201, 202] and partial liquid ventilation [203–205]. The delivery and pulmonary distribution of surfactant drugs could also potentially be improved by the use of low viscosity formulations to reduce transport resistance after instillation. Whole surfactant and animal-derived exogenous surfactants have complex non-Newtonian, concentration-dependent viscosities that vary significantly among preparations [206, 207]. Finally, extensive experience from surfactant therapy in animal studies and preterm infants suggests that early surfactant administration (i.e., within hours of lung injury) generates improved responses compared to delayed administration, possibly as a result of better intrapulmonary drug distribution coupled with minimized ventilator-induced lung injury. Intuitively, similar advantages might accompany early surfactant administration in patients with ALI/ARDS.

Lastly, a major issue with regard to surfactant therapy in ALI/ARDS involves its potential use in combination with other agents or interventions that target additional aspects of the complex pathophysiology of acute pulmonary injury. This kind of combination therapy approach may be particularly important in adults with ALI/ARDS, where responses to exogenous surfactant have so far been disappointing. Even if exogenous surfactant as an individual agent is mechanistically effective in mitigating surfactant dysfunction and acutely improving respiration in ALI/ARDS, clinical benefits to long-term outcomes may not be apparent in patients due to remaining elements of lung injury pathology. The use of multiple therapeutic agents or interventions based on specific rationales for potential synergy might significantly enhance patient outcomes in complex disease processes involving inflammatory lung injury. The use of exogenous surfactant therapy in the context of specific combined-modality interventions is described in detail elsewhere [67, 208, 209]. Examples of agents that might be synergistic with exogenous surfactant in ALI/ARDS include anti-inflammatory antibodies or receptor antagonists, antioxidants, and vasoactive agents such as inhaled nitric oxide (iNO). In addition, specific ventilator modalities or ventilation strategies that reduce iatrogenic lung injury may be equally important to consider in conjunction with surfactant therapy. Given the known importance of surfactant dysfunction in inflammatory lung injury, it is likely that on-going research will continue to identify specific populations of patients with ALI/ARDS or related acute respiratory failure who can benefit from exogenous surfactant therapy, with or without complementary agents or interventions.

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Extracorporeal Life Support

12

Richard T. Fiser

Abstract

This chapter provides a review of the use of extracorporeal membrane oxygenation (ECMO) for the support of acute, refractory respiratory failure in children. A brief history of ECMO use is provided, as is a discussion of the indications for pediatric ECMO support and patient selection. Equipment used in ECMO support is reviewed, including the differences in centrifugal and roller-head pumps and newer types of oxygenators. Differences in the two primary modes of ECMO support – venoarterial and venovenous – are discussed extensively. The chapter reviews principles of gas exchange in the ECMO circuit as well as hemodynamic effects of ECMO. A section on patient management issues, including anticoagulation, renal support, sedation, nutrition, and weaning from ECMO is included. Complications of ECMO, including mechanical complications, central nervous system complications, bleeding, and infection are reviewed. The chapter highlights recent literature regarding the outcomes of patients supported with ECMO for respiratory failure and discusses the use of ECMO is specific situations, such as extracorporeal cardiopulmonary resuscitation (ECPR), patients with septic shock, "non-traditional" patient populations, and adults with acute hypoxemic respiratory failure.

Keywords

Extracorporeal membrane oxygenation • Extracorporeal life support • Extracorporeal cardiopulmonary resuscitation • Acute respiratory distress syndrome • Septic shock

History of Extracorporeal Life Support (ECLS)

The history of extracorporeal life support (ECLS) for cardiopulmonary failure is inextricably linked with the development of cardiopulmonary bypass for cardiac surgery. In 1953, Dr. J.H. Gibbons first used a "heart-lung machine" on a human patient, utilizing roller pumps originally devised in the 1930s by Dr. Michael DeBakey [1]. The introduction of the bubble oxygenator in 1955 by Drs DeWall and Lillehei was a milestone in the field of cardiac surgery, and these type oxygenators remained in wide use for two decades. These early technological breakthroughs, though, were designed for short-term cardiopulmonary support. Early model oxygenators were not designed for long-term gas exchange in an extracorporeal circuit. Dr. Theodore Kolobow introduced a spiral, silicone membrane oxygenator suitable for long-term support of gas exchange with a blood pump in the early 1970s [1].

The first published use of ECLS for prolonged management of acute respiratory failure occurred in 1972. Dr. J. Donald Hill and colleagues reported the use of a roller pump and membrane "lung" for successful support of a 24 year old man with refractory hypoxemia from post-traumatic "shock lung" [2]. The patient was supported with partial cardiopulmonary bypass for 75 h and ultimately survived to be discharged from the hospital. This success, coupled with interest

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in the newly described "adult respiratory distress syndrome" [3], rapidly led to initiation of an NIH-funded prospective, randomized, controlled trial of extracorporeal membrane oxygenation (ECMO), as the new technology came to be called, in adult patients with ARDS. Unfortunately, the trial was discontinued due to excessive mortality in both the ECMO (86 %) and conventional (92 %) groups [4]. In retrospect, this trial was plagued by design flaws. Some of the most serious flaws included excessive duration of mechanical ventilation prior to randomization (mean = 10 days), use of anticoagulation strategies analogous to those used in cardiopulmonary bypass, and the fact that 2/3 of the study centers had no prior ECMO experience. This initial prospective trial set ECMO support of adults back 10–15 years.

The use of ECMO for support of refractory hypoxemic respiratory failure in neonates met with more success, thanks in large part to the pioneering efforts of Dr. Robert Bartlett. In 1975, Bartlett first used ECMO to rescue a newborn with profound hypoxemia from meconium aspiration, and he went on to report promising results with the use of ECMO in a series of moribund infants suffering from refractory respiratory failure [5, 6]. By 1982, Bartlett and colleagues at the University of Michigan reported 45 cases of refractory neonatal respiratory failure managed with ECMO, with a 55 % survival [7]. In 1985, Bartlett, et al. published a randomized prospective trial of ECMO vs conventional ventilator management in term newborns with significantly better survival in the ECMO arm [8]. This trial used a "randomized play the winner" statistical technique, aimed at minimizing the ethical problems associated with a trial in which the conventional arm was thought to have a 90 % mortality rate and the treatment arm as high as a 90 % survival rate [9]. A few years later, O'Rourke, et al. published a prospective randomized trial of ECMO vs conventional ventilation in term infants with persistent pulmonary hypertension demonstrating a 90 % survival in the ECMO group as compared to 60 % in the conventional group [10]. Enthusiasm for ECMO as a supportive technology for severe, acute cardiopulmonary failure by that time had become widespread enough that the Extracorporeal Life Support Organization (ELSO) was founded in 1989. With membership consisting of representatives from ECMO centers around the world, ELSO has served as the primary advocate for research into the use of ECLS and continues to maintain a registry of patients supported with this technology. As of this writing, more than 46,500 neonates, children, and adults with respiratory or cardiac failure have been supported with ECMO worldwide, with a 62 % overall survival [11].

Experience with the use of ECMO for support of older children with respiratory failure, and with the use of ECMO for support of cardiac failure, grew out of the neonatal experience. A review of ECLS for primary cardiac support is presented elsewhere in this textbook. An early series reporting on ECMO for support of older children with severe acute respiratory failure noted a 60 % survival rate in patients with a mean age of approximately 4 years [12]. A recent study of the ELSO Registry for support of pediatric respiratory failure with ECMO reviewed more than 3,200 patients and reported 57 % overall survival, with survival rates ranging from 39 to 82 % based on the underlying etiology of respiratory failure [13].

Patient Selection for ECLS

Since the early years of ECMO, investigators have attempted to develop reliable predictors of mortality as a guide to the most appropriate utilization of ECMO rescue [14–18]. Some of these studies were small and retrospective, and most attempted to use some objective measure of the severity of respiratory failure as a predictor of mortality. Examples of pre-ECMO criteria studied include:

- Alveolar – arterial oxygen gradient
- Oxygenation index (OI) [$OI = \{100 \times (\text{Mean airway pressure} \times FiO_2)\}/PaO_2$
- Peak inspiratory pressure
- Requirement for FiO_2 >0.60 to maintain arterial oxygen saturation >85 %
- PaO_2/FiO_2
- Duration of mechanical ventilation prior to ECMO cannulation.

While some of these respiratory indices, such as an OI >29 [17] or an $AaDO_2$ >450 [18] demonstrated strong positive predictive values for mortality in small studies in the early years of ECMO use, investigators have questioned whether these criteria are applicable in the current era, given the more widespread adoption of "lung-protective" conventional mechanical ventilation strategies and other adjunctive treatments for hypoxemic respiratory failure, such as inhaled nitric oxide, high frequency oscillatory ventilation, and surfactant. A study by Peters, et al. published in the late 1990s demonstrated in 118 children with acute hypoxemic respiratory failure that such indices as the OI and $AaDO_2$ predicted death very poorly and that mortality was most strongly associated with non-respiratory organ failure [19]. A more recent study found no oxygenation index that was clearly associated with mortality in a cohort of 131 children with acute hypoxemic respiratory failure, but did show relationship over time between worsening OI and mortality [20].

No strict criteria exist for the use of ECMO in pediatric patients. Generally speaking, pediatric patients supported with ECMO have failed to respond to conventional mechanical ventilation and often to adjunctive therapies such as inhaled nitric oxide, prone positioning, and high frequency oscillatory ventilation. ECMO deployment is intended for the support of a cardiopulmonary illness that is both acute

and reversible, to the best of one's ability to predict. Some debate over the years has centered on the question of the specific duration of pre-ECMO mechanical ventilation that is likely to predict irreversible lung disease. While this question remains open to discussion, a recent study of the ELSO Registry for cases of ECMO support of pediatric respiratory failure between 1993 and 2007 found that all patients ventilated for ≤14 days prior to ECMO had similar survival rates, but patients ventilated >14 days prior to ECMO had significantly lower survival [13]. Most ECMO centers prefer that a patient have no evidence of severe neurologic injury prior to initiation of ECMO. Severe coagulopathy certainly increases the risk of bleeding complications with the use of ECMO. The use of ECMO to support refractory respiratory failure in patients with co-existing severe morbidities, such as malignancy, will be discussed below.

Modes of ECMO Support

Essentially, two basic types of ECMO support are currently used, namely venoarterial ECMO (Fig. 12.1) and venovenous ECMO (Fig. 12.2). While the equipment and circuit used are similar for both types of support, sites of cannulation differ between the two. Open surgical placement of ECMO cannulas under direct visualization has been the norm throughout most of the ECMO community, but some centers prefer percutaneous placement of ECMO cannulas using a modified Seldinger technique [21, 22]. Although the use of venovenous ECMO is increasing, venoarterial ECMO remains the most common type of support used for pediatric patients, and thus cannulation for venoarterial ECMO will be discussed first [11].

Venoarterial ECMO

Venoarterial ECMO involves draining desaturated blood from the body via a venous cannula, oxygenating the blood in the ECMO circuit, and pumping oxygenated blood back into a large artery via an arterial cannula (Fig. 12.1). Most commonly, the venous cannula is inserted into the right atrium, often via the internal jugular (IJ) vein. In cases of cervical cannulation via the IJ vein, some ECMO centers advocate placement of a smaller, retrograde catheter to the level of the jugular venous bulb in order to augment cerebral venous drainage and improve venous return to the ECMO circuit [23]. This catheter is then connected to the larger venous drainage line with a Y-connector. While placement of a cephalad cannula is somewhat controversial [24], some clinicians have advocated use of one as a means of monitoring jugular venous bulb oxygen saturation and thus indirectly monitoring cerebral oxygen delivery [25].

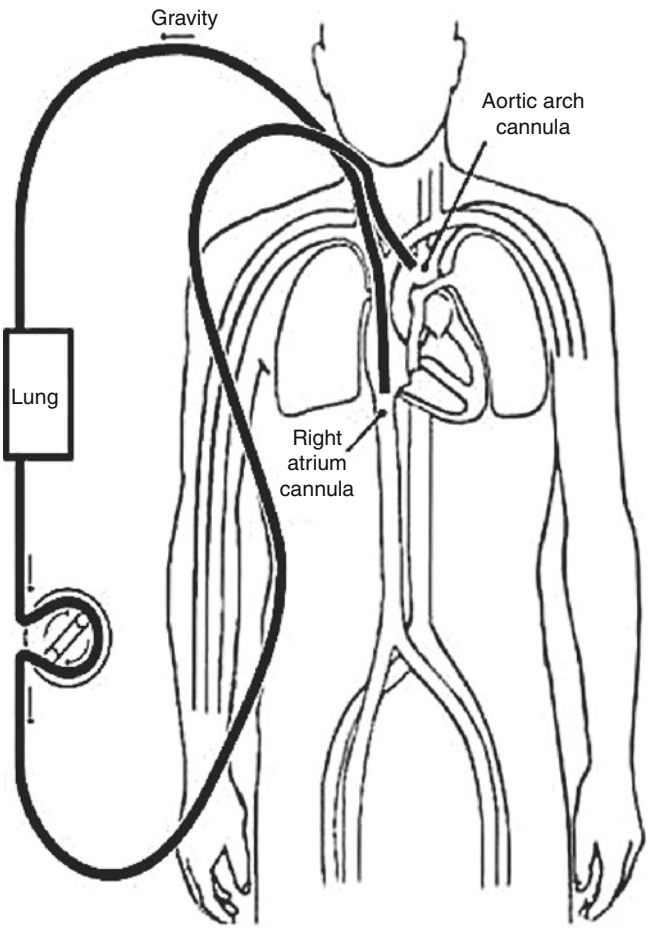


Fig. 12.1 Schema of venoarterial support

Venous drainage may also be achieved via the femoral veins, with the cannula advanced up the inferior vena cava (IVC), ideally to the level of the right atrial-IVC junction. The venous return achieved with femoral vein cannulation may not equal that of right atrial cannulation, but may be adequate to allow enough flow through the ECMO circuit to support tissue oxygenation. Due to limitations inherent in the size of the femoral vessels, femoral vein cannulation for ECMO is usually restricted to older, larger children and to adults, while a cervical approach via the IJ vein is more commonly used in infants and small children.

Arterial cannulation for venoarterial ECMO is accomplished most commonly via the right carotid artery, the femoral artery, or, in the case of transthoracic cannulation, via cannula insertion into the aorta under direct vision. With cervical cannulation, the arterial cannula is inserted into the right carotid artery and advanced to the aortic arch. If the cannula is inserted such that its tip is directed at the aortic valve, the valve may be damaged by the high-velocity flow of blood from the ECMO circuit, with resultant aortic insufficiency. Additionally, the high-velocity flow of blood from an arterial cannula placed in the ascending aorta creates

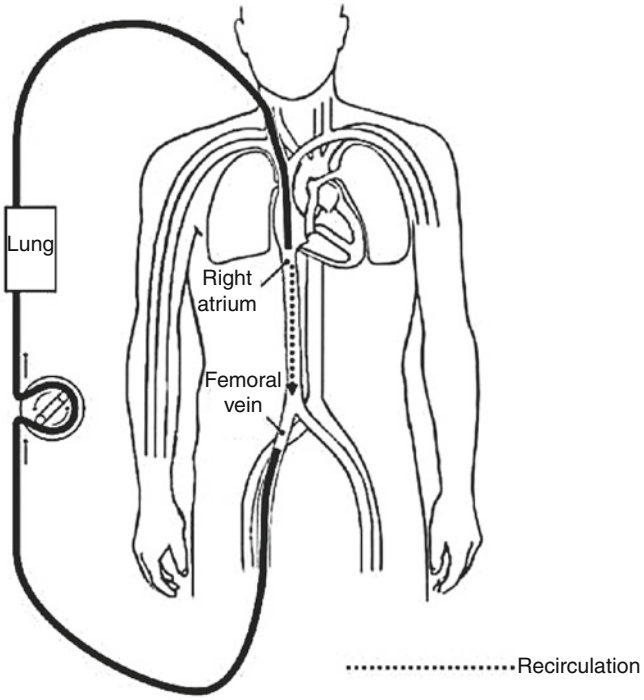


Fig. 12.2 Schema of venovenous support

additional afterload for the left ventricle. In some cases, this afterload may contribute to left ventricular dysfunction in patients supported with venoarterial ECMO [26]. If the arterial cannula is inserted too far into the descending aorta, flow into the left carotid artery, and thus cerebral blood flow, may be seriously compromised.

Cannulation of the femoral artery may also be used for venoarterial ECMO support and is preferred by some centers due to the potential for long-term neurologic sequelae related to carotid cannulation and ligation. It should be noted that, as of this writing, the magnitude of any potential long-term risk of stroke or other abnormalities in survivors of venoarterial ECMO who have undergone carotid cannulation is unknown. Femoral artery cannulation for ECMO support is itself not without risks. A risk of lower extremity ischemia exists secondary to occlusion of arterial flow to the distal limb by the cannula. A recently published single-center study reviewed the incidence of limb ischemia in patients supported with venoarterial ECMO via cannulation of the common femoral artery [27]. The study consisted largely of pediatric patients (age range 2–22 years) and reported limb ischemia requiring intervention in 11/21 patients. Placement of a distal perfusion catheter to improve perfusion to the leg, either at the time of cannulation, or if signs of limb ischemia develop, has been proposed [28, 29]. If such a catheter is placed, it is connected by a 'Y' to the main arterial cannula. Even with placement of a distal perfusion catheter, compartment syndrome and limb ischemia has been reported, thus requiring close attention to signs of these complications.

Another potential difficulty with cannulation of the femoral artery for venoarterial ECMO support involves the length of the arterial cannula. Delivery of oxygenated blood from the ECMO circuit to the brain, heart, and upper body can be accomplished by placement of an arterial cannula long enough to reach into the thorax. However, a cannula of this length inherently has higher resistance to flow. If a low-lying arterial cannula is placed, oxygenated blood from the ECMO circuit will have to flow retrograde up the aorta to reach the upper body. If left ventricular function is poor and antegrade flow out the aorta is diminished, this may be achieved with adequate cerebral oxygen delivery. However, if left ventricular function is normal or hyperdynamic, the majority of flow to the upper body may come from antegrade flow of less oxygenated blood from the ventricle, with oxygenated blood from the ECMO circuit predominately perfusing the lower body. If a short femoral arterial cannula is used, consideration should be given to monitoring upper body oxygenation with a pulse oximeter probe on the right hand or ear and to assessing adequacy of cerebral tissue oxygenation with near-infrared spectroscopy.

Venovenous ECMO

The primary difference between venovenous and venoarterial ECMO lies in the fact that venovenous ECMO involves draining deoxygenated blood from the venous side of the circulation, oxygenating the blood in the ECMO circuit, and then returning oxygenated blood back to the right side of the heart (Fig. 12.2). Thus, venovenous ECMO is dependent upon the patient having adequate cardiac function to pump oxygenated blood through the systemic circulation. It is used for the support of primary respiratory failure and not for support of failed cardiac function.

Cannulation for venovenous ECMO can be accomplished using one, two, or multiple sites for venous drainage, depending on the size of the patient, vessel size, and cannula availability. Cannulation typically occurs via the right internal jugular vein or the femoral veins [23, 30]. Cannulas with multiple lumens for venous drainage and infusion of oxygenated blood are produced by different companies and exist in a wide range of sizes, from 12 to 31 Fr. These cannulas are designed to be inserted into the right internal jugular vein to allow single-site cannulation for venovenous ECMO. Each of these cannulas is produced with drainage and infusion lumens separated by a certain distance in an effort to minimize recirculation of oxygenated blood. Drainage for venovenous ECMO can also be achieved using single lumen catheters at multiple sites, usually the internal jugular and femoral veins, for venous drainage and return.

Chest radiography is used to confirm positioning of ECMO cannulas both for venoarterial and venovenous

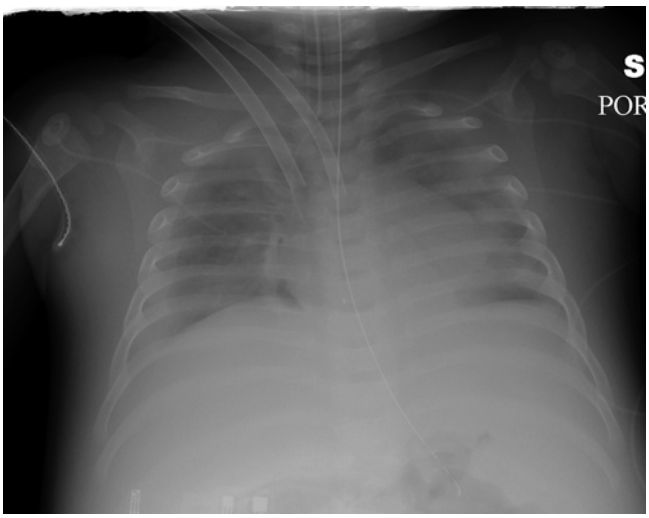


Fig. 12.3 Chest radiograph of patient supported with venoarterial ECMO demonstrating usual position of tips of venous drainage cannula (*white dot*) and arterial cannula

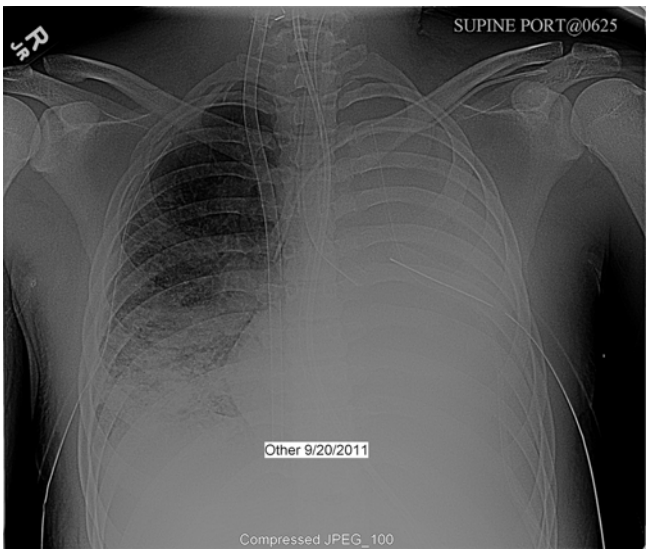


Fig. 12.4 Chest radiograph of patient supported with venovenous ECMO demonstrating multilumen cannula inserted through right internal jugular vein into right atrium

ECMO. In the case of venoarterial ECMO with cervical cannulation, chest radiography should reveal the tip of the venous cannula in the right atrium and the tip of the arterial cannula in the aortic arch (Fig. 12.3). Chest radiography should demonstrate the tip of a multilumen cannula for venovenous ECMO placed via the right internal jugular vein into the right atrium (Fig. 12.4). If any question exists regarding proper positioning of an ECMO cannula, echocardiography should be performed for further evaluation. Echocardiography may be of particular benefit in obtaining proper positioning of a multilumen cannula for venovenous use, to ensure that drainage and infusion lumens are properly oriented. A recent study of echocardiography to evaluate ECMO cannula position noted that 25 % of the studies ordered demonstrated problems with cannula position requiring intervention and that none of these were suspected based on chest radiography [31].

Venovenous and venoarterial ECMO differ in a number of important aspects in addition to cannulation. Table 12.1 lists several key differences between the two modes of ECMO support. As noted above, venovenous ECMO returns oxygenated blood from the circuit to the right side of the heart and is dependent on adequate native cardiac output to circulate oxygenated blood systemically. Venovenous ECMO provides no direct support of cardiac function. However, venovenous ECMO support offers important indirect benefits to cardiac function. First, by returning well-oxygenated blood to the right ventricle, venovenous support ensures that the pulmonary vascular bed is perfused with oxygenated blood, thus decreasing pulmonary vascular resistance and right ventricular afterload [23, 33, 34]. Since oxygen-saturated blood is returned to the left ventricle, venovenous ECMO also ensures that the coronary arteries are perfused with oxygenated blood, which has beneficial effects on myocardial performance and differs significantly from venoarterial ECMO, in which the coronaries are primarily perfused with relatively hypoxic blood that has returned to the left ventricle [35]. Since venovenous ECMO depends upon native cardiac output, normal physiologic pulsatile blood flow is maintained, which may have beneficial effects particularly in the cerebral and renal vascular beds [28, 36]. For these reasons, although venovenous ECMO provides no direct cardiac support, cardiac performance has been shown to improve in some patients on venovenous support, and inotropic support often is able to be weaned after venovenous ECMO is initiated [23, 33].

Recirculation of oxygenated blood is a feature of venovenous ECMO that must be understood, as it can potentially limit one's ability to provide adequate support to the patient. Since blood is both removed from and returned to the venous side of the circulation, some amount of oxygenated blood from the ECMO circuit will be drawn back into the venous return cannula before it can be pumped through the systemic circulation (Fig. 12.5). Careful attention to the placement of multilumen catheters for venovenous ECMO support, as well as attention to positioning of single-lumen catheters with an adequate distance between the venous return and reinfusion lumens can help minimize recirculation. If using dual site cannulation, recirculation can be minimized by draining blood from the femoral vein cannula and reinfusing oxygenated blood into the right atrium [37]. While it is difficult to accurately measure recirculation during venovenous ECMO in practice, a high displayed venous saturation in the ECMO circuit coupled with low patient arterial oxygen saturation suggests an increased percentage

Table 12.1 Comparison of venoarterial and venovenous ECMO support

	Venoarterial	Venovenous
Clinical uses	Support of cardiac and/or respiratory failure	Support of respiratory failure with stable cardiac function
Cannulation sites	Vein/artery (common carotid, femoral. Aorta)	Internal jugular/femoral veins (one-site or multiple sites)
Circulatory support	Direct	No direct support; Beneficial indirect effects
Cardiac effects	Decrease preload to RV	No decrease in preload
	Decrease preload to LV	Normal pulsatility maintained
	Increase afterload to LV	Decreased afterload to RV
	Coronary perfusion potentially hypoxic	Coronaries perfused with well-oxygenated blood
Effect on pulmonary blood flow	Markedly diminished at full flow	Pulmonary blood flow maintained with oxygenated blood
Risk of thromboembolism	To systemic circulation	Primarily to pulmonary circulation

Modified from Fortenberry et al. [32]. With permission from Extracorporeal Life Support Organization

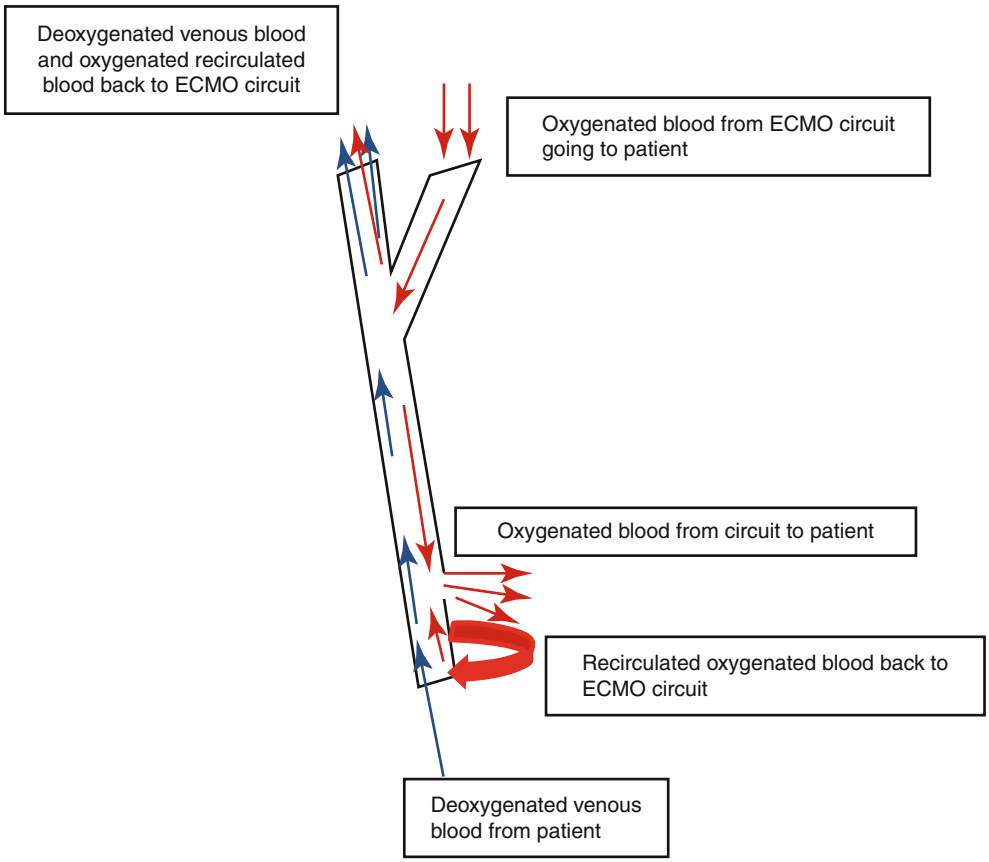


Fig. 12.5 Diagram demonstrating recirculation of blood through double lumen cannula during venovenous ECMO support (Modified from Fortenberry et al. [32]. With permission from Extracorporeal Life Support Organization)

of recirculated oxygenated blood. Other factors in addition to cannula position that may affect recirculation include: right atrial preload, cardiac output, and pump flow [32]. Decreased intravascular volume increases the likelihood that oxygenated blood returned to the right atrium will be recirculated into the ECMO circuit. Likewise, poor cardiac output slows the circulation of oxygenated blood out of the right atrium and increases recirculation. The percentage of recirculated blood increases in an essentially linear manner with ECMO pump flow, thus increasing pump flow does not necessarily increase the patient's overall systemic oxygen delivery, as is usually the case with venoarterial ECMO. The most effective pump flow will be the flow at which systemic oxygen delivery is optimized with a minimum amount of recirculation [32].

Finally, venovenous ECMO may offer some safety advantage over venoarterial support. One obvious potential benefit is the avoidance of both carotid artery cannulation and ligation or the risk of lower extremity ischemia associated with the use of the femoral artery. Additionally, it may confer a better safety profile from the standpoint of thromboembolic risk, as thromboemboli or air emboli introduced into a venovenous ECMO circuit would be filtered through the pulmonary circulation rather than

directly into the systemic arterial circulation. A review of central nervous system complications during ECMO support in pediatric patients found that, in patients supported primarily for respiratory failure, use of venoarterial ECMO was associated with a significantly higher risk of stroke or intracranial hemorrhage than was use of venovenous support [38]. Although use of venovenous as opposed to venoarterial ECMO has been associated with improved survival in pediatric respiratory failure patients [13], all such comparisons must be tempered by the potential for selection bias, with sicker patients being supported with venoarterial ECMO for the purpose of direct cardiac support.

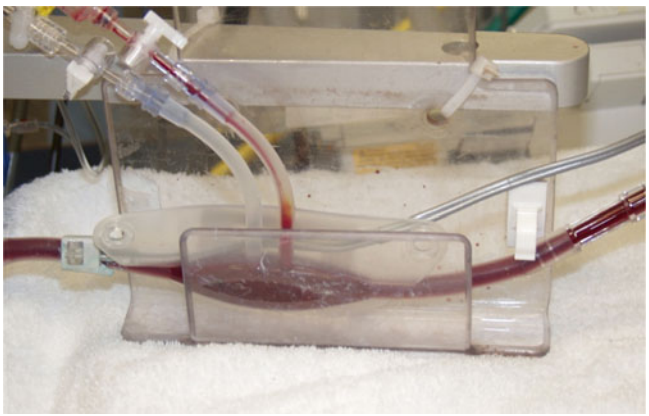


Fig. 12.6 Venous reservoir in ECMO circuit

ECMO Circuit Components and Equipment

Venous Reservoir

Venous blood drains into the ECMO circuit by gravity, from the venous cannula through a length of tubing and into a reservoir, or "bladder." The venous reservoir is often a device that sits horizontally at the lowest point of the ECMO circuit, acts as a trap for air, and includes ports for the aspiration of air (Fig. 12.6). Blood is drawn from the reservoir into the pump, and the reservoir can function as a servo regulator of ECMO pump flow. Any factor that decreases venous return to the ECMO circuit, such as hypovolemia, pneumothorax, or pneumopericardium, will decrease the volume of blood that is available to the pump. One potential drawback to the traditional, horizontal "bladder" is the risk of thrombus formation along the inferior aspect of the bladder. A newer reservoir device ("Better Bladder;" Circulatory Technology, Inc.; Oyster Bay, NY) has recently been developed and consists of a piece of collapsible tubing in a hard plastic casing (Fig. 12.7). The Better Bladder device is designed to be oriented vertically, which reduces the risk of clot formation in the reservoir. Like the traditional bladder device, the Better Bladder is designed to servo regulate forward flow through the ECMO pump. With a decrease in venous return to the reservoir, the collapsible tubing will contract, signaling negative venous pressure.



Fig. 12.7 "Better-Bladder" venous reservoir device

Venous Saturation Monitor

A venous saturation monitor placed on the venous drainage side of the circuit provides useful information regarding the balance between tissue oxygen delivery and oxygen extraction (Fig. 12.8). The displayed venous saturation must be interpreted cautiously in patients with left-to-right atrial shunting, left atrial drains, and patients supported with venovenous ECMO.

ECMO Pumps

Roller-Head Pumps

The "work-horse" pump for most ECMO centers through the years has been the roller-head pump (Fig. 12.9) [39]. A

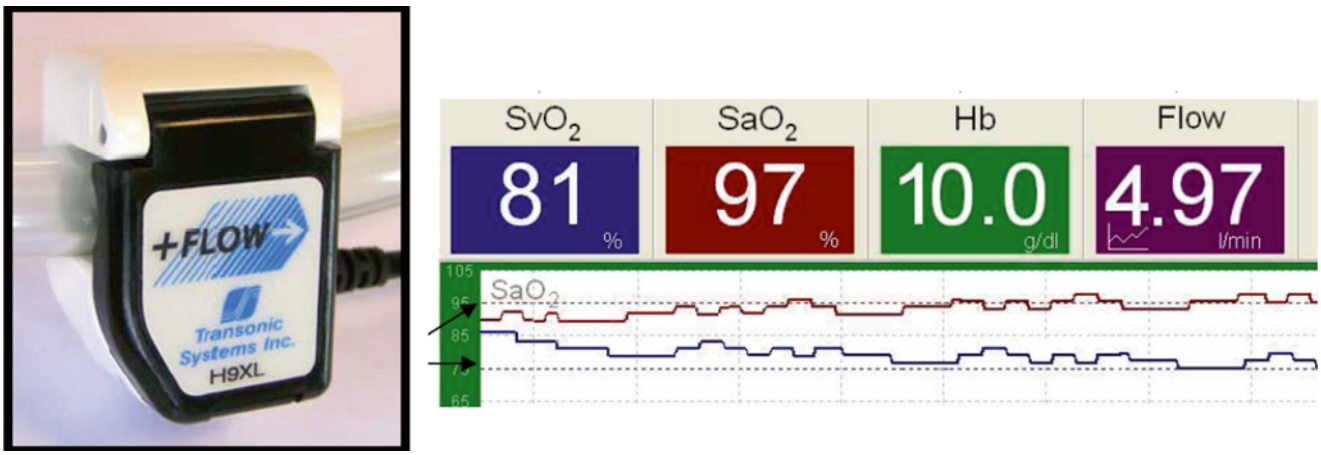


Fig. 12.8 Venous saturation monitor and flow probe

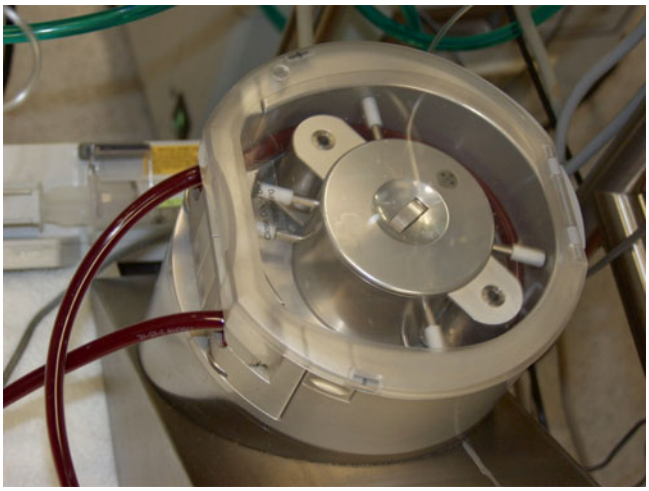


Fig. 12.9 Roller-head ECMO pump

roller-head pump propels blood forward by means of steel roller heads which rotate and compress blood-filled tubing that is enclosed in the pump housing. The ECMO circuit tubing that is enclosed in the pump housing and in contact with the steel roller heads is called the "raceway." Raceway tubing is made of an extremely durable material, as it is exposed to great mechanical stress from the constant compression of the roller heads, and rupture of raceway tubing could potentially have catastrophic consequences. The volume of blood propelled through the ECMO circuit by a roller-head pump is dependent on the number of revolutions per minute of the roller heads, the diameter of the tubing, and the degree of compression, or occlusion, between the roller head and the tubing. Proper occlusion of the roller heads is achieved during circuit setup by measuring the volume of fluid displaced by a rotation of the pump. If pump occlusion is too loose, the volume of blood advanced through the pump will be inappropriately low for the given tubing size and pump speed. If occlusion is too tight, hemolysis may be increased due to shear stress on red blood cells in the pump, and the risk of raceway ruptures increases. Most ECMO pumps display the actual volume of blood moved through the circuit, and a flow probe may be placed on the arterial limb of the circuit as well.

As discussed above, the output of the ECMO pump is dependent upon adequate venous return. If venous return decreases beyond a certain point with a roller head pump, continued rotation of the pump can result in generation of excessive negative pressure in the circuit, which can in turn lead to hemolysis and cavitation of air [40]. Such extreme negative pressures can also result in damage to the right atrium, with the cannula tip being sucked into the atrial wall. As noted previously, one function of the venous reservoir is to protect the patient by servo regulating pump revolution to venous return. If venous return is lost or decreases below a critical threshold, the collapse of the venous reservoir sends a signal to the roller-head pump to slow rotations or to stop completely until adequate venous return is re-established. Sudden changes in ECMO flow rate, as seen with stopped roller head revolution due to servo regulation, have been associated with potentially harmful alterations in cerebral blood flow [41]. Newer models of roller-head pumps and newer venous reservoir technology attempt to provide "gentler" servo regulation, with slowing and gradual resumption in forward flow in response to changes in venous return.

The propulsion of blood forward through the circuit by the roller heads produces high pressures distal to the pump, on the "arterial" limb of the ECMO circuit. Anything producing sudden and marked increase in resistance to blood flow on the "arterial" side of the circuit, such as kinking or inadvertent clamping of the arterial cannula, may result in a sudden increase in pressure. In the extreme, such a sudden spike in pressure can result in rupture of the ECMO circuit, which may have lethal consequences. Constant monitoring of pressure on the high-pressure side of the circuit is used as a safety mechanism to



Fig. 12.10 Centrifugal ECMO pump

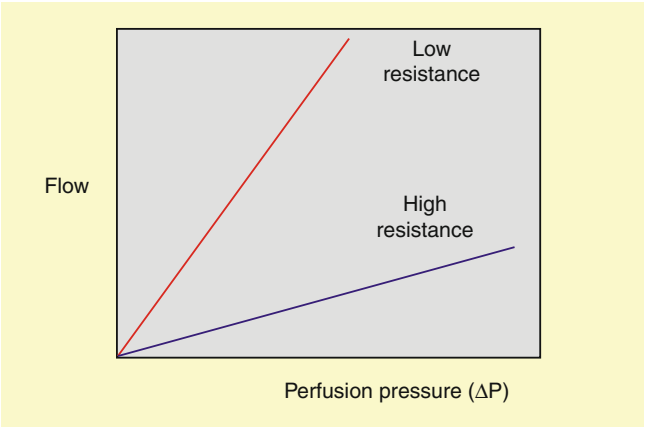


Fig. 12.11 Relationship between flow and afterload for centrifugal ECMO pump

prevent such a devastating complication. Critical thresholds for pressure in the arterial limb vary somewhat based on pump flow, tubing diameter and length, and cannula size, but generally should be ≤350 mmHg. Monitoring of these pressures provides another site for servo regulation of pump flow.

Centrifugal Pumps

Centrifugal pumps (Fig. 12.10) function quite differently from roller-head pumps. Essentially these pumps move blood by creating a constrained vortex, with rapid revolution of impellers or cones creating a pressure differential, resulting in the forward movement of blood. Centrifugal pumps are completely non-occlusive. The spinning of the pump at a given speed (revolutions per minute) creates a certain pressure. Since flow = pressure/resistance, a number of factors influence the actual flow generated by a centrifugal pump for a given pump speed. For this reason, many ECMO centers incorporate a flow probe into the arterial limb of the circuit when using a centrifugal pump. While a roller-head will generate fairly constant flow regardless of afterload (up to the safety limit of servo regulation), the forward output from a centrifugal pump varies with resistance, or afterload, for a given pressure (Fig. 12.11). Whether the afterload is induced by a patient-related factor, such as increased systemic vascular resistance, or a mechanical factor, such as increased circuit tubing length or a smaller arterial cannula, flow from a centrifugal pump will decrease with increased afterload. Output from a centrifugal pump is also dependent upon adequate preload, as with a roller-head pump. However, the vortex created by the spinning pump generates a certain degree of suction, which augments venous return. Centrifugal pumps are thus not as dependent on gravity for venous return as are roller-head pumps. For this reason, a centrifugal pump may be placed at any level in relation to the patient, increasing the ease of patient transport [42]. A potential advantage to centrifugal pumps as compared to roller-head pumps is that distal occlusion, such as might be caused by kinking or clamping of arterial side tubing, does not generate excessive back pressure in the circuit and thus cannot lead to circuit rupture. In such a situation, forward flow would decrease or cease, but the circuit would be safe from catastrophic rupture. Close monitoring of venous pressures and arterial pressures, with servo regulation, is still crucial for patient safety, just as with roller-head pumps.

Although use of roller-head pumps remains more common than use of centrifugal pumps in many pediatric ECMO centers, recent technological developments in centrifugal pumps have caused a number of centers to change to these pumps [39]. Earlier models of centrifugal pumps were associated with marked hemolysis in neonates supported with ECMO [43, 44]. In these reports, investigators speculated that hemolysis was linked to blood stasis and heat generation caused by impellers and bearings in early model centrifugal pumps. An *in vitro* study evaluating hemolysis with newer technology centrifugal pumps found less hemolysis associated with these pumps compared to a roller-head pump [45]. A recently published clinical comparison of hemolysis in pediatric cardiac ECMO patients found less hemolysis, as measured by plasma free hemoglobin concentrations, with a newer-generation, magnetically levitated centrifugal pump as compared to a roller-head pump [46].

Oxygenators

The predominant oxygenator used for most ECMO support has consisted of a silicone membrane wound in a spiral

fashion around a polycarbonate spool. Blood and gas flow through the membrane oxygenator in a counter-current manner, which contributes to the efficiency of gas exchange. Another type of oxygenator used during ECMO support is the hollow fiber oxygenator. These devices consist of hydrophobic, microporous capillary tubes, which may be produced of polymethylpentene. Blood flows between the inside and outside of these tubes, and gas exchange occurs across tiny pores in the capillary tubes. Hollow fiber oxygenators have the advantages of requiring very small priming volumes as compared to silicone membrane oxygenators, and they typically have a much lower resistance to blood flow. However, early models of hollow fiber oxygenators commonly had difficulty with plasma leakage after only a few hours of use, limiting the usefulness of these devices for long-term ECMO support. Newer models, though, have demonstrated excellent gas-exchange performance over a long period of time without significant plasma leakage. Due to their small priming volume, low resistance, and exceptional gas exchange efficiency, hollow fiber oxygenators have gained in popularity among ECMO centers in recent years [39, 47]. Either type of oxygenator can fail over time, often due to clotting within the oxygenator, structural defects in the oxygenator, or excessive build-up of condensation. Monitoring of the pressure drop across the oxygenator and blood gas measurements obtained from circuit blood pre- and post-oxygenator are helpful in giving early warning of impending oxygenator failure. Oxygenators can be changed when necessary, which usually is a quite rapid process.

Gas Exchange

Each membrane, or hollow fiber, oxygenator has a defined diffusion coefficient, or permeability, for oxygen and carbon dioxide. Gas exchange across the membrane is a function of the diffusion coefficient, the membrane surface area available for gas exchange, the pressure gradient of oxygen and carbon dioxide between the blood and the gas phase, and the amount of time that the blood and gas interact across the membrane. Each membrane has a certain maximal blood flow, termed the "rated flow," beyond which the thickness of the blood film will not allow any further transfer of oxygen.

Carbon dioxide has a very high solubility in blood and diffuses rapidly across the membrane. Since the driving pressure for CO_2 between the venous blood and the gas introduced to the oxygenator is relatively low (approximately 45 Torr), CO_2 transfer is primarily dependent on maintenance of that gradient by gas flow rate through the membrane (termed the "sweep flow") and is relatively independent of the blood flow rate. CO_2 transfer is also dependent on the membrane surface area available for gas exchange. Post-membrane PCO_2 is a very sensitive indicator of membrane oxygenator function. Generation of clots within the membrane oxygenator is one factor which can decrease the efficiency of gas exchange in the oxygenator and ultimately result in oxygenator failure. Oxygen is much less soluble in blood than is CO_2, and it diffuses more slowly across the membrane. Thus, although the pressure gradient for oxygen between membrane gas and venous blood is quite high, oxygen transfer is not significantly dependent on the gas flow rate but rather on the flow rate of blood through the membrane. Oxygen transfer also is a function of the thickness of the blood path, on membrane surface area, and on specific physical characteristics of the membrane [48]. Oxygenation of blood can also be improved up to a point by increasing the FiO_2 of the sweep gas delivered to the membrane.

Hemodynamics of Venoarterial ECMO

Typical blood flow rates during "full" venoarterial ECMO support are approximately 100–150 mL/kg/min in infants and small children. Increasing ECMO flow rate with venoarterial ECMO diverts more of the patient's systemic venous return away from the pulmonary circulation and into the ECMO circuit. Since more blood then becomes fully oxygenated in the ECMO circuit, the patient's systemic oxygen delivery (DO_2) increases. DO_2 is the product of cardiac output and arterial oxygen content. At flow rates approaching "complete" cardiopulmonary bypass, enough flow is diverted away from the patient's circulation that DO_2 becomes the product of the ECMO pump rate and the oxygen content of blood leaving the oxygenator. Relatively little blood flow transits the patient's pulmonary circulation at such high pump flow rates, and the patient's right ventricle is almost completely "unloaded." At "full" ECMO flow rates, almost all systemic blood flow comes from the ECMO circuit and is non-pulsatile in nature. This is reflected in a narrowed pulse pressure on the patient's arterial line waveform. Indeed, if native cardiac function is poor, the arterial line waveform may be essentially flat at ECMO flow rates of 100–150 mL/kg/min, displaying only the mean arterial pressure. Oftentimes such high ECMO flow rates are not necessary and a patient may be adequately supported with lower flows, allowing some contribution from the native cardiac output and pulmonary circulation. As a patient is weaned from venoarterial ECMO support, essentially more venous return is diverted away from the ECMO circuit and to the patient's own circulation. Monitoring of indicators of tissue oxygen balance, such as mixed venous saturation, cerebral near-infrared spectroscopy [49, 50], and serum lactate can serve as guides to the adequacy of DO_2 during weaning of venoarterial ECMO flow.

Certain aspects of venoarterial ECMO support of the patient with a failed left ventricle deserve special attention. As noted previously, the high-velocity jet of flow directed from the arterial cannula to the systemic circulation imposes

a substantial afterload on the systemic ventricle, making it even more difficult for a failing ventricle to eject. Despite near-complete capture of pulmonary blood flow by the ECMO circuit, the left atrium continues to receive some pulmonary venous return as well as return from the deep bronchial veins and the Thebesian veins, which can lead to progressive left atrial distension [51]. This situation can result in left atrial hypertension. Increased left atrial pressure is transmitted into the pulmonary veins, which can result in pulmonary hemorrhage in the anticoagulated patient. Such pulmonary hemorrhage is often a fatal complication of cardiac ECMO support [52]. To avoid this complication, patients receiving venoarterial ECMO support for left ventricular failure need decompression of the left atrium if left atrial distension develops. Left atrial decompression can be accomplished either with a left atrial vent tube connected to the ECMO circuit [53–55], or via cardiac catheterization with a blade or balloon septostomy [56, 57]. Finally, as left atrial distension worsens, left ventricular end-diastolic volume and pressure will also increase, which may compromise coronary perfusion. As the coronary arteries are primarily perfused with relatively hypoxic blood from the left ventricle during venoarterial ECMO, this combination of factors can be detrimental to adequate myocardial perfusion [58].

Management of the Patient Supported with ECMO

Anticoagulation

Systemic anticoagulation is necessary during ECMO support to prevent thrombosis induced by contact of the blood with foreign surfaces. The standard medication for anticoagulation of the ECMO patient and circuit is unfractionated heparin. Clot formation in an ECMO circuit occurs as a function of the interplay among protein deposition in the circuit, flow rate and flow patterns, and platelet aggregation and function. Support of a patient with ECMO may be viewed as a low-grade consumptive coagulopathy, as a certain degree of fibrin formation and fibrinolysis occurs constantly. The purpose of heparin is to inhibit thrombin formation, which in turn leads to the activation of fibrinogen and the ultimate production of cross-linked fibrin. Unfractionated heparin has the advantages of being readily available, inexpensive, and easily titrated. Typically a bolus dose of 100 units/kg heparin is administered at the time of cannulation for ECMO. An infusion of heparin is then administered and titrated, with infusion doses of 25–100 units/kg/h commonly used. Heparin acts on multiple clotting factors as well as on platelets, and its effect on whole blood has historically been measured by the activated clotting time (ACT) in patients supported with ECMO. Most ECMO centers measure the ACT at least hourly and titrate heparin to maintain the ACT in a range of 180–220 s. Many factors affect the measured ACT, including platelet activation and number. Thus, to maintain a desired range of measured ACT, the ECMO specialist must increase the heparin infusion after platelet administration and decrease the infusion during periods of thrombocytopenia. Unfractionated heparin is cleared via the kidneys, so renal dysfunction will serve to decrease the required dose of heparin while aggressive diuresis may result in the need for more heparin to maintain the desired ACT.

The ACT has been in use for measuring heparin effect during cardiopulmonary support since the 1970s [59]. While it is a fairly crude test, it has the advantage of being rapidly performed at the point-of-care. The range of ACT measurements usually quoted as the desired target in pediatric ECMO practice has largely been extrapolated from cardiopulmonary bypass data and based on surveys of practices [60]. More recent studies have noted a poor correlation between measured ACT values and heparin dose [61, 62]. A large, single-center retrospective study demonstrated a poor correlation between heparin dose and ACT and found that increased heparin dosing was independently associated with patient survival while measured ACT was not [62]. Authors of this study speculated that adherence to the range of ACT measurements traditionally used in pediatric ECMO support may lead to inadequate anticoagulation and microvascular thrombosis, thus perhaps contributing to worsened end-organ dysfunction.

In the presence of antithrombin III, unfractionated heparin binds to and inactivates activated Factor Xa. Thus, measurement of anti-Factor Xa activity is another measure of heparin effect. A retrospective study of neonatal ECMO patients found a correlation between the heparin dose and anti-Factor Xa concentration that was significantly stronger than the correlation between heparin and ACT [61]. While the measurement of anti-Factor Xa concentrations may prove useful in monitoring of anticoagulation during ECMO, as of this writing the desired range of anti-Factor Xa during ECMO is not known, nor is its relationship to such parameters as circuit life yet known. Additionally, measurement of the anti-Factor Xa concentration is not at this time a point-of-care test. Monitoring of a thromboelastograph (TEG) has also been used in a variety of settings as a whole-blood, point-of-care test yielding information about clot formation, clot strength, and fibrinolysis [63]. Routine monitoring of TEG has not yet become the norm in most ECMO centers [64].

Adequate amounts of antithrombin III (ATIII) activity are necessary for effective action of heparin, as ATIII greatly accelerates the inactivation of Factor Xa by heparin. AT III concentrations vary developmentally, with normal newborns expressing lower ATIII activity than older children and adults [65]. A variety of factors common in critical illness

can result in a deficiency of ATIII, including endothelial injury, disseminated intravascular coagulation, ongoing protein losses, and hepatic insufficiency. Antithrombin III concentrations may also be diluted due to initiation of cardiopulmonary bypass or ECMO [66]. In recent years, more ECMO centers have begun monitoring ATIII concentrations in patients supported with ECMO and treating ATIII "deficiency" with either synthetic ATIII concentrate or fresh frozen plasma, which contains small, variable amounts of ATIII. While the rationale behind ATIII monitoring and treatment to improve anticoagulation in ECMO patients is apparent [67], infusions of ATIII concentrate are quite costly, and no study to date has demonstrated tangible benefit such as extended ECMO circuit life with such measures.

Ventilator Management

The over-arching goal of ECMO support for patients with refractory respiratory failure is maintenance of tissue oxygen delivery while avoiding further ventilator-associated lung injury (VALI). Thus, mechanical ventilator settings are usually decreased substantially once ECMO support is initiated for a patient, and mechanical ventilation is usually continued with settings thought to provide "lung rest." Optimal ventilator settings for "lung rest" are unknown, but many experienced ECMO centers maintain a moderate degree of positive end-expiratory pressure (PEEP), in the range of 5–12 cmH_2O, to help maintain lung volume near functional residual capacity, while using quite low respiratory rate, tidal volume, and FiO_2 to minimize further toxicity to the lungs. Patients with severe air leak syndromes, such as pneumothoraces and pulmonary interstitial emphysema, may benefit from apnea during full venoarterial ECMO support, perhaps with a small amount of continuous positive airway pressure (CPAP) applied via the endotracheal tube. Some evidence exists to suggest that such a strategy may promote healing of lung parenchyma, and this strategy has been used with beneficial effects in patients with a variety of air leak syndromes, including necrotizing pneumonia [68, 69]. In patients supported with venoarterial ECMO, manipulation of mechanical ventilator settings has little effect on exchange of CO_2 and O_2, as most gas exchange occurs within the ECMO oxygenator. Patients supported with venovenous ECMO receive less bypass support and may require slightly higher levels of mechanical ventilator support while managed with ECMO.

Nutrition and Fluid Management

Provision of adequate nutritional support is absolutely critical to patients supported with ECMO, many of whom have massive inflammatory responses from their underlying diseases. Enteral nutrition during ECMO support of neonates, children, and adults has been shown to be safe and effective [70, 71]. If parenteral nutrition is provided, the use of lipid emulsion in an ECMO circuit has been associated anecdotally with decreased oxygenator function, and infusion of lipid emulsion into the patient via a separate central or peripheral venous catheter is a common practice [72].

Close attention to fluid balance and renal function is important in the care of ECMO patients. Many patients supported with ECMO have fluid overload, edema, and diminished renal function related to their underlying conditions, and the use of diuretic therapy is common in this population. Additionally, non-pulsatile blood flow occurring in venoarterial ECMO as well as hemolysis associated with the ECMO pump and circuit may have detrimental effects on renal function. Increasing duration of ECMO support has been linked with development of acute renal failure (ARF) [73]. In several studies, the existence of renal failure has been noted to be independently associated with increased mortality in ECMO patients [13, 73–75]. Institution of continuous renal replacement therapy (CRRT) for patients undergoing ECMO support has become a common practice at many centers. CRRT sometimes is used to improve fluid balance even prior to the onset of gross renal dysfunction [76]. Continuous venovenous hemofiltration (CVVH), with or without dialysis, can be performed either via the insertion of a hemofilter into the ECMO circuit with blood flow supplied by the ECMO pump, or via a stand-alone CRRT machine connected in-line to the venous limb of the ECMO circuit [77]. One large retrospective study of ECMO patients from a single center who received concomitant CVVH noted survival in 68/144 (44 %) patients and recovery of renal function prior to hospital discharge in 65/68 (96 %) survivors [77].

Sedation and Analgesia

Maintenance of adequate sedation and analgesia is of key importance in the care of the ECMO patient, as it is for any critically ill child. Infusions of benzodiazepines and narcotics are commonly used for sedation and analgesia in patients supported with ECMO [78]. Clearance of morphine and its active metabolites is diminished in neonates supported with ECMO, particularly if concomitant renal dysfunction exists [79, 80]. Large amounts of fentanyl, and to a lesser extent phenobarbital and morphine, are lost due to adhesion to components of the ECMO circuit [81, 82]. As much as 98 % of propofol infused pre-oxygenator may be adsorbed by circuit components [81, 83]. A growing trend exists towards use of minimal sedation in adult patients supported with ECMO for respiratory failure [84]. A recent prospective, observational trial in 20 neonates supported with ECMO found that scheduled interruption of midazolam and mor-

phine infusions was feasible without any adverse effects on patient sedation scores or safety measures such as device dislodgement [85].

Weaning of ECMO Support

Weaning from ECMO support can be accomplished in a number of different ways. Once clinical signs of improving pulmonary compliance and aeration are present, ECMO support often is weaned gradually until ECMO flow is decreased to approximately 50 mL/kg/min, as long as arterial and mixed venous oxygen saturation measurements are adequate. Concomitant increases in ventilator support may be necessary. If the patient remains hemodynamically stable with adequate gas exchange at low ECMO flow rates, many centers will then perform a "trial off," during which the ECMO cannulas are clamped and recirculation of ECMO flow through the bridge is allowed. During the "trial off," it is important that any medications such as inotropes and sedatives which might have been infused into the ECMO circuit be changed to be infused directly into an intravenous catheter. If the patient remains hemodynamically stable and demonstrates adequate gas exchange at with non-injurious ventilator settings during the trial off, ECMO cannulas can then be removed.

Complications of ECMO

Mechanical Complications

Given the invasive nature of ECMO support and the ECMO patient's dependence on complex technology, a number of mechanical complications are possible. A review of >28,000 courses of ECMO support reported to the ELSO Registry from 1987 to 2007 evaluated the incidence of mechanical component failure (defined as: oxygenator failure, raceway rupture, other tubing rupture, pump malfunction, pigtail connector crack, heat exchanger malfunction, and air in the circuit) and found an overall incidence of 15 % [86]. Examining the entire study group, the rate of oxygenator failure was 6.5 % while air in the circuit occurred in 4.3 % of cases and pump failures in 1.8 % [86]. The same investigators found on multivariate analysis that duration of ECMO, patient age, and indications for ECMO were all independently associated with mechanical component failure.

Central Nervous System Complications

Perhaps the most feared and catastrophic complications of ECMO support are central nervous system (CNS) complications, including infarction and intracranial hemorrhage. Such complications may be related to the patient's underlying disease state as well as to the need for anticoagulation, the risk of thromboembolism, and the risk of carotid artery cannulation in the case of cervical cannulation for venoarterial ECMO. A review of almost 5,000 children between the ages of 1 month and 18 years supported with ECMO found acute, severe CNS complications (intracranial hemorrhage, brain infarction, brain death) reported in 12.9 % [38]. Not surprisingly, these investigators found that cardiopulmonary arrest prior to ECMO support significantly increased the risk of an acute, severe CNS complication [38]. Table 12.2 lists the rates of intracranial hemorrhage and infarction for different age groups reported by the Extracorporeal Life Support Organization [11]. Many ECMO centers perform routine ultrasonography of the brain to screen for intracranial hemorrhage in infants with open fontanelles receiving ECMO support. In older children and adults, an acute change in the neurologic exam should prompt urgent computed tomography of the brain to evaluate for CNS infarction or hemorrhage. A recent study of the safety and efficacy of intra-hospital transport of ECMO patients for diagnostic procedures found significant intracranial pathology necessitating a change in management in 14/15 patients transported for urgent computed tomography of the brain [42].

Table 12.2 Rates of CNS infarction and hemorrhage for different categories of ECMO support

	CNS infarction (%)	CNS hemorrhage (%)
Neonatal respiratory failure	7.5	7.0
Pediatric respiratory failure	3.8	6.0
Adult respiratory failure	2.2	3.9
Cardiac ECMO age 0–30 days	3.5	11.2
Cardiac ECMO age 31 days–1 year	4.3	5.6
Cardiac ECMO age 1–16 years	4.4	3.6
Cardiac ECMO age >16 years	3.3	1.4

Adapted from ELSO International Summary [11]. With permission from Extracorporeal Life Support Organization

Bleeding

Bleeding related to systemic anticoagulation, and sometimes to the patient's underlying disease state, is a constant and serious risk of ECMO support. While intracranial hemorrhage is the most feared bleeding complication of ECMO, bleeding from cannulation sites, chest tubes, and surgical sites can occur, as can pulmonary and gastrointestinal hemorrhage. Table 12.3 lists rates of bleeding complications at sites other than intracranial reported to the ELSO Registry [11].

If significant bleeding occurs, the patient may benefit from reduced heparinization, or even from discontinuation of the heparin infusion for a period of time. During such

Table 12.3 Non-CNS bleeding complication rates for different patient groups supported with ECMO

	GI hemorrhage (%)	Cannulation site bleeding (%)	Surgical site bleeding (%)	Pulmonary hemorrhage (%)	Disseminated intravascular coagulation (%)
Neonatal respiratory failure	1.7	7.1	6.3	4.5	2.5
Pediatric respiratory failure	4.1	16.3	14.4	7.8	5.2
Adult respiratory failure	5.3	18.2	18.2	8.4	3.8
Cardiac ECMO age 0–30 days	1.0	10.6	31.9	5.7	3.6
Cardiac ECMO age 31 days – 1 year	2.0	11.8	33.8	5.3	3.0
Cardiac ECMO age 1–16 years	2.8	17.1	29.8	5.8	4.1
Cardiac ECMO age >16 years	4.0	20.8	27.3	4.1	5.1

Adapted from ELSO International Summary [11]. With permission from Extracorporeal Life Support Organization

periods, vigilant monitoring of the ECMO circuit for thrombus should be performed. In some instances, drugs such as aminocaproic acid are used to inhibit fibrinolysis. Aminocaproic acid acts to inhibit the conversion of plasminogen to plasmin and the interaction of plasmin with fibrin. It is often administered as a loading dose followed by a continuous infusion, and its dose must be reduced in the presence of renal dysfunction. A prospective, randomized trial of routine, prophylactic use of aminocaproic acid in neonates undergoing ECMO support demonstrated no difference in either the rate of intracranial hemorrhage or the number of blood transfusions required between the placebo and treatment groups [87]. However, aminocaproic acid still is used in many ECMO centers for patients with a particularly high risk of bleeding, such as those with ARDS after traumatic injuries [88]. While use of an antifibrinolytic agent such as aminocaproic acid is often considered a risk for circuit thrombosis, a recent retrospective study from an ECMO center in which aminocaproic acid is routinely used as part of a "bleeding protocol" found no difference in ECMO circuit life with or without aminocaproic acid [89].

In recent years, several case reports and case series have discussed a potential role of recombinant activated Factor VII (Factor VIIa) in patients with refractory bleeding while on ECMO support [90–93]. After administration of one or more doses of Factor VIIa, some reports have noted marked decrease in surgical site and thoracostomy tube bleeding with no significant thrombotic complications in the ECMO circuit in patients supported with ECMO post-cardiotomy and in patients with "medical" diseases such as necrotizing pneumonia [90–93]. In contrast to these reports, two published reports have noted fatal thrombosis after administration of Factor VIIa to patients supported with ECMO [94, 95]. In both of these reports, the patients exhibited disseminated intravascular coagulation prior to administration of Factor VIIa and had received transfusions of blood products such as fresh frozen plasma and platelets. One of the reported patients also received aprotinin, a serine protease inhibitor of fibrinolysis, before administration of Factor VIIa [94]. Data on the use of Factor VIIa for refractory bleeding in pediatric patients supported with ECMO remains limited enough to preclude any recommendations.

Infection

As is the case for any critically ill patient, the development of a hospital-acquired infection (HAI) can be a significant complication of ECMO support. The presence of multiple indwelling catheters as well as factors related to the underlying disease process place the ECMO patient at risk for HAI. The reported prevalence of HAI in neonatal and pediatric ECMO patients varies from approximately 11–30 % [96–100], while retrospective analyses of HAI in adult ECMO patients report prevalence of 9–13 % [101, 102]. However, a recent analysis of the ELSO Registry from 1998 to 2008 reviewed all culture-proven infections felt to have occurred after initiation of ECMO and found the highest rate in adult patients versus pediatric and neonatal patients (30.6 vs. 20.8 vs. 10.1 infections per 1,000 ECMO days) [96]. In that study, coagulase-negative *Staphylococci* were the most common organisms causing HAI, followed by *Candida* species and *Pseudomonas* [96]. Not surprisingly, HAI prevalence increases with duration of ECMO support, particularly as ECMO support exceeds 14 days [96, 97, 99]. All studies of HAI in pediatric ECMO patients have noted an association between development of an HAI and measures of morbidity, such as prolonged hospitalization, and most have noted a positive association between HAI and increased mortality [96–99, 103].

Significant variation exists among ECMO centers regarding practices aimed at the prevention of HAI. A recently published survey of ECMO centers found that most administer antimicrobial prophylaxis to patients supported with ECMO, though no standardization existed regarding antibiotic choice or duration [104]. The same survey reported that almost half of ECMO centers perform routine surveillance cultures but with great variation in frequency and type. Despite the fact that Candida species represent the second-most common organism causing HAI in ECMO patients [96] and that HAI with fungal organisms is associated with a very high mortality in this population [97, 99, 105], very few ECMO centers currently administer routine antifungal prophylaxis [104].

Outcomes of Patients Supported with ECMO

Table 12.4 is modified from a recent report of the ELSO Registry and lists both survival to discontinuation of ECMO support and survival to hospital discharge for a variety of patient groups. While the overall survival rate for pediatric patients with respiratory failure supported with ECMO has remained fairly stable at 55–60 %, the number of children supported with ECMO who have significant co-morbidities has substantially increased [13]. It is noteworthy that, according to a recent study, the survival rate for children with no underlying co-morbid conditions has increased from 57 % in the early 1990s to 72 % more recently [13]. Survival rates vary greatly with both cause of respiratory failure and underlying co-morbidities. Table 12.5 lists survival rates reported to the ELSO Registry by member centers for different respiratory failure etiologies. As can be seen from Table 12.4, survival to hospital discharge for neonatal ECMO patients with respiratory failure remains quite high, despite the fact that more neonates receive treatment with inhaled nitric oxide, surfactant, and high frequency oscillatory ventilation prior to ECMO than in earlier eras [106, 107]. One of the most challenging groups of neonatal patients supported with ECMO for respiratory failure remains those with congenital diaphragmatic hernia, in whom survival rates remain approximately 50 % [108–110]. Outcomes of patients supported with ECMO for primary cardiac failure are discussed elsewhere in this text. While pediatric patients supported with ECMO for respiratory failure encompass a broad variety of disease states, a more detailed analysis of certain subgroups is presented below.

Table 12.4 Survival rates for ECMO support of respiratory failure and ECPR in different age groups

	Survival to weaning from ECMO (%)	Survival to hospital discharge (%)
Neonatal respiratory failure	85	75
Neonatal ECPR	63	39
Pediatric respiratory failure	65	56
Pediatric ECPR	53	40
Adult respiratory failure	63	55
Adult ECPR	38	29

Adapted from ELSO International Summary [11]. With permission from Extracorporeal Life Support Organization

Table 12.5 Survival rates by etiology of respiratory failure

Survival rates by etiology of respiratory failure	%
Meconium aspiration syndrome	94
Persistent pulmonary hypertension of the newborn	78
Congenital diaphragmatic hernia	51
Viral pneumonia	63
ARDS related to trauma	59
ARDS not related to trauma	53

Adapted from ELSO International Summary [11]. With permission from Extracorporeal Life Support Organization

Septic Shock

Although septic shock, particularly vasodilatory shock, was once considered a relative contraindication to ECMO, more recent studies have suggested encouraging outcomes in some patients with refractory septic shock supported with ECMO [111–117]. MacLaren and colleagues at Royal Children's Hospital in Melbourne, Australia reported on 45 children with septic shock refractory to inotropic and pressor support who were supported with venoarterial ECMO with a 47 % survival to hospital discharge [115]. Many of these children suffered from meningococcemia, and 18/45 had suffered cardiac arrest prior to ECMO initiation. The authors noted that central, transthoracic ECMO cannulation was associated with improved survival in this study group and speculated that the positive association may be related to shorter cannulation times and the ability to achieve higher ECMO flow [115]. In a second study of 23 children with refractory septic shock who received central cannulation for venoarterial ECMO, the same investigators recently reported survival to hospital discharge in 74 % [111]. Results of ECMO support for children with refractory, catecholamine-resistant septic shock are encouraging enough that recent guidelines for the hemodynamic support of infants and children with septic shock state that ECMO should be considered in this situation [118, 119].

"Non-traditional" Patients with Respiratory Failure

Serious underlying conditions, such as malignancy, immunodeficiency, and major burns were once considered relative contraindications for ECMO support of children with severe acute hypoxemic respiratory failure [12]. However, as the long-term prognosis for many of these conditions has improved, physicians caring for these children have become more willing to consider aggressive, invasive support for acute cardiopulmonary failure related to such conditions as sepsis and pneumonia [120, 121]. Gow and colleagues recently analyzed the ELSO Registry from 1994 to 2007 for pediatric patients with an underlying malignancy who were supported with ECMO [122]. Most of these children required ECMO support for primary respiratory failure, and 42 % survived to discontinuation of ECMO support, with no difference in mortality between children with hematologic malignancies versus solid tumors [122]. This study also surveyed ELSO member centers regarding willingness to offer

ECMO support to a child with malignancy and of the 89 % who responded, 95 % responded affirmatively [122]. ECMO support for children who have undergone hematopoietic stem cell transplantation (HSCT) appears to carry a much worse prognosis. A review of the ELSO Registry published in 2006 noted only 19 children who had been supported with ECMO after HSCT, and only 4 (21 %) survived to successful discontinuation of ECMO support [123]. In a review of 183 immunocompromised patients supported with ECMO for respiratory failure, including patients with congenital or acquired immunodeficiency, cancer, and solid organ or bone marrow transplants, the presence of an immunodeficiency was associated with reduced survival, with survival ranging from 35 % for solid organ transplant recipients to zero for bone marrow transplant recipients [124]. Thus, while it appears that ECMO may offer life-saving support for some patients with cancer and other immunocompromising conditions, caution should be exercised when discussing prognosis with patients' families. Regarding the use of ECMO support for pediatric burn patients with severe respiratory failure, although a relatively small number of patients have been supported, a recently published review of ELSO Registry data from 1999 to 2008 found that survival was comparable to that of non-burn related pediatric respiratory failure at 53 % in 36 patients [68].

ECPR

Extracorporeal cardiopulmonary resuscitation (ECPR) refers to the use of ECMO initiated during refractory cardiac arrest. Several recent investigations have examined the outcomes of patients supported with ECPR [125–133], and Table 12.6 describes reported outcomes. In general, survival rates after ECPR appear to be higher in patients with cardiac disease as opposed to patients who suffer cardiac arrest from other causes [125, 126, 131, 134, 135]. Many ECMO centers maintain a crystalloid-primed "rapid-deployment" circuit for use in emergency initiation of ECMO, such as for ECPR [136]. Although somewhat counterintuitive, studies of ECPR use in children with in-hospital cardiac arrest thus far have not found a consistent statistical association between duration of cardiac arrest and survival when ECPR is used [126, 129, 130, 135, 137, 138]. However, a higher pre-ECMO blood pH, which may be a surrogate marker for duration of cardiac arrest and quality of conventional CPR, has been associated with favorable odds for survival and for good neurologic outcome after ECPR [131, 138]. The importance of good quality CPR prior to the initiation of extracorporeal life support cannot be overemphasized. Although long-term follow-up studies using sophisticated testing of neurocognitive function in survivors of ECPR are lacking, several reports note a high percentage of survivors with favorable scores on gross measures of neurologic function such as the Pediatric Cerebral Performance Category and Pediatric Overall Performance Category [125, 126, 135, 139]. A recent review of a cohort of ECPR patients reported to the ELSO Registry noted brain death, brain infarction, or intracranial hemorrhage in 22 % of cases [138]. The 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science state that ECPR may be considered for children with refractory cardiac arrest from a potentially reversible etiology [140].

ECMO Support for Adults with Respiratory Failure

Although ECMO was first used for support of respiratory failure in an adult patient [2], the failure of the subsequent National Institutes of Health-sponsored trial of ECMO support for adult respiratory failure led to a lack of interest in ECMO at many adult centers [4]. Interest in ECMO support for adult patients with ARDS has increased in recent years, however, related both to the publication of another randomized trial in adults with severe respiratory failure [141] and to several reports of successful ECMO support of adult patients with ARDS due to pandemic H1N1 influenza pneumonia

Table 12.6 Summary of recent published outcomes of ECPR in children

Summary of recent published outcomes of pediatric extracorporeal cardiopulmonary resuscitation	Patient population	Number of patients	Percent survival	Duration of CPR (minutes) Median (range)
Raymond et al. [125]	Mixed medical and surgical	199	43.7 %	Survivors: 46 (26–68) Non-survivors: 7 (38–71)
Prodhan et al. [126]	28 cardiac; 6 medical	32	73 %	Survivors: 43 (15–142) Non-survivors: 60 (20–76)
Chan et al. [128]	Cardiac disease	492	42 %	Not reported
Huang et al. [130]	Mixed medical and surgical	27	41 %	Survivors: 45 (25–50) Non-survivors: 60 (37–81)
Thiagarajan et al. [131]	Mixed medical and surgical	682	38 %	Not reported
Morris et al. [133]	Mixed medical and surgical	64	33 %	Survivors: 50 (5–105) Non-survivors: 46 (15–90)

[142–150]. Peek and colleagues in the United Kingdom completed a prospective, randomized trial in which adults with severe respiratory failure were randomized to conventional management or referral to an ECMO center for consideration of ECMO support [141]. In this study, 180 adult patients were randomized, with 90 patients in each group. In the group that was randomized to consideration of ECMO, 68/90 (75 %) patients actually were supported with ECMO, and 63 % of patients randomized to consideration of ECMO survived 6 months without disability compared to 47 % in the conventional group, which reached statistical significance [141]. Recent published series from Australia-New Zealand and Italy report survival rates of 68–71 % in adult patients supported with ECMO for severe ARDS caused by pandemic H1N1 pneumonia [149, 151]. Due to the recent increase in demand for ECMO services for adult patients, some experienced pediatric ECMO centers have assisted in training and implementation of ECMO programs for adults [152].

Long-Term Outcome After ECMO Support

Although ECMO has been a common support modality for neonatal and pediatric patients with severe cardiopulmonary failure for over 20 years, the literature on long-term neurodevelopmental and neuropsychological outcomes among survivors remains relatively scant. Early reports of neurocognitive testing in survivors of ECMO for neonatal respiratory failure noted normal cognitive scores in a majority of survivors, a significant percentage with sensorineural hearing loss, and similar neurodevelopmental outcome to infants with similar diagnoses managed without ECMO [153–155]. Several studies of neurodevelopmental outcome of infants supported with ECMO reported follow-up times of only 1 year, and most noted worse outcomes among survivors who had been supported for congenital diaphragmatic hernia as opposed to other diagnoses [156–158]. A study of 37 survivors of neonatal ECMO at age 5 years revealed major disabilities in 17/103 children [159]. A small study of infants supported with ECMO after cardiac surgery reported normal neuromotor scores in 75 % and normal cognitive scores in 50 % of survivors with a median follow-up time of 55 months [160]. One center reported that, in 32 survivors of neonatal ECMO tested at age 7–9 years, a diagnosis of seizures before or during ECMO was associated with a significantly higher risk of having a lower intelligence quotient, cerebral palsy, and speech-language disorders than was seen in survivors without seizures or children referred for ECMO but managed medically [161]. Regarding long-term pulmonary outcomes among survivors, one group of investigators reported that 17 children who had been supported with ECMO for meconium aspiration syndrome were tested at age 10–15 years and found to have mild baseline and post-exercise abnormalities in pulmonary function tests, but normal aerobic capacity [162]. Unfortunately, very little has been published regarding long-term neuropsychological and neurocognitive outcomes in older pediatric patients and adults who have been supported with ECMO.

Inter-hospital Transport of Patients Supported with ECMO

Occasionally the need arises for inter-hospital transport of a child supported with ECMO, either because the referring center does not have an ECMO program, or because the patient requires specialized services, such as ECMO used for "bridging" to heart transplantation. The first report of a patient transported while supported with ECMO was published by Bartlett and colleagues in 1977 [163]. Since that time, a limited number of ECMO centers have maintained active capability to transport patients on ECMO. In the United States, the bulk of transport ECMO experience has been reported by the University of Michigan [164], Wilford Hall United States Air Force Medical Center [165–167], and Arkansas Children's Hospital [168–170]. The Karolinska Hospital in Sweden and the Virchow-Klinikum in Berlin have reported their experiences with transport of ECMO patients in Europe [171, 172]. In a review of 104 patients transported by the ECMO team from Arkansas Children's Hospital, Clement and colleagues noted that survival to hospital discharge for patients transported was statistically equivalent to survival for "in-house" ECMO patients at that center and to outcomes reported by the ELSO Registry [169]. Consistent with the experience reported by the ELSO Registry, survival rates for patients transported on ECMO for primary cardiac indications are lower than for those with respiratory failure as an indication for ECMO support [169, 170]. Although inter-hospital transport of ECMO patients is expensive, labor-intensive, and time-consuming, such a service offered by an experienced ECMO team can be life-saving. The advent of newer generation centrifugal pumps and lightweight, compact ECMO equipment may allow easier, more rapid transport of patients requiring ECMO support [173].

Future Directions in ECMO Support

A number of opportunities and challenges face the ECMO community in the coming years. With documented success in rapidly deploying ECMO technology and personnel for use in ECPR comes the challenges inherent to defining the appropriate role of such technology in cardiopulmonary resuscitation [125, 126, 140, 174]. Such challenges will include defining the proper role for ECPR in out-of-hospital

cardiac arrest, as has been practiced for some time in Japan [175, 176]. Zabrocki and colleagues recently reported that an increasing percentage of pediatric ECMO patients supported for respiratory failure have significant co-morbidities [13]. Continued expansion of the use of extracorporeal support for patients with serious underlying conditions, such as malignancies, will require thoughtful and compassionate application of technology into these situations. New developments in equipment used for extracorporeal support hold the promise of improved patient safety [173, 177–179], as do increases in the depth of our understanding of proper anticoagulation management during ECMO [62, 180]. Advances in ECMO team training using high-fidelity simulation may yield great benefit in terms patient safety and outcomes [181–183]. Finally, as highlighted above, a great need exists for thorough research into measures of long-term health in ECMO survivors.

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Ventilator-Induced Lung Injury

13

Shinya Tsuchida and Brian P. Kavanagh

Abstract

Clinical and experimental studies have clearly established that mechanical ventilation with large tidal volumes is harmful to the lung. However, there is uncertainty about the micromechanics of injured lungs as well as many unanswered questions about the optimal levels of PEEP and tidal volume in individual patients. In this chapter we focus on the mechanical and molecular mechanisms of ventilator-induced lung injury, the characteristics of bronchopulmonary dysplasia and the eventual feasibility of selective targeted therapy for these conditions.

Keywords

Ventilator-induced lung injury • Acute respiratory distress syndrome • Bronchopulmonary dysplasia • Lung recruitment • Multiple-organ dysfunction syndrome

Introduction

When considering mechanical ventilation, is it important to avoid an injurious ventilator strategy in the treatment of acute respiratory distress syndrome (ARDS) patients? We believe that the answer is "absolutely yes", because two landmark studies have conclusively demonstrated that how the mechanical ventilator is set has a direct effect on patient mortality [1, 2]. Indeed, as reviewed throughout this chapter, such work represented the clinical confirmation of multiple laboratory studies [3]. Amato and colleagues [1] demonstrated the superiority of a protective strategy comprising low tidal volume, high positive end-expiratory pressure (PEEP) and recruitment maneuvers. Focusing on the tidal volume alone, the investigators from the ARDS Network [2] clearly demonstrated that ventilation with 6 mL/kg predicted body weight resulted in a lower mortality than ventilation with 12 mL/kg. Although Eichacker et al. [4] pointed out in their meta-analysis that control groups in these trials might not have reflected contemporary tidal volume choices, it is clear that mechanical ventilation can have an impact on mortality.

The theory of a lung protective strategy is twofold: prevention of atelectasis and prevention of lung overinflation. In fact, there are many practical issues in the application of a lung protective strategy for clinical use. This is further complicated in the pediatric intensive care unit, because the most important data, those studies demonstrating an effect of ventilation on outcome [1, 2], are from adult studies only. Furthermore, the accumulating data from the experimental studies, although teaching us to be "gentle" with the injured lung [3], have not elucidated the precise mechanisms of ventilator-induced lung injury, nor have they informed us of the optimal mode of protective ventilation. These "clinical unknowns" are the rationale for reviewing clinical trials and experimental studies in this chapter.

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Low Tidal Volume Lessens Ventilator-Induced Lung Injury

In their classic *in vivo* experiments in laboratory rats, Webb and Tierney [5] found that high peak inspiratory pressure combined with zero PEEP was fatally injurious. This was the first demonstration of lethal pulmonary *barotrauma*. Dreyfuss et al. [6] bound the chests of *in vivo* anesthetized animals, thereby developing high airway pressures -but limiting the tidal volumes. They found that elevated tidal volume, as opposed to airway pressure *per se*, was paramount in inducing ventilator-induced lung injury, thus establishing the concept of *volutrauma* [6]. This elegant concept was challenged by Broccard et al. [7], who compared independently the effects of mean airway pressure *versus* tidal volume under conditions of constant pulmonary blood flow using *ex vivo* perfused rabbit lungs. They concluded that mean airway pressure contributed more than tidal volume to the increase in pulmonary vascular permeability. They attributed the mechanism whereby high mean airway pressure promoted lung edema formation to an increase in pulmonary vascular resistance increasing the (extra-alveolar) vascular transmural pressure [7]. Although high stretch has been investigated in terms of the peak airway pressure, tidal volume, and mean airway pressure, it is unclear which of these three factors is most crucial to the progression of ventilator-induced lung injury in man.

Given that some combination of high tidal volume and elevated airway pressure is harmful, a reasonable supposition might be that lower tidal volumes will naturally result in better outcomes. Unfortunately, this is also a complex issue. Atelectasis may develop through the use of low tidal volume ventilation especially in the absence of PEEP. Chiumello et al. demonstrated in their studies of rats following acid-aspiration lung injury that, although high tidal volume was adverse (particularly in terms of inflammatory cytokine production), the greatest mortality occurred in those animals ventilated with low tidal volume in the absence of PEEP [8]. A similar finding was reported in the absence of preexisting lung injury, wherein a high mortality rate occurred with low tidal volume ventilation (without PEEP or supplemental oxygen) and was attributed to right ventricular failure [9]. In contrast, in acid-injured *in vivo* rats, very low tidal volumes (as low as 3 mL/kg) were more protective than higher tidal volumes at the same (elevated) level of PEEP (10 cmH_2O) [10]. Although the atelectasis may partly depend on the PEEP level, it is unclear whether low tidal volume is protective against atelectasis-associated lung injury, and if so, how. Indeed, more questions continuously evolve in this area [11].

A particularly important thesis is the possibility that, because of the heterogeneous nature of the disease, a given tidal volume may ventilate only the healthy (*i.e.* aerated) portion of the ARDS lungs. This possibility was proposed by Gattinoni et al. [12], who examined the amount of aerated lung tissue and the pressure-volume (PV) curve at different PEEP levels in ARDS patients. As a result, they suggested that the PV curve in ARDS reflects only the residual healthy zones and does not directly estimate the injured zones. Hence, apparently a low tidal volume based on the body weight could conceivably be too high for the remaining aerated portion of lung, resulting in ventilator-induced lung injury caused by the overdistention (the so-called baby lung concept; Fig. 13.1). Substantiating this concept is the observation that air cysts and bronchiectasis prevail in the non-dependent (better-ventilated) areas in ARDS patients [13].

High Positive End-Expiratory Pressure Protects Against Injury with Low Tidal Volumes

A clinical trial (*i.e.*, the ALVEOLI study) performed by the ARDS Network [14] was unable to find differences in clinical outcomes of ARDS patients who were assigned to a higher PEEP strategy (13.2 ± 3.5 cmH_2O) *vs.* lower PEEP strategy

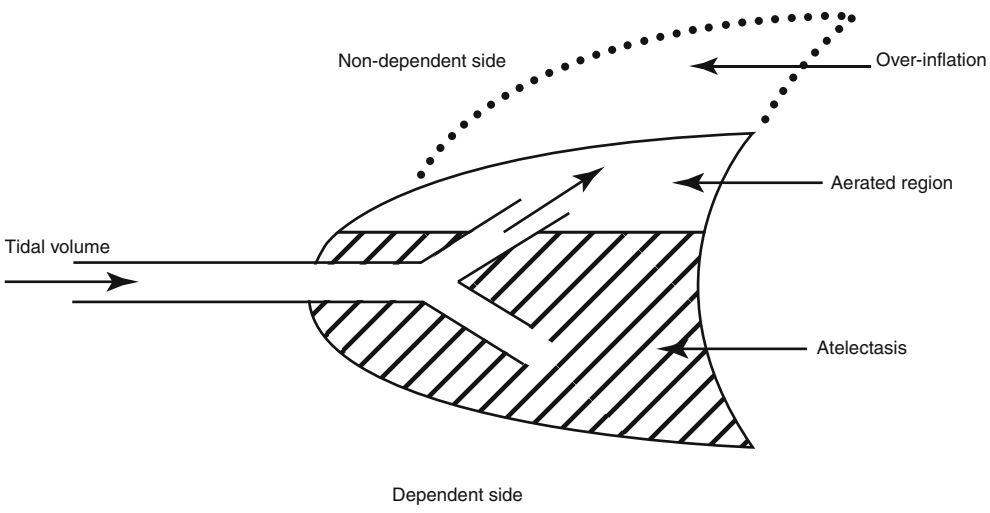


Fig. 13.1 A schematic illustration of the baby lung concept. In an extensively atelectatic lung, tidal volume will be shifted toward the small aerated lung (baby lung), resulting in overdistention in this region

(8.3 ± 3.2 cmH_2O), with the targeted tidal volume being the same in both groups (6 mL/kg). This whole area is problematic, however, as the stated hypothesis was that elevated PEEP may help in some situations and harm in others [14]. Such a dual hypothesis is of course completely defensible on physiologic grounds, as these contrasting effects of PEEP are precisely what is predicted based on many years of physiologic research. This negative trial follows another study conducted 20 years earlier [15] that demonstrated that the early application of 8 cmH_2O PEEP was not useful for the prevention of ARDS compared with zero PEEP at the same tidal volume (12 mL/kg). What arise from these clinical studies are the questions of whether the level of PEEP has an impact on outcome and whether PEEP has been subjected to testing with sufficient pre-randomization physiologic stratification.

Important work is available from the laboratory. Muscedere et al. [16] compared 0, 4, and 15 cmH_2O PEEP ventilated with the same low tidal volume (6 mL/kg) in *ex vivo*, non-perfused saline-lavaged rat lungs. They found that 15 cmH_2O PEEP (*i.e.*, above the inflection point on the PV curve) was protective, and, notably, the injured sites depended on the PEEP level. While 4 cmH_2O PEEP (*i.e.*, below the inflection point on the PV curve) showed mainly alveolar injury, zero PEEP exhibited mostly bronchiolar injuries. The investigators attributed these differences to the repetitive opening and closing of airways at different sites (Fig. 13.2). According to Tremblay's *ex vivo*, non-perfused ventilation model in which end-inspiratory lung volume was made equivalent, high tidal volume without PEEP was more injurious, producing more tumor necrosis factor-α (TNF-α) protein and c-*fos* mRNA than the combination of "moderate" tidal volume with high PEEP [17]. Indeed, the progression of ventilator-induced lung injury was reported to be delayed in proportion to the increasing level of PEEP employed in an *in vivo* rat model, where end-inspiratory lung volume was matched [18]. Indeed, the superiority of high PEEP over low PEEP in *in vivo* saline-lavaged rabbits had been demonstrated a decade earlier, where mean airway pressure and plateau pressure are similar [19].

However, not all studies are so positive. Higher PEEP (10 cmH_2O) has been compared with lower PEEP (3 cmH_2O) in an *in vivo* rabbit model of acid aspiration with no significant differences in histologic findings between the two groups [20]. Interestingly, 3–4 cmH_2O PEEP is most frequently used for surfactant-treated infants with respiratory distress syndrome (RDS). A comparison of 0, 4, and 7 cmH_2O PEEP in surfactant-treated preterm lambs that were ventilated with 10 mL/kg tidal volume [21] demonstrated that, whereas both 4 and 7 cmH_2O PEEP were more protective than zero PEEP, the use of 7 cmH_2O PEEP was associated with superior oxygenation but with an adverse increase in pulmonary vascular permeability. Naik et al. [22] also administered surfactant to the pre-term lambs and compared the effects of 0, 4, and 7 cmH_2O PEEP on the expression of pro-inflammatory cytokine production and pulmonary morphometry. Surprisingly, 4 cmH_2O PEEP was most protective among the three different PEEP levels. There was more atelectasis with zero PEEP and a higher proportion of overdistended alveoli with 7 cmH_2O PEEP, suggesting that the injurious mechanism may be different between 0 and 7 cmH_2O PEEP. In addition, the optimal PEEP level may depend on the lung maturity. We know that PEEP is important; however, it is unlikely that a single optimal level of PEEP and tidal volume apply across populations and how best to individualize PEEP or tidal volume is unclear.

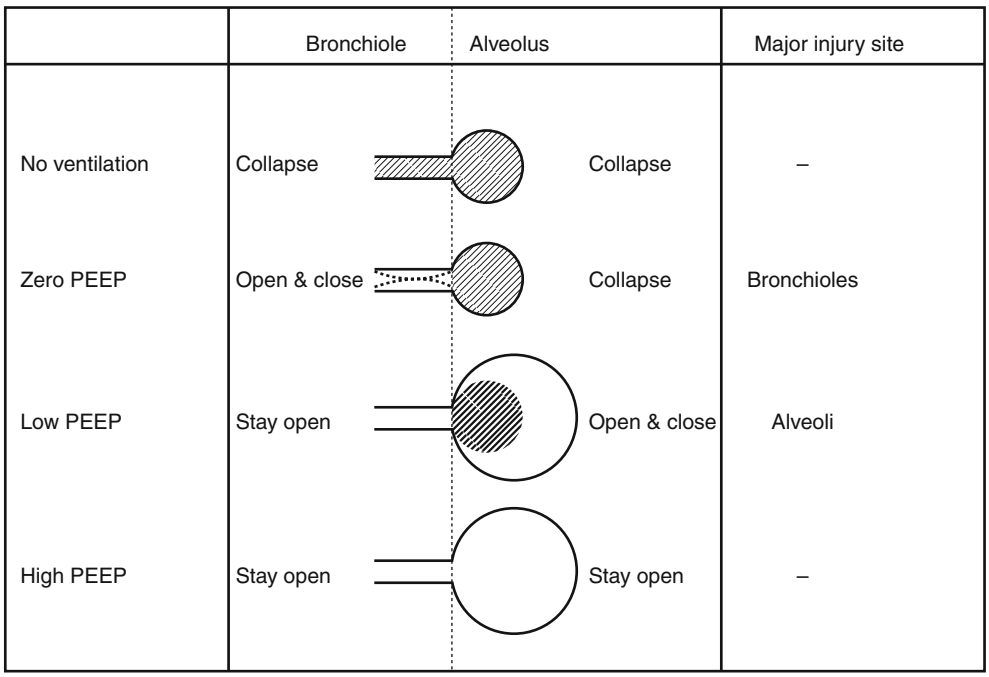


Fig. 13.2 A schematic illustration of repetitive opening and closing of airways as a cause of atelectasis-associated lung injury. The degree of lung recruitment is a determinant of lung injury and its site in an atelectasis-prone lung. The repetitive opening and closing of distal airways is essential in the progression of atelectasis-associated lung injury. *PEEP* positive end-expiratory pressure

Recruitment Is Essential to Lung Protection

The recruitment maneuver has been suggested as a pivotal issue in lung protection. Rimensberger et al. [23] demonstrated that the recruitment maneuver enabled the ventilatory cycles to relocate onto the *deflation* limb of the PV curve during low tidal volume ventilation, where low tidal volumes (5 mL/kg) were combined with PEEP set to less than the lower inflection point (Fig. 13.3). A comparison of the effects of two different maneuvers (*i.e.*, recruitment maneuver and PEEP titration) on the regional aeration of saline-lavaged *in vivo* dogs using sequential computed tomography demonstrated that the recruitment maneuver resulted in the tidal ventilation being localized on the deflation limb [24]. These were similar in concept to the earlier findings of Rimensberger et al. [23]. However, use of the recruitment maneuver tended to induce a greater increase in hyperaerated lung volume than did use of PEEP titration. Their study shows that alveolar recruitment may occur at the expense of hyper-inflation and therefore any advantages of the recruitment maneuver must be weighed against this complication. Using saline-lavaged *in vivo* sheep, Musch et al. found that recruitment maneuvers can –transiently- worsen oxygenation in acute lung injury by diverting pulmonary blood flow from aerated to nonaerated regions [25].

In a clinical trial carried out by the ARDS Network [26], investigators were unable to find sustained improvement in oxygenation or lung mechanics following the recruitment maneuver in ARDS patients ventilated with high PEEP (13.8 cmH_2O) and low tidal volume (6 mL/kg). Indeed, it is possible that the higher PEEP level used in this trial might have concealed the potential for improvements related to recruitment maneuvers [26]. Conversely, others have reported greater effects of recruitment on oxygenation when ARDS patients were ventilated with relatively lower PEEP (9.4 cmH_2O) [27]. In addition to the basal PEEP levels, the effects of a recruitment maneuver may depend on the phase of ARDS. While early ARDS patients mechanically ventilated for less than 3 days showed transient improvements in the lung compliance, venous admixture, and end-expiratory lung volume, patients in later phases of ARDS (*i.e.*, those ventilated for more than 7 days) showed no improvement in these parameters [28]. In both ARDS phases, arterial oxygenation did not change in response to recruitment maneuvers. The investigators pointed out the possibility that alveolar overdistention might redistribute blood flow and increase intrapulmonary shunt. Grasso et al. [29] also found differences in the phases of ARDS between the responders and non-responders to recruitment maneuvers and attributed the poor responses in late ARDS patients to impaired pulmonary mechanics. Thus, at this time, we should consider the issues of both recruitment maneuvers and optimal level of PEEP to be unresolved in the clinical context.

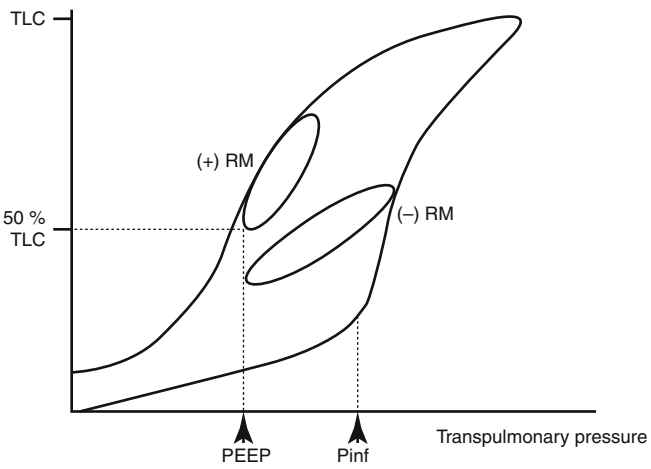


Fig. 13.3 Effects of a recruitment maneuver (*RM*) on the ventilatory cycles. The RM enables the ventilatory cycles to relocate onto the deflation limb of the pressure-volume curve, where positive end-expiratory pressure (*PEEP*) is set to less than the lower inflection point (P_{inf}). *TLC* total lung capacity

Susceptibility to Ventilator-Induced Lung Injury: Adults *vs.* Infants

Intensivists are concerned about ventilator-associated lung injury caused by indiscriminate use of higher tidal volume. Compared with adults, pediatric patients demonstrate a spectrum of lung development, spanning neonatal, infant, juvenile stages up to early adult stages. There are important structural and functional differences between infant and adult lungs, raising an important question: does the lung maturation have an effect on the susceptibility to ventilator-induced lung injury?

Adkins et al. [30] ventilated *in vivo* young and adult rabbits with comparable peak inspiratory pressures (pressure-controlled ventilation) and showed that the younger rabbits developed greater microvascular permeability and macroscopic air leak. They speculated that the younger rabbits might have been exposed to disproportionately larger tidal volumes (per kg body weight), because the use of pressure-controlled ventilation might have resulted in far greater tidal volumes in the younger animals, in which respiratory system compliance was clearly greater.

In volume-controlled ventilation, tidal volume is usually expressed based on the body weight. Because the ratio of airway volume to body weight changes with age [31], tidal volume based on body weight might occupy a different fraction of total lung capacity (TLC) in the adult *versus* the infant, resulting in proportionally more lung stretch and thereby more lung injury. Copland et al. [32] ventilated *in vivo* neonatal and adult rats with high tidal volume based on body weight. As a result, all adult rats exposed to a tidal

volume of 40 mL/kg developed severe lung injury and died within 20 min, but all neonatal rats survived for 3 h while developing only a small decrement in respiratory system compliance. On the basis of measured compliance, edema formation, and histology, ventilation with 25 mL/kg was also more injurious to adult rats than to newborns [32]. Their findings are supported by the work of Kornecki et al. [33], who compared *ex vivo*, non-perfused infantile and adult lungs ventilated with high tidal volume (30 mL/kg) and reported that adult lungs are more susceptible than infantile lungs to ventilator-induced lung injury, as evidenced by lung mechanics and histology. In addition, they performed dynamic subpleural microscopy on the adult and infantile rats, finding greater and more heterogenous alveolar stretch in adult lungs. In summary, great caution should be exercised in the translation to pediatric practice of any recommendations for clinical practice that are based on adult studies.

Bronchopulmonary Dysplasia and Ventilator-Induced Lung Injury

Survival of the premature infants has been dramatically improved since respiratory management with mechanical ventilation and exogenous surfactant replacement for respiratory distress syndrome was established. Nowadays, lung injury caused by long-term mechanical ventilation and oxygen therapy is one of the greatest issues in the respiratory management of neonates, especially of extremely premature infants born at less than 28 weeks of gestation [34]. In this section, we will review the factors contributing to bronchopulmonary dysplasia (BPD).

BPD is defined as oxygen dependence for at least 28 postnatal days for infants born at 32 weeks or greater gestational age (GA) or oxygen dependence at 36 weeks postmenstrual age for infants born before 32 weeks GA [35]. The greatest difference between BPD and ventilator-induced lung injury is that BPD is caused by the physical factors such as mechanical stress, strain, and oxygen toxicity insulting the developing immature lungs with incomplete alveoli. Human lung development is subdivided into the following 5 stages: embryonic stage (4–6 weeks GA), pseudoglandular stage (6–16 weeks GA), canalicular stage (16–26 weeks GA), terminal saccular stage (26–36 weeks GA), and alveolar stage (36 weeks GA to 2 years) [36]. Extremely premature infants born at less than 24 weeks of gestation would be mechanically ventilated during the late canalicular stage of lung development when neither alveoli nor alveolar sacs are completed.

The lungs of premature infants with respiratory distress syndrome are characterized by the propensity of their immature alveoli to readily collapse due to the lack of endogenous surfactant; the lungs are thus prone to extensive atelectasis. These atelectasis-prone lungs are susceptible to ventilator-induced lung injury, and such type of lung injury was termed *atelectrauma* in the 1990s [37]. It was previously hypothesized that *atelectrauma* is caused by the shear stress which occurs when airways or alveoli repetitively open and close in the atelectatic lung regions [16] (Fig. 13.2). However, no direct evidence demonstrating the above hypothesis has been shown to date. On the contrary, tidal volumes are predominantly redistributed towards the aerated, non-atelectatic lung regions, and over-distention of aerated alveoli caused by the "large" tidal volume relative to the "small" baby lung may be one of the mechanisms of atelectasis-associated trauma [38] (Fig. 13.4). Indeed a recent study utilizing PET scanning of the lung to identify areas of active inflammation reported similar findings in adults with ARDS [39].

In the presence of inflammation such as infection and endotoxemia, acute lung injury may be caused by mechanical ventilation with moderate tidal volume [40], or even by continuous positive airway pressure (CPAP) [41], which in the absence of sepsis is unlikely to cause lung injury. It has been suggested that premature infants born in the setting of chorioamnionitis are likely to suffer from severe BPD [42]. In such cases, not only mechanical ventilation but CPAP or oxygen therapy can be a "second hit" to the development of lung injury following the "first hit" of intrauterine inflammation. Such respiratory failure in preterm infants was previously termed Wilson-Mikity syndrome [43], and was distinguished from BPD; as the mechanisms of BPD have been elucidated by experimental and clinical research, the diagnosis of Wilson-Mikity syndrome has been incorporated in the BPD spectrum. Indeed, premature infants with chorioamnionitis often avoid respiratory distress syndrome because intrauterine inflammation can augment the maturation of the endogenous surfactant system. When these patients are conventionally ventilated (e.g. PIP/PEEP <20/5 cmH_2O), there can be increased susceptibility to *volutrauma* because the surfactant administration will increase lung compliance and distension [44].

Although classical BPD was described in preterm infants of 31–34 weeks of gestation by Northway et al. in 1967 [45], such patterns of BPD are now primarily seen in extremely preterm newborns of less than 28 weeks in gestational age. Banerjee et al. observed airway injury and inflammation, peribronchial fibrosis, and hypertensive vascular changes in BPD, and the term 'BPD' reflects these histologic findings [46]. Survival of more immature infants has increased since the mid-1980s when exogenous surfactant therapy was employed in clinical neonatology; indeed the pathological characteristics of BPD have also changed [47]. In order to reproduce the pathological findings of the current BPD, Coalson et al. created a BPD model of extremely immature baboons, and examined histologic findings of their lungs [48]. The animals were delivered at 125 days (term gestation,

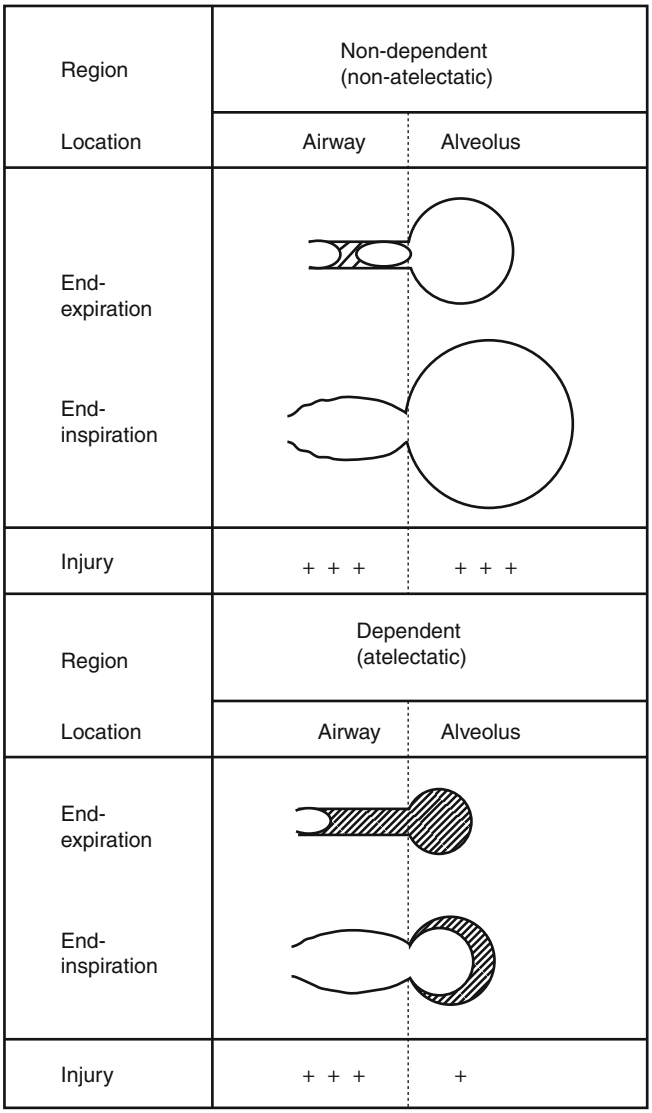


Fig. 13.4 A schematic explanation of regional lung injury associated with dependent atelectasis. Endexpiratory alveolar size is smaller in the dependent than in the non-dependent region. At end-inspiration, alveolar overdistention occurs in the non-dependent region, resulting in marked alveolar injury therein. In contrast, distal airway injury is equally distributed between the dependent and non-dependent regions (Reprinted with permission of the American Thoracic Society. Copyright © 2013 American Thoracic Society. Tsuchida et al. [38]. Official Journal of the American Thoracic Society)

185days), and treated with antenatal steroid, postnatal exogenous surfactant replacement, parenteral nutrition, PDA ligation if necessary, and maintained on appropriate oxygen and positive pressure ventilation at least for 1–2 months. A 125-days baboon fetus corresponds to a human fetus at 24–26 weeks of gestation (late canalicular stage). The key differences between 'classical' BPD and the 'new BPD' are that in the former, the lungs were more mature but were injured primarily by a combination of hyperoxia and high tidal volumes. In the 'new' BPD, the lungs are more immature and the lesion is one of arrested development (Table 13.1). The baboon BPD lungs showed large "simplified" alveolar saccules with various degrees of fibrosis, decreased number of alveoli, and hypoplasia of capillary development within the saccular walls [48]. While pathological findings of the original BPD were primarily localized in airways, impaired alveolarization and capillary development was the predominant finding in the current BPD, which has been termed 'new' BPD to be discriminated from the original one [35].

The transition of pathological findings seems to be related with prevalent use of the exogenous surfactant and high-frequency ventilation since the late 1980s. Muscedere et al. ventilated surfactant-depleted *ex vivo* lungs with varying degrees of lung recruitment, and found that the injury sites depended on the degrees of lung recruitment [16] (Fig. 13.2). Based on their experiments, the prevalence of alveolar impairment in new BPD may at least partly reflect recruited lungs of premature infants treated with exogenous surfactant and exposed to mechanical ventilation since the late 1980s. Mechanical ventilation of extremely premature infants of less than 26 weeks of gestation, who are born before alveolar sacs or alveoli are completed (during the late canalicular stage), may be the direct cause of "alveolar arrest" observed in new BPD. This speculation is supported by the histologic findings of impaired capillary development described by Coalson et al. [48].

A hypothesis that cross talk exists between airway epithelium and vascular endothelium in the developing lung has been proposed [49]. In developing lungs, distal airspace epithelial cells express vascular endothelial growth factor (VEGF), suggesting that the epithelium may regulate the

Table 13.1 Comparison of classical BPD and the new BPD

	Classical BPD	New BPD
Gestational age	More mature (>28 weeks)	Less mature (<28 weeks)
Respiratory management	High Paw	HFOV
	High V_T	Surfactant
	High F_IO_2	
Main sites of injury	Bronchus	Alveolar saccule
	Bronchiole	Alveolus
Main histologic lesions	Bronchial hyperplasia and squamous metaplasia	Decreased number of alveoli
	Bronchiolar fibrosis	Capillary hypoplasia
	Bronchiolar smooth muscle hypertrophy	

development of alveolar capillaries [50]. Bhatt et al. compared lungs from 5 infants dying from BPD with lungs from 5 infants dying from non-pulmonary causes [51]. BPD lungs exhibited decreased mRNA and protein of PICAM-1, a specific marker of endothelial cells. The BPD lungs also showed decreased VEGF mRNA and decreased VEGF immunostaining. Messages for the angiogenic receptors Flt-1 and TIE-2 were decreased in the BPD lungs. Flt-1 (VEGFR1) is a tyrosine kinase receptor mediating VEGF actions. TIE-2 is also a tyrosine kinase receptor of Ang-1 which converts endothelial tubes into mature vessels. Decreased expression of these angiogenic growth factors and their receptors may contribute to the hypoplasia of capillary development observed in new BPD.

How long does BPD affect the respiratory function of BPD survivors? According to a population-based case–control study in Washington State [52], 18–27-year-old adults born less than 1,500 g were more frequently hospitalized than control adults of equivalent ages, especially due to asthma, respiratory infection, and respiratory failure requiring mechanical ventilation. The histology of BPD survivors is characterized by diffuse alveolar damage and neutrophilic inflammation leading to fibrosis, suggesting that the influence of mechanical ventilation and oxygen on the developing lung at alveolar stage would not be offset after growing into adulthood [53, 54].

In the above study, young adults, whose birth weights were between 1,500 and 2,500 g showed similar trend of hospitalization to the very low birth weight, suggesting – because BPD is not common in this population- that low birth weight in the absence of BPD may confer an increased risk of adult respiratory disease. This trend would be partly explained by the disrupted lung development due to the environmental factors such as fetal and neonatal malnutrition. This speculation is based on the hypothesis of the "Developmental Origins of Health and Disease (DOHaD)" which was proposed by Barker et al. [55]. Walter et al. calculated that low birth weight may account for over 21,000 adult hospitalizations per year, with charges in excess of $225 million per year in the USA [52]. This calculation cannot be directly extrapolated to other countries, because their medical system may be quite different from that of U.S. However their report is worth paying serious attention to, considering for example, the rapidly increasing rate of low (and very low) birth weight infants in Japan [56].

Stretch Increases Production of Biochemical Mediators (Mechanotransduction)

It has been demonstrated that mechanical ventilation induces the intrapulmonary production of pro-inflammatory (e.g., interleukin-1β (IL-1β), IL-6, and TNF-α) and anti-inflammatory (e.g., IL-10) cytokines, as well as chemokines (e.g., MIP-2), in the presence of underlying lung injury. In patients with ARDS, pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) were increased in the bronchoalveolar lavage (BAL) of the control arm but not where protective ventilation (higher PEEP, lower tidal volume) was used [57]. In laboratory studies of conventional *versus* high-frequency ventilation, Takata et al. reported that intrapulmonary expression of TNF-α mRNA was high with conventional ventilation but not with high-frequency ventilation [58]. Using a comparable model (*i.e.*, the atelectasis-prone, surfactant-depleted rabbit), Imai et al. [59] demonstrated that conventional ventilation increased the production of TNF-α protein in the BAL compared with high-frequency ventilation. Chiumello et al. [8] found the increased TNF-α and MIP-2 protein in the BAL of acid-injured *in vivo* rats ventilated with high tidal volume (16 mL/kg) and zero PEEP. Most animal studies using "pre-injured" lungs show the involvement of pro-inflammatory cytokines.

In the absence of preceding injury, it is unclear whether injurious ventilation *per se* can induce the intrapulmonary production of TNF-α at mRNA and protein levels [60, 61]. Injurious ventilation increased TNF-α at both mRNA and protein levels in *ex vivo*, nonperfused lungs [17] as well as in ventilated *ex vivo*, perfused mouse lungs [62]. A significant increase in TNF-α protein has been reported in an *in vivo* rat model ventilated with high tidal volume but without underlying lung injury [63]. Consistent with this, Copland et al. [32] ventilated rats *in vivo* with high tidal volume (25 mL/kg) and zero PEEP, resulting in the increased expression of TNF-α mRNA at only 30 min. On the contrary, others failed to find a large increase of TNF-α protein in the BAL following high tidal volume ventilation in the *ex vivo* rat lung [64]. Verbrugge et al. [65] and Imanaka et al. [66] ventilated rats with high peak inspiratory pressure and zero PEEP and found no increase in TNF-α protein [65] or mRNA [66] respectively. In contrast to TNF-α, MIP-2 protein (the murine homolog of IL-8) has been consistently found in most animal studies [17, 32, 64, 67, 68]. Quinn et al. [67] ventilated rats with high tidal volume (20 mL/kg) and, interestingly, MIP-2 protein was not increased in the BAL immediately after the ventilation but was significantly increased at 6 h after extubation while breathing room air.

Wilson et al. [68] ventilated *in vivo* mice with high tidal volume and exhibited a transient increase in TNF-α protein and more sustained increase in MIP-2 protein in the BAL. Their findings are supported by those of Tremblay et al. [69], who ventilated the *ex vivo*, nonperfused rats with high tidal volume (40 mL/kg) and demonstrated using *in situ* hybridization that the proportion of pulmonary epithelial cells expressing TNF-α mRNA peaked at 30 min and returned to baseline thereafter. The transient nature of TNF-α upregulation may help explain the previous controversies regarding the involvement of cytokines in ventilator-induced lung injury.

Copland et al. [32] ventilated newborn rats *in vivo* with high tidal volume and observed the temporal mRNA expression of several cytokines. They showed that the most prominently upregulated genes were MIP-2 and IL-10 at 30 min, whereas at 3 h of high tidal volume ventilation IL-6 and MIP-2 were the most strongly induced cytokines. They also referred to the balance between the pro- and antiinflammatory cytokines. With regard to this balance, the compartmentalization of the inflammatory response should be taken into account as well as the temporal factors. Dugernier et al. [70] observed the pro- and antiinflammatory activities in the three different compartments (e.g. ascites, lymph, and blood) of patients suffering from severe acute pancreatitis. They concluded that the peritoneal compartment was the site of proinflammatory response and that an early, dominant, and sustained anti-inflammatory activity took place in the circulating compartments. Their findings, although obtained from the patients with severe acute pancreatitis, may provide insight into how a local organ inflammation propagates into an inflammatory response in the systemic circulation.

Does Ventilator-Induced Lung Injury Lead to Multiple-Organ Dysfunction Syndrome?

The leading cause of death in ARDS patients is multiple-organ dysfunction syndrome (MODS) rather than respiratory insufficiency. In the ARDS Network trial [2], plasma IL-6 concentration on day 3 was higher in ARDS patients of the control group associated with the higher mortality. Ranieri et al. [57] reported an increase in proinflammatory cytokines (IL-6 and TNF-α) not only in the BAL but also in the plasma of ARDS patients in the control arm. Accumulating evidence from multiple experimental studies suggest that ventilator-induced lung injury can lead to systemic inflammation.

von Bethmann et al. [62] used the isolated, perfused mouse lung in which frequent perfusate sampling allows determination of mediator release into the nonrecirculated perfusate. They demonstrated that hyperventilation increased the mRNA expression of TNF-α and IL-6, peaking at 30 and 150 min, respectively. Furthermore, they found that hyperventilation increased the perfusate concentration of TNF-α and IL-6 protein as ventilation time elapsed, establishing the concept of translocation of proinflammatory cytokine from the lung tissue to the circulation. Held et al. [71] used the same isolated model and found that high stretch and lipopolysaccharide were nearly indistinguishable in terms of their effects on lung nuclear factor-κB (NF-κB) activation and the release of chemokines and cytokines into the perfusate. As lipopolysaccharide is known to elicit the inflammation *via* NF-κB activation, they concluded that NF-κB activated by the high stretch is associated with the translocation of chemokines and cytokines [71]. Using *in vivo* saline-lavaged rabbits, Murphy et al. [72] demonstrated that an adverse ventilatory strategy caused pulmonary-to-systemic translocation of endotoxin. They also found that plasma endotoxin levels were higher in eventual non-survivors than survivors, suggesting that the poor outcome was associated with systemic spreading of endotoxin [72]. These findings are in line with the results of Chiumello et al. [8], who used *in vivo* acid-injured rats and demonstrated that high tidal volume ventilation without PEEP gave rise to the greater increases of TNF-α and MIP-2 in both of the BAL and plasma levels. It should be noted that both studies referred to the alveolar capillary stress failure as the translocation mechanism, regardless of whether endotoxin or the cytokine is shifting compartments [8, 72].

Another potential mechanism whereby ventilator-induced lung injury might lead to MODS is translocation of intact bacteria from the airspaces into the circulation. Following the tracheal instillation of *Escherichia coli*, Nahum et al. [73] found that an adverse ventilatory strategy caused a higher incidence of bacteremia than the less injurious strategy. Using *in vivo* saline-lavaged newborn piglets, van Kaam et al. [74] intratracheally instilled Group B *streptococcus*, which is the leading cause of serious infections in human newborns, and induced severe pneumonia. They found that reducing atelectasis by means of exogenous surfactant and open lung ventilation with sufficient PEEP prevented bacterial translocation. However, given that the organisms responsible for the clinical ventilator-associated pneumonia are not usually detectable in the systemic circulation, it seems unlikely that bacterial translocation can account for the chief mechanism of ventilator-induced lung injury spreading to the systemic inflammation.

Injurious mechanical ventilation may induce distal organ dysfunction *via* circulating soluble factors, such as soluble Fas ligand. Imai et al. [75] ventilated *in vivo* acid-injured rabbits with injurious or protective ventilatory strategies. They found that the injurious ventilatory strategy led to the epithelial cell apoptosis in the kidney and small intestine. They also demonstrated that the induction of apoptosis was increased in the *in vitro* renal tubular cells incubated with plasma from rabbits treated with the injurious ventilatory strategy, suggesting that distal organ dysfunction could be caused, in part, by the circulating soluble factors [75].

Finally, recent experimental proof that lung-derived circulating soluble factors may be pathogenic in the development of VILI was provided in a series of experiments where injury was greater in the setting of recirculating (*vs.* non recirculating) lung perfusate, the assumption being that with recirculation any lung-derived factors would be concentrated [76]. In addition, in that report the exposure of perfusate derived from lungs that had been injured caused significant injury in previously healthy lungs ventilated with low tidal volumes, whereas exposure to the perfusate from un-injured

lungs was not injurious. Finally, 'injurious' perfusate decreased the integrity of cultured epithelial cells *in vitro*. The specific identity of the soluble mediators remains unknown but physico-chemical analysis indicates that the mediators are part-protein and part-lipid soluble.

Potential Targeted Therapy of Ventilator-Induced Lung Injury and Bronchopulmonary Dysplasia

To date, no targeted therapy has been shown to improve outcomes specifically in patients with ARDS, but a large body of literature indicates that pro-inflammatory cytokines play an important role in the development of ventilator-induced lung injury. The utilization of knockout and/or transgenic mice has contributed to the elucidation of molecular mechanisms of lung injury.

Lipopolysaccharide is known to initiate transcription of proinflammatory mediators *via* activation of the membrane bound Toll-like receptor 4 (TLR4), which when activated, initiates translocation of NF-κB into the nucleus. Such NF-κB translocation is also elicited by ventilatory stretch, resulting in the release of proinflammatory cytokines that appear to contribute to the pathogenesis of ventilator-induced lung injury [71]. The activation of NF-κB is associated with degradation of IκB-α, the transcription of which is upregulated by steroid [71]. TLR4-TRIF (a downstream protein of TLR) pathway was found to play a key role that controls the severity of ventilator-induced lung injury [77]. The importance of this pathway in the development of ventilator-induced lung injury was corroborated by Vaneker et al. who demonstrated that mechanical ventilation induced a TLR4-TRIF pathway dependent inflammatory response in healthy mice [78]. Recently, TAK-242, a novel TLR4 signal transduction inhibitor, showed potent therapeutic effects in an *Escherichia coli*-induced sepsis model [79]. These studies suggest that TLR4 may be a promising therapeutic target for ventilator-induced lung injury.

High-mobility group box 1 (HMGB1) protein is a DNA binding protein that stabilizes nucleosomes and facilitates transcription. HMGB1 has been demonstrated to participate in inflammatory processes, including delayed endotoxin lethality and acute lung injury [80]. HMGB1 can interact with both TLR2 and TLR4, and induce cellular activation and generate inflammatory responses that are similar to those initiated by lipopolysaccharide [81]. In a rabbit model of ventilator-induced lung injury, intratracheal administration of anti-HMGB1 antibody improved oxygenation, limited microvascular permeability and neutrophil influx into the alveolar lumen, and decreased concentrations of TNF-α in bronchoalveolar lavage fluid [82]. These studies suggest that HMGB1 may be an appropriate target in ventilator-induced lung injury.

Early growth response-1 (EGR1), a nuclear transcription factor, functions as a convergence point for many signaling pathways in inflammation and apoptosis [83]. *EGR1* gene may link several signaling pathways that are activated by extracellular stimuli, and through production of the EGR1 protein alter the expression of EGR1 target genes such as *Tissue Factor*, *Hsp70*, the *EGR1* gene itself, and *Ptges* that synthesizes the inflammatory prostaglandin E_2 (PGE_2). In a recent study performed by Ngiam et al. [84], EGR1 induced PGE_2 synthase that increased the synthesis of PGE_2, which worsened lung injury by activating pulmonary EP1 receptors; in addition, blockade of the EP1 receptors attenuated ventilator-induced lung injury.

Indirect acute lung injury (ALI) accounts for about 43 % of total ALI and is caused mainly by non-pulmonary sepsis and trauma [85]. Perl et al., using a mouse model of indirect ALI induced by successive exposure to hemorrhagic shock and cecal ligation and puncture, found that early activation of the Fas receptor on pulmonary epithelial cells took place [86]. The activated Fas receptor not only induced the onset of apoptosis but also triggered chemotactic/inflammatory responses [86]. Consequently, inhibiting Fas activation in lung epithelial cells may be a candidate therapy for mitigating the development of indirect ALI.

Treatment of neonatal rats with antiangiogenic agents, including fumagillin and thalidomide, decreased alveolarization and lung growth, resulting in similar lung histology as in BPD [87]. As mentioned above, VEGF is an essential angiogenic growth factor and decreased expression of VEGF and its receptors may contribute to the hypoplasia of pulmonary capillary development observed in new BPD. Kunig et al. demonstrated that recombinant human VEGF (rhVEGF) treatment enhanced alveolarization after hyperoxic lung injury in neonatal rats [88]. In their following study, however, systemic administration of rhVEGF transiently increased lung edema but enhanced lung structure after neonatal hyperoxic lung injury [89]. Indeed, VEGF may have diverse roles including that of permeability factor by promoting early lung edema after injury. Additionally, VEGF may have adverse effects on the development of retinopathy of prematurity [90]. These problems need to be resolved before the clinical application of VEGF treatment for BPD.

Increased pulmonary neuroendocrine cells containing bombesin-like peptides were observed in infants dying with BPD [91]. Bombesin-like peptides can induce macrophage activation and fibroblast proliferation, inhibit alveolarization, and cause bronchoconstriction. Subramaniam et al. demonstrated that blockade of bombesin-like peptides (with anti-bombesin antibody) improved alveolarization and angiogenesis in a baboon BPD model [92]. This blockade may provide a useful approach for preventive therapy of BPD in high-risk infants.

IL-1 is consistently increased in amniotic fluid with chorioamnionitis [93]. At present there are no selective

treatments for chorioamnionitis-associated fetal inflammation. Kallapur et al., using a fetal sheep model, demonstrated that blockade of IL-1 signaling (with recombinant human IL-1 receptor antagonist: rhIL-1ra) in the amniotic compartment inhibited fetal lung inflammation and simultaneously lung maturation in response to lipopolysaccharide-induced chorioamnionitis [94]. Combined with antenatal maternal glucocorticoids and postnatal surfactants, intraamniotic administration of rhIL-1ra may be useful for the prevention of a part of BPD which is associated with intrauterine infection.

Finally, a recent study reported that prolonged (12–24 h) ventilation in neonatal rats caused arrested alveolar development that was associated with increased expression (and nuclear localization) of Cdk cell-cycle inhibitor proteins, thus identifying a morphologic pattern of ventilator-induced developmental arrest and a potential molecular basis [95].

Conclusion

After numerous studies in both clinical and experimental settings, investigators have recommended the use of low tidal volume and high PEEP for the prevention of ventilator-induced lung injury. However, the optimal levels of PEEP and the associated tidal volume are still unresolved issues. Although the recruitment maneuver has been suggested as a pivotal issue in the lung protection, clinical studies of unselective application of higher *vs.* lower PEEP levels have demonstrated marginal advantages of higher levels of PEEP. One should consider the issue of recruitment maneuvers to be unresolved in the clinical context.

Pediatricians often reflect on the aphorism: 'Children are not small adults', and this holds true in the application of mechanical ventilation. Indeed, great caution should be exercised in the translation to pediatric practice of any recommendations that are based on adult studies. Several studies have made a breakthrough by showing that mechanical forces such as high stretch can induce biochemical mediators; however, a more integrated understanding of these mechanisms may require more studies elaborating on the spatial and temporal dimensions of mechanotransduction. Mechanical ventilation has greatly contributed to the decreasing mortality of the extremely premature infants, but has simultaneously increased the morbidity associated with BPD. Not only the inflammatory factors following the mechanical stress and strain, but also the angiogenic factors associated with the lung development appear to be involved in the progression of BPD. After survival, the presence of BPD used to be considered to be self-limited, but this belief is counter to the accumulating evidence of long-term sequelae.

The leading cause of death in ARDS patients is MODS rather than respiratory insufficiency, thus further studies are required to elucidate the mechanisms whereby a local pulmonary inflammation propagates into an inflammatory response in the systemic circulation and, ultimately, to distal organ dysfunction. The employment of genetically modified animals in the experimental studies has contributed to the elucidation of molecular mechanisms of acute lung injury, which may be useful for the establishment of the selective targeted therapy in the near future.

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Neonatal Lung Diseases

14

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Abstract

Lung diseases are one of the main causes of neonatal morbidity and mortality. The majority of them result from lung immaturity and difficulties in the transition from intrauterine to extrauterine life. Respiratory distress syndrome occurs primarily due to surfactant deficiency and is the most common cause of respiratory distress in the preterm infant, but can also be seen in infants born at term. Transient tachypnea of the newborn is a common cause of neonatal respiratory dysfunction and results from delayed absorption of fetal lung fluid. Bronchopulmonary dysplasia is a form of chronic lung disease which is today primarily seen in the most preterm infants and is characterized by the need for prolonged respiratory support and oxygen supplementation. Other lung diseases affecting the newborn infant include pneumonias, aspiration of meconium stained amniotic fluid and congenital anomalies. These conditions are sometimes further complicated by persistent pulmonary hypertension, which is more commonly seen in the term than the preterm infant. Advances in the management of lung diseases affecting the newborn infant have resulted in marked improvement in their survival. These therapies include the administration of pulmonary surfactant, the use of nitric oxide for persistent pulmonary hypertension and extracorporeal membrane oxygenation therapy. Advances in respiratory support have resulted in decreased ventilatory-induced lung injury and thus improved pulmonary outcome.

This chapter gives an overview of fetal lung development, neonatal respiratory physiology and the clinical presentation of respiratory dysfunction in the neonate. The etiology and pathophysiology of the most common neonatal lung diseases and their management are also discussed.

Keywords

Newborn • Preterm • Lung diseases • Respiratory distress syndrome • Persistent pulmonary hypertension of the newborn • Surfactant • Bronchopulmonary dysplasia • Congenital diaphragmatic hernia

Introduction

Respiratory diseases are one of the major causes of neonatal morbidity and mortality. The main causes of respiratory dysfunction in the neonate are delay in transition from intrauterine to extrauterine life and lung immaturity. Other causes include infections, aspiration of meconium stained amniotic fluid, and congenital anomalies. These conditions are sometimes further complicated by persistent pulmonary

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hypertension, which is more commonly seen in the term than the preterm infant. Neonates with respiratory distress should be monitored carefully and interventions performed in a timely manner, as they may deteriorate quickly if not provided with adequate support. This chapter provides an overview of fetal lung development, the principles of neonatal respiratory physiology as well as the clinical presentation of respiratory dysfunction in the neonate. The most common respiratory diseases in the term and preterm infant and their management are also discussed.

Lung Development

Fetal lung development is traditionally divided into five chronologic but overlapping stages of organogenesis [1]:

Embryonic stage (*weeks 3–7*). The airway first appears as an outpouching of the ventral surface of the primitive foregut, penetrating the thoracic mesoderm. The endoderm gives rise to the epithelial lining of the future airway, but other tissues of the lung and pleura develop from the mesoderm.

Pseudoglandular stage (*weeks 5–17*). Due to complex interaction between the epithelial cells and the surrounding mesenchyme the airway branches, forming the future tracheo-bronchial tree. During this stage of fetal lung development the airway resembles an exocrine gland, composed of branching tubules lined with columnar epithelium. The branching is completed at 16 weeks of gestation when 20–24 branches have been formed.

Canalicular stage (*weeks 16–26*). Further extension of the distal airway results in the formation of the future acini, the gas-exchanging unit of the lung. Initially the distal airway is lined by cuboidal cells, which subsequently differentiate into Type I and Type II alveolar epithelial cells. The surfactant containing lamellar bodies can be identified in the Type II cells around 24 weeks of gestation, 4–5 weeks before surfactant can be detected in the amniotic fluid. During the canalicular stage vascular canals, or capillaries, are being formed and due to progressive thinning of the extracellular matrix they approach the potential air spaces. Towards the end of the canalicular stage of lung development the still immature air-blood barrier is thin enough and the surface area large enough to allow adequate gas exchange necessary for survival.

Saccular stage (*weeks 24–38*). At this stage the most distal airway takes the form of sac-like structures. Secondary crests appear which divide each saccule into subsaccules or primitive alveoli, which have flattened epithelium and double capillary network. This results in a sudden increase in the inner surface area of the lung. By the end of this period the organization pattern of the gas-exchanging portion of the lung is complete.

Alveolar stage (*weeks 36–3 years post-term*). This last stage of lung development is marked by the formation of secondary alveolar septa which partition the saccules into true alveoli and by maturation of the alveolar-capillary membrane. The septa are initially relatively thick with a double capillary network on each side of a central core of connective tissue. The reconstruction of the saccules into a true alveolus consists of lengthening and thinning of the secondary septa, and fusion of the two capillary networks into one. This further increases the surface area of the lung available for gas exchange. Approximately 50 million alveoli are present at term gestation. The formation of alveoli continues after birth to reach the adult number of 300 million at 3 years of age.

Neonatal Respiratory Physiology

Lung Liquid

The potential air spaces of the lungs are filled with liquid during fetal life. The source of the lung liquid is active transport of chloride ions across the alveolar epithelium, followed by passive transport of sodium due to an ionic gradient and transfer of water due to an osmotic gradient [2]. Near term, the amount of lung liquid produced is 250–300 ml per day. Because of periodic adduction of the vocal cords the liquid is maintained under a pressure gradient across the larynx, which stretches the lung periodically and thus promotes normal lung growth. Prior to labor there is a progressive reduction in lung liquid production, and during labor the chloride transport ceases and the lung epithelium switches to active transport of sodium from the alveolus to the interstitium, reversing the transfer of water across the alveolar epithelium. This is enhanced by the catecholamine surge which normally occurs during labor, as activation of β-receptors stimulates sodium transfer across the alveolar epithelium. After birth, the clearance of liquid from the alveoli is enhanced by the rapid increase in oxygen tension, which further enhances sodium transport across the alveolar epithelium. The lung liquid accumulates in the interstitial space of the lung, particularly in the loose connective tissue of the perivascular areas, from where it is gradually removed into the pulmonary circulation and by the lymphatics over 4–6 h. Conditions which may delay normal clearance of lung liquid, such as Cesarean section without labor, can result in transient respiratory distress.

Pulmonary Vessels and Pulmonary Blood Flow

During fetal life, the vascular resistance in the pulmonary circulation is relatively high and the resistance in the

placental vascular bed is relatively low, resulting in higher blood pressure in the pulmonic than the systemic circulation. This causes shunting of blood away from the lungs through the foramen ovale and the ductus arteriosus. The high vascular resistance in the pulmonic circulation is mainly due to relative fetal hypoxia, to which the pulmonary arteries respond by constriction. After birth, upon the establishment of breathing, the vascular resistance in the pulmonary circulation normally decreases abruptly as the response to the activation of stretch receptors following lung inflation and the increase in partial pressure of oxygen of the blood, resulting in a marked increase in pulmonary blood flow. However, certain conditions such as hypoxia due to respiratory diseases and acidosis due to perinatal asphyxia can result in the persistence of high pulmonary vascular resistance, resulting in a vicious circle which can only be broken by appropriate respiratory support and other necessary therapeutic measures.

Collateral Airways

In the adult lung collateral channels connect the distal airways allowing ventilation distal to an obstructive airway, but anatomic evidence of collateral ventilation is not found until after infancy. Interalveolar channels (pores of Kohn) appear around 1–2 years of age and bronchiole-alveolar channels (canals of Lambert) appear around 6 years of age [3]. The lack of collateral airways poses the newly born infant presumably at risk for atelectasis or overinflation and consequent ventilation/perfusion (V/Q) mismatching.

Chest Wall and Respiratory Muscles

The neonatal diaphragm performs the majority of the work of breathing, and the main role of the intercostal muscles is to stabilize the compliant chest wall during inspiration. Paralysis of one or both of the hemidiaphragms in the neonate results in respiratory failure. If unilateral, plication of the paralyzed hemidiaphragm is usually enough for the infant to be able to breathe without respiratory support. However, infants with bilateral diaphragmatic paralysis usually require prolonged respiratory assistance.

The rib cage of the newborn is poorly mineralized which results in sternal retractions in the spontaneously breathing infant with decreased lung compliance, most commonly seen in the preterm infant. This increases the risk of atelectasis and V/Q mismatching. Furthermore, due to the distortion of the chest wall during inspiration a portion of the work of breathing is wasted, predisposing the infant to fatigue of the respiratory muscles, which may lead to respiratory failure.

Clinical Presentation of Respiratory Disorders in the Neonate

Tachypnea is defined as a respiratory rate greater than 60 breaths per minute in the newborn infant and usually indicates decreased lung compliance. By breathing rapidly with small tidal volumes the infant attempts to maintain normal minute ventilation, and thus normocarbia, with minimal work of breathing. Tachypnoea can also be seen in infants with metabolic acidosis without a lung disease, for example as the result of perinatal asphyxia.

Chest retractions are inward retractions of the soft portions of the chest wall, usually seen in the intercostal and subcostal regions. Sternal retractions may also occur due to the highly compliant costo-chondral joints in the newborn, especially in the preterm infant. Chest retractions indicate increased work of breathing due to decreased lung compliance or increased airway resistance.

Expiratory grunting is heard when the infant expires against adducted vocal cords, which raises intrathoracic pressure, resulting in higher residual lung volumes, which decreases intrapulmonary shunting and improves oxygenation. It occurs primarily in preterm infants with respiratory distress syndrome, but can also be seen in term infants.

Nasal flaring is enlargement of the nostrils during inspiration. By this the infant is able to decrease airway resistance to some extent and thus decrease the work of breathing.

Cyanosis is blue discoloration of the skin and mucous membranes because of increased amount of desaturated hemoglobin in the capillary bed. It is important to differentiate between central and peripheral cyanosis. Central cyanosis indicates low oxygen saturation of the arterial blood. It is manifested by discoloration of the mucous membranes of the mouth as well as the skin. Central cyanosis is usually caused by respiratory disease or structural heart disease. On the contrary, with peripheral cyanosis, arterial hemoglobin may have normal oxygen saturation, but oxygen saturation of hemoglobin in localized areas, such as hands and feet, is decreased. This occurs due to slow blood flow in these tissues, which results in increased oxygen extraction and thus increased amount of desaturated hemoglobin in the capillaries, causing visible cyanosis. Cyanosis of the hands and feet (acrocyanosis) is a common normal finding in the newborn during the first few days of life. For central cyanosis to be visible the amount of desaturated hemoglobin in arterial blood has to be at least 40–50 g/L. Therefore, central cyanosis will be detectable at relatively high arterial saturation in infants with high hemoglobin concentration, whereas central cyanosis will not be detected in anemic infants until their arterial oxygen saturation is relatively low.

Respiratory Monitoring of the Neonate

Respiratory monitoring of the sick neonate is critically important. Both invasive and noninvasive methods are available. Indwelling umbilical or peripheral artery catheters provide the best estimate of blood gas and pH levels, as well as continuous monitoring of blood pressure, whereas the benefits of continuous noninvasive monitoring include early detection of respiratory compromise, the avoidance of invasive procedures and less blood loss. As noninvasive monitoring may be less accurate under certain conditions, it may have to be confirmed by arterial blood sampling.

The umbilical vessels can be catheterized during the first few days of life. A No. 5 French polyvinylchloride catheter is most commonly used in the term infant and 3.5 French in the preterm infant. Appropriate positioning of the umbilical catheter is important. The tip of the umbilical arterial catheter should be at the level of the 6th–9th thoracic vertebrae (high position) or the 3rd–4th lumbar vertebrae (low position). The radial, ulnar and posterior tibial arteries are also frequently used for arterial canulation. Attempts should be made to prevent hyperoxia in the preterm infant, as it is an important risk factor for retinopathy of prematurity. Potential complications of indwelling arterial catheters include ischemic injuries as the result of thromboembolism, and infections.

Capillary blood gas measurements on blood obtained from a heel stick or a finger stick are usually a reliable estimate of arterial pH and $paCO_2$ measurements. However, partial pressure of oxygen in capillary blood is unreliable as it may either overestimate or underestimate paO_2. Measurements of venous blood can also be used as a somewhat less reliable estimate of arterial pH and $paCO_2$, but not paO_2.

Noninvasive methods of blood oxygen and carbon dioxide estimation include pulse oxymetry and transcutaneous blood gas monitoring. *Pulse oxymetry* estimates the fractional oxygen saturation (SpO_2) of hemoglobin in the blood. It is based on the principle that reduced hemoglobin absorbs more red light (wavelength 660 nm) than infrared light (wavelength 940 nm), and oxygenated hemoglobin absorbs more infrared than red. An oximeter probe consisting of a light-emitting diode and a photosensor is attached to a thin part of the body, usually a hand, foot, finger or a toe. An equal amount of red and infrared light is emitted, while the photosensor detects the ratio of red and infrared light transmitted through the tissues and thus the proportion of oxygenated and reduced hemoglobin, which is displaced as SpO_2. Disadvantages of pulse oxymetry include its limited ability to detect hyperoxia, as on the flat part of the oxygen-hemoglobin dissociation curve large changes in arterial paO_2 result in only small changes in SpO_2.

Inspired oxygen is usually adjusted to maintain SpO_2 between 93 and 98 % in term infants. In preterm infants SpO_2 is usually maintained lower because of their risk of developing retinopathy of prematurity (ROP). However, the optimal SpO_2 range for preterm infants has not been determined [4]. A recent large randomized study on infants born at less than 28 weeks of gestation revealed that maintaining SpO_2 between 85 and 89 % resulted in lower incidence of ROP but higher mortality rate at 36 weeks postmenstrual age than in those infants where SpO_2 was maintained between 91 and 95 % [5]. Therefore, until more data become available it may be reasonable to target SpO_2 between 89 and 93 % in preterm infants.

Transcutaneous blood gas monitors provide monitoring of both oxygen ($TcpO_2$) and carbon dioxide ($TcpCO_2$). It consists of two electrodes which usually are combined into a single device. To optimize the correlation between the transcutaneous and arterial pO_2 and pCO_2 measurements the skin surface is usually heated to 43.5–44.5 °C, which results in vasodilation and increased skin blood perfusion. This requires that the sensor must be relocated every 2–4 h to minimize the risk of skin burn. However, in the preterm infant excellent correlation of arterial and $TcpCO_2$ may be obtained at lower electrode temperatures (40 °C), with decreased risk of skin burns [6].

Continuous end-tidal CO_2 measurements can be used for detecting abnormal arterial pCO_2 values in ventilated neonates. However, due to relatively large deadspace they are considered less precise than $TcpCO_2$ measurements for that purpose, especially in preterm infants [7]. On the contrary, end-tidal CO_2 measurements are more accurate than transcutaneous monitoring in any older age group.

Respiratory Diseases of the Neonate

Respiratory Distress Syndrome

Respiratory distress syndrome (RDS), previously called hyaline membrane disease, is a clinical entity which occurs due to lack of pulmonary surfactant. It occurs most commonly in preterm infants and is one of the leading causes of neonatal morbidity and mortality (Table 14.1). The incidence of RDS is inversely related to gestational age. The incidence is approximately 50 % in infants born between 26 and 28 weeks of gestation and decreases with advanced gestational age to be less than 1 % in term infants [8]. Besides prematurity, other risk factors for RDS include maternal diabetes with poor metabolic control, antepartum hemorrhage, second twin, perinatal asphyxia, male sex and Cesarean delivery without labor.

RDS develops because of pulmonary immaturity, primarily surfactant deficiency. Pulmonary surfactant is a complex

Table 14.1 Classification of respiratory disorders in the neonate

Disorders affecting primarily the preterm infant	
Respiratory distress syndrome	Laryngeal cysts and laryngocele
Apnea of prematurity	Laryngeal cleft, webs and atresia
Bronchopulmonary dysplasia	Tracheal strictures and cysts
Pneumonias	Tracheoesophageal fistula
Bacterial pneumonia	Tracheal vascular compression
Viral pneumonia	Hemangiomas
Fungal pneumonia	Encephalocele
Ureoplasma pneumonia	Thoracic cysts and tumors
Air leaks	Cystic adenomatoid malformation of the lung
Pneumothorax	Congenital cysts
Pneumomediastinum	Congenital lobar emphysema
Pulmonary interstitial emphysema	Sequestration
Aspirations	Congenital pulmonary lymphangiectasis
Meconium aspiration syndrome	Pulmonary alveolar proteinosis
Blood aspiration	Immobile cilia syndrome
Disorders affecting the pulmonary circulation	Neurogenic tumors
Persistent pulmonary hypertension	Thymoma
Alveolar-capillary dysplasia	Chest wall disorders
Pulmonary hemorrhage	Osteogenesis imperfecta
Diaphragmatic disorders	Achondrogenesis
Diaphragmatic hernia	Achondroplasia
Eventration of the diaphragm	Asphyxiating thoracic dystrophy
Diaphragmatic paralysis	Failure of sternal fusion
Agenesis of the diaphragm	Neuromuscular disorders
Fluid in the pleural spaces	Werdnig-Hoffmann disease
Chylothorax	Myopathies
Hydrothorax	Myasthenia gravis
Hemothorax	Spinal cord disorders
Airway disorders	Non-pulmonary causes of respiratory distress
Micrognathia	Acidosis
Macroglossia	Ascites
Choanal atresia	Congestive heart failure
Vocal cord paralysis	Congenital heart disease
Subglottic stenosis	Polycytemia
Laryngomalacia	Hypothermia
Tracheomalacia	Hyperthermia
Cystic hygroma	Hypoglycemia
Thoroglossal duct cyst	Intracranial hemorrhage
	Other
	Pulmonary hypoplasia
	Surfactant protein B deficiency
	Surfactant protein C deficiency

mixture of phospholipids and proteins produced by the type II alveolar cells and stored as lamellar bodies. Surfactant phospholipids form a monolayer at the gas-liquid interface on the inner surface of the alveoli, thus reducing the surface tension in the alveolar wall and decreasing the tendency of the alveoli to collapse during expiration. The main function of the surfactant proteins is to enhance the dispersion of the phospholipids on the alveolar surface. Surfactant deficiency results in alveolar collapse, microatelectasis, decreased lung compliance and low functional residual capacity. This results in increased work of breathing and ventilation-perfusion mismatching, causing arterial hypoxemia. In the most premature infants, structural immaturity of the lungs contributes to the respiratory insufficiency in RDS.

Infants with RDS develop respiratory distress shortly after birth, which typically progresses with a peak severity at 48–72 h. As the disease progresses oxygen requirement increases, sometimes associated with signs of fatigue, such

as apneas. Radiographs typically show low lung volume, air bronchograms, fine granular densities and frequently increased lung fluid. Blood gas analysis may reveal hypoxemia and usually various degrees of hypercarbia and acidosis.

The mainstays of therapy for infants with RDS are oxygen supplementation, assisted ventilation and surfactant replacement. Oxygen is commonly given to spontaneously breathing infants by oxygen supplementation of the air in their incubators or through oxygen hoods. Continuous positive airway pressure (CPAP) is usually provided via nasal prongs and is considered to decrease alveolar collapse and thus decrease the need for supplemental oxygen and the need for mechanical ventilation. Mechanical ventilation is most commonly initiated if the infant requires more than 60 % oxygen with or without CPAP to maintain adequate oxygenation (SO_2 >90 %), or if it develops considerable respiratory acidosis (pH <7.25). Most infants requiring mechanical ventilation can be managed with conventional ventilation, but high frequency ventilation (HFV) may be superior in infants with severe RDS [9]. Early use of HFV in very-low-birthweight infants may modestly reduce their risk of developing bronchopulmonary dysplasia, compared to conventional ventilation [10].

Surfactant replacement is usually provided to infants who require mechanical ventilation for RDS. It improves static lung compliance, improves oxygenation, facilitates the weaning from the ventilator, decreases the risk of pneumothorax and improves survival. Potential complications of surfactant administration are hypotension, hypoxia or bradycardia during administration, blockage of the endotracheal tube or airways, and pulmonary hemorrhage.

Complications of RDS include pneumothorax, persistence of the ductus arteriosus, intracranial hemorrhage and bronchopulmonary dysplasia.

The most premature infants are vulnerable and their resuscitation and initial stabilization after birth requires good skills and coordination between medical personals. It is believed that the care that these infants receive in the delivery room and during the first few hours after birth may have a considerable impact on their long-term outcome. Ventilation with high inflation pressures during initial stabilization after birth has been shown to induce lung injury and blunt the response to surfactant administration in immature animals [11]. Therefore, during resuscitation of the preterm infant inflation pressures should be limited to what is necessary to achieve improvement in heart rate or chest expansion [12]. This is usually achieved with pressures of 20–25 cm H_2O, although higher pressures may occasionally be required. Pressure regulated T-piece mechanical devices are commonly used for this purpose. By such device, the spontaneously breathing infant can also be provided with continuous positive airway pressure (CPAP), which compared to intubation has been shown to reduce the need of mechanical ventilation and surfactant use in infants at 25–28 weeks of gestation [13]. If available, blend of air and oxygen should preferably be used rather than 100 % oxygen as it decreases the risk of hyperoxia, which may be of concern in the preterm infant [14]. Pulse oxymetry is a convenient way of monitoring oxygenation of the infant in the delivery room and during its transport to the nursery [12].

Transient Tachypnea of the Newborn

Transient tachypnea of the newborn (TTN) is a common cause of respiratory difficulties in the immediate newborn period and is considered to be caused by decreased absorption of lung liquid. It is usually a mild and self-limiting disorder, typically seen in the full term infant, but can also occur in preterm infants. Risk factors include Cesarean section, induction of labor, prolonged labor, decreased gestational age, maternal diabetes and maternal asthma [15]. These infants typically develop respiratory distress immediately following birth with initial grunting, chest retractions and nasal flaring. As the grunting resolves, it is followed by tachypnea which may last from a few hours up to 2–3 days. The need for oxygen supplementation is usually minimal or none. These infants may have mild respiratory acidosis, especially if they are grunting. Chest radiographs characteristically show prominent perihilar streaking, representing fluid accumulation in perivascular tissues and engorged lymphatic vessels. This may cause compression on the bronchioles, resulting in air trapping and increased lung volumes with flattening of the diaphragms. There is typically fluid in interlobar fissures and frequently also pleural fluid. Alveolar fluid may appear as fluffy densities.

The management consists of close monitoring of the infants and oxygen supplementation as needed. Oxygen saturation should be maintained over 90 %. CPAP can be used to decrease the respiratory distress in the most symptomatic infants. Mechanical ventilation is rarely needed. Furosemide does not affect the clinical course. As TTN may be difficult to differentiate from pneumonia, most of these infants are evaluated for infection and treated with antibiotics pending definite diagnosis.

Meconium Aspiration Syndrome

Meconium staining of the amniotic fluid occurs in approximately 12 % of all deliveries. Although most infants born in meconium stained amniotic fluid are asymptomatic, aspiration of meconium may result in respiratory compromise, i.e. meconium aspiration syndrome (MAS), which today occurs in approximately 0.1–0.2 % of all deliveries [16].

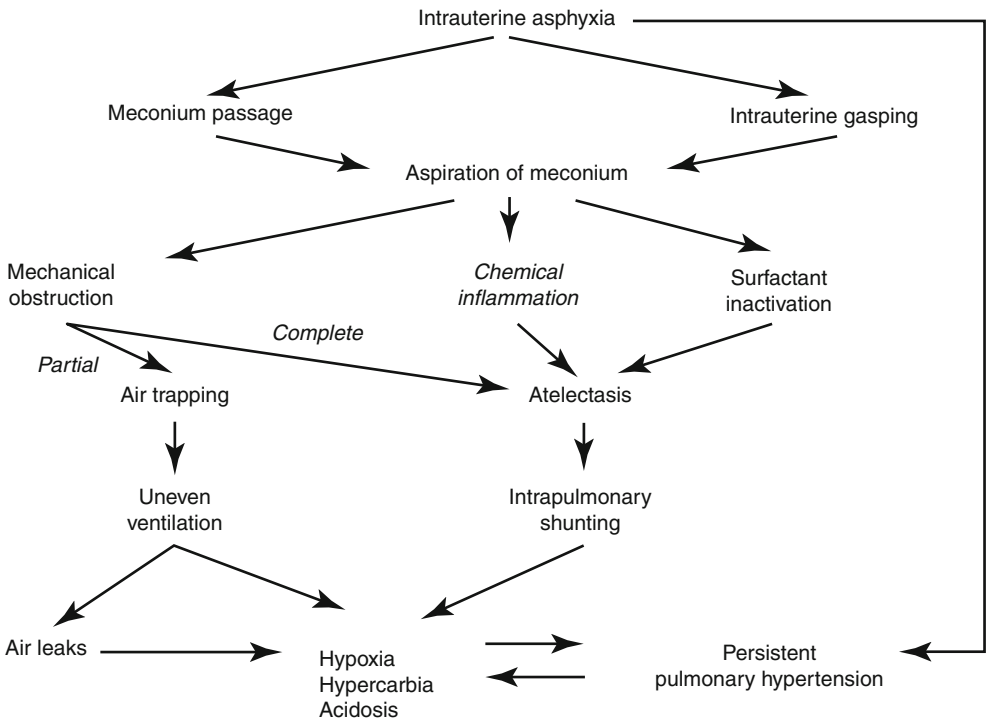


Fig. 14.1 Pathogenesis of meconium aspiration syndrome

Passing meconium in utero is usually associated with postmaturity, intrauterine asphyxia or both. As pregnancy advances the incidence of meconium-stained amniotic fluid increases and approximately one third of infants born at 42 weeks of gestation have passed meconium in utero. This probably reflects the maturation of peristalsis in the fetal intestine. Intrauterine asphyxia is associated with MAS. It has been shown experimentally that decreased blood flow to the fetal intestines results in increased peristalsis and relaxation of the anal sphincter, resulting in fetal passage of meconium. This may be exaggerated by the diving reflex, which shunts the blood from fetal viscera and other non-vital organs to the brain, heart and adrenal glands. Intrauterine asphyxia may also cause gasping of the fetus which can result in intrauterine aspiration of meconium. Furthermore, chronic fetal asphyxia is known to result in increased muscularization of the distal pulmonary vessels, making the newborn infant prone to develop persistent pulmonary hypertension (Fig. 14.1).

The respiratory dysfunction seen in MAS is mainly due to acute airway obstruction, decreased lung compliance, V/Q mismatching and persistent pulmonary hypertension. Meconium aspiration results in partial or complete obstruction of the proximal and smaller airways. Partial obstruction causes distal hyperinflation due to ball-valve mechanism, which results in increased anterior-posterior chest diameter, increased functional residual capacity and increased expiratory lung resistance. Hyperinflation may also result in pulmonary air leak. Complete obstruction of the airways causes distal atelectasis, resulting in decreased lung compliance and arterial hypoxia due to V/P mismatching. Meconium has also been shown to inactivate the pulmonary surfactant. This is frequently further complicated by persistent pulmonary hypertension, causing right-to-left shunting of the blood from the lungs, resulting in systemic hypoxemia.

Infants who develop MAS usually show signs of respiratory distress immediately following birth. The anterior-posterior diameter of the chest is frequently increased and chest auscultation reveals diffuse coarse rales. Radiographic findings typically consist of increased lung volumes, with patchy areas of atelectases and areas of focal hyperinflation. Pneumothorax or pneumomediastinum may also be seen.

MAS appears to be primarily an intrauterine event resulting from intrauterine hypoxia. Therefore, good antenatal care is critical for the prevention of MAS [16]. Suctioning of the oropharynx and nasopharynx of the infant at the perineum upon delivery of the head is no longer recommended [12]. However, if the infant is depressed it should be intubated immediately after birth and suctioned below the vocal cords. This is, however, not needed for the vigorous infant. Infants who develop respiratory distress should be monitored closely and hypoxia prevented. Some infants may require intubation and mechanical ventilation to maintain adequate oxygenation and ventilation. Surfactant administration should then be considered, as it has been shown to decrease the incidence of air leak and the need for ECMO [17]. High frequency ventilation may be superior to conventional ventilation in the most severe cases of MAS [18]. Infants who have evidence of persistent pulmonary hypertension should be managed with nitric oxide [19]. ECMO therapy may be salvaging for infants refractory to other modes of therapy.

Respiratory Dysfunction in Infants Born by Elective Cesarean Section

Infants born by elective Cesarean section without labor have been found to be at increased risk of developing respiratory dysfunction, which is inversely related to their gestational age [20]. This is most commonly a mild and transient respiratory disorder, but some infants develop severe respiratory illness. Three different factors appear to be involved in the pathogenesis of this disorder: (a) inadequate clearance of lung liquid resulting in transient tachypnea; (b) surfactant deficiency resulting in respiratory distress syndrome; and (c) persistent pulmonary hypertension. The process of normal labor facilitates the clearance of lung liquid from the airways, mainly due to increased secretions of catecholamines. When infants are born by Cesarean section without labor the catecholamine surge is minimal, predisposing the infants to transient tachypnea due to delayed clearance of lung liquid.

Some infants who are delivered by Cesarean section without labor develop respiratory distress syndrome as the result of inadequate production of pulmonary surfactant. This occurs if the Cesarean section is performed before the pulmonary surfactant system has reached full maturity. In order to decrease the risk of this iatrogenic disease The American College of Obstetricians and Gynecologists recommends that no elective delivery should be performed prior to 39 weeks of gestation [21]. Moreover, the Royal College of Obstetricians and Gynaecologists recommends that antenatal corticosteroids should be given to all women for whom an elective caesarean section is planned prior to 39 weeks of gestation [22].

Cesarean section without labor appears to pose the infant to increased risk of developing persistent pulmonary hypertension. These infants have been shown to have a slower fall in their pulmonary artery pressure than infants born by normal vaginal delivery [23]. They have also lower plasma concentrations of vasodilating prostaglandins in their cord blood [24]. Furthermore, these infants have been found to be at increased risk of requiring extracorporeal membrane oxygenation management which emphasizes the potential severity of this condition [25]. Therefore, infants who develop respiratory distress after elective Cesarean section should be monitored closely and hypoxia prevented, as it aggravates pulmonary hypertension and increases the risk of severe respiratory morbidity.

Neonatal Pneumonia

Pneumonia is a relatively common cause of respiratory distress in the neonatal period. These infections can be acquired transplacentally, but more commonly during the birth process causing early-onset pneumonia. Late-onset pneumonia is usually due to nosocomial infection. Neonatal pneumonias are most commonly caused by bacteria, but less commonly by viruses or fungi.

Listeria monocytogenes and *Treponema pallidum* can infect the fetus by transplacental passage. However, neonatal infections are more commonly caused by bacteria which colonize the birth canal and gain access to the uterus, causing chorioamnionitis and thus infect the fetus, especially after rupture of fetal membranes. Early-onset bacterial pneumonias can also be caused by aspiration of colonized amniotic fluid or vaginal secretions during passage through the birth canal. The bacteria which most commonly cause neonatal infections are Group B streptococci (GBS), *Escherichia coli*, *Klebsiella* and enterococci. The main risk factors for early-onset pneumonias are preterm birth, prolonged rupture of membranes (>24 h) and chorioamnionitis.

Group B streptococci are the most common cause of pneumonia in the immediate neonatal period. Approximately 25 % of women of childbearing age are colonized with Group B streptococci and the incidence of neonatal GBS infections is 1–4/1,000 births. Approximately one third of newborns who develop GBS infections are preterm and the mortality of those infants is considerably higher than in term infants. Intrapartum antibiotic prophylaxis to women who are colonized with GBS has been shown to decrease the risk of GBS infections in the neonate [26].

Infants who develop pneumonia show signs of respiratory distress shortly after birth. Radiographs may show infiltrates but radiographic finding are frequently nonspecific, and it may be difficult to differentiate pneumonia from RDS and TTN. Antibiotic therapy should be initiated without delay after appropriate cultures have been obtained. Antibiotics of choice are usually a penicillin and an aminoglycoside. Neonates with severe pneumonia may require cardiorespiratory support.

Nosocomial pneumonias can occur in infants who require intensive care, most commonly those who require prolonged respiratory support. Endotracheal intubation may give access for organisms to their lungs. Those bacteria which most commonly cause nosocomial pneumonias are staphylococcus aureus, staphylococcus epidermidis, pseudomonas aeruginosa and *E. Coli*. Preterm infants are at risk for pneumonia due to Candida albicans.

Viruses which can cause pneumonia in neonates include cytomegalovirus, herpes simplex virus, varicella zoster, human immunodeficiency virus, adenovirus, enteroviruses and influenza virus.

Persistent Pulmonary Hypertension

During fetal life, the resistance in the pulmonary circulation is relatively high, causing most of the right ventricular output

to bypass the lungs through the ductus arteriosus. The maintenance of high pulmonary vascular resistance (PVR) is facilitated by the low oxygen tension present during fetal life and release of the endogenous vasoconstrictors endothelin-1 and thromboxane. After birth, the onset of breathing and subsequent rise in arterial oxygen tension results in rapid decrease in PVR, mainly mediated through the release of the endogenous vasodilators nitric oxide and prostacyclin (PGI2), causing up to ten fold increase in pulmonary blood flow [27].

In newborn infants who have persistent pulmonary hypertension (PPHN) the PVR remains high. If pulmonary artery pressure exceeds systemic blood pressure, right-to-left shunting of blood occurs away from the pulmonary to the systemic circulation through the foramen ovale and ductus arteriosus, resulting in desaturation of the systemic blood.

The cause of increased PVR is commonly associated with other underlying diseases. Chronic intrauterine hypoxia, as the result of placental insufficiency, may lead to increased muscularization of the pulmonary arteries, making these infants prone to develop PPHN. These infants are frequently depressed at birth and may have passed meconium in utero. PPHN has also been associated with respiratory distress syndrome, pulmonary hypoplasia secondary to congenital diaphragmatic hernia or oligohydramnios, and sepsis. Primary PPHN, i.e. when the infants have hypoxemia in the absence of a recognizable parenchymal lung disease or structural heart disease, accounts for approximately 27 % of PPHN cases [27].

PPHN occurs primarily in term or late preterm infants. The hallmark of PPHN in newly born infants is cyanosis. The presence of associated respiratory distress is determined by the presence or absence of underlying lung disease. If oxygen saturation measured in the right arm is higher than oxygen saturation measured in a lower extremity it indicates right-to-left shunting of blood through the ductus arteriosus. The absence of ductal shunting does, however, not exclude PPHN as significant shunting often occurs through the foramen ovale, resulting in little or no difference in pre- and postductal oxygen saturations.

An echocardiography (ECHO) is essential in the evaluation of the infant with cyanosis. Congenital heart defects need to be excluded. In the absence of structural heart defects ECHO can be used to estimate the level of pulmonary hypertension and monitor response to treatment. Right to left shunting at the atrial and/or ductal levels is the hallmark of pulmonary arterial hypertension. The presence of tricuspid regurgitation (TR) provides a good estimate of the right ventricular pressure and thus pulmonary arterial pressure, in the absence of pulmonary artery stenosis. By using the modified Bernoulli equation for the right ventricular and right atrial pressure difference (peak pressure difference = 4 × (peak TR velocity)^2) measured with continuous Doppler, pulmonary artery pressure can be estimated by adding this difference to predicted right atrial pressure (0–10 mmHg). In those infants where TR or ductal shunting is not present, indirect indicators of elevated pulmonary pressures, such as size and function of the right ventricle, flattening of the interventricular septum, and blood flow profile in the pulmonary artery, can be helpful in making the diagnosis of PPHTN and to evaluate the response to treatment.

The infant with PPHN who requires supplemental oxygen to avoid cyanosis must be considered critically ill and should be managed carefully during diagnostic studies. Hypoxemia should be corrected as rapidly as possible and for that mechanical ventilation may be required. Oxygen should be administered to keep the infant well oxygenated (SO_2 >90 % or paO_2 60–100 mmHg). The ventilator strategy should target recruitment of atelectatic segments of the lungs, while avoiding overdistension as it may lead to lung injury and increased resistance to pulmonary blood flow. Infants who require mechanical ventilation should receive adequate sedation and analgesia, for example with midazolam and morphine infusions. Acidosis should be corrected by alkali administration, but hyperventilation should be avoided.

Inhaled nitric oxide (iNO) is a pulmonary vessel dilator which decreases pulmonary artery pressure and improves pulmonary blood flow. iNO diffuses rapidly into vascular smooth muscle cells where it increases the production of cyclic guanosine monophosphate (cGMP), which decreases the influx of Ca^{2+} and thus causes relaxation of the smooth muscle. In the circulation, iNO is rapidly inactivated by hemoglobin and therefore has negligible effects on systemic blood pressure. In clinical trials iNO has been shown to improve oxygenation and decrease the need for ECMO [28]. However, nearly 30 % of newborns with PPHN do not respond to iNO. The administration of iNO is usually well tolerated, but potential side effects are methemoglobinemia, exposure to nitrogen dioxide and bleeding due to platelet dysfunction.

Prostacyclin (PGI2), given as inhalation or a continuous infusion, has been used for infants who do not respond to iNO therapy [29]. PGI2 acts by increasing cyclic adenosine monophosphate (cAMP) in vascular smooth muscle cells which, like cGMP, decreases Ca^{2+} influx and thus causes smooth muscle relaxation. PGI2 has been shown to improve oxygenation in infants with PPHN, but no clinical trials have been performed to evaluate its efficacy. A PGI2 analogue, iloprost, can be given by intermittent nebulization.

Sildenafil, which increases intracellular cGMP by phosphodiesterase-5 inhibition, has been shown to improve oxygenation and decrease mortality in neonates with PPHT [30]. Milrinone, which increases intracellular cAMP by phosphodiasterase-3 inhibition, improves oxygenation in infants with severe PPHN, but no clinical trials have yet been performed to evaluate its efficacy in PPHN [31].

Extracorporeal membrane oxygenation (ECMO) is a therapeutic option for infants with protracted hypoxemia despite conventional therapy. The goal of this therapy is to maintain adequate tissue oxygenation and prevent irreversible lung injury while the pulmonary hypertension resolves. Commonly, ECMO is started when oxygen index (OI) is ≥40 if the infant is on a conventional ventilator and ≥60 if the infant is on a high frequency ventilator. Contraindications for ECMO therapy are intracranial hemorrhage, cerebral infarction and gestational age less than 34 weeks.

Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia (BPD) is the major form of chronic lung disease in neonates. It is mainly seen in the most preterm infants who require prolonged respiratory support and oxygen therapy due to lung immaturity. Today, BPD is most commonly defined as requirement for oxygen supplementation beyond 36 weeks postmenstrual age in an infant who is at least 28 days old [32]. The incidence of BPD is inversely related to gestational age, and a recent study revealed the incidence of BPD in infants born at 22–28 weeks gestation to be 42 % [33].

In 1967 Northway et al. described BPD in a group of moderately preterm infants born in late saccular stage of lung development, who had received prolonged respiratory support with high concentrations of supplemental oxygen [34]. These infants had evolving radiographic pattern of lung injury, and a histology characterized by interstitial fibrosis, regional hyperinflation alternating with regions of atelectasis, and airway abnormalities, including squamous metaplasia and excessive muscularization. This disease was considered to be caused by lung injury as the result of prolonged positive pressure ventilation and oxygen toxicity. Because of more general use of prenatal steroids for pregnant women with imminent parturition at <34 weeks of gestation, the introduction of surfactant therapy in the late 1980s and advances in respiratory management, the classical form or "old" BPD described by Northway et al. is infrequently seen today. However, these and other advances in maternal and neonatal care have resulted in a marked increase in survival of very low birth weight infants who, due to their immaturity, are prone to developing a new form of chronic lung disease, so-called "new" BPD.

"New" BPD is characterized by a histological pattern consistent with a disruption of lung organogenesis at the late canalicular and early saccular stages of lung development. Specifically, there is an arrest of alveolar septation resulting in decreased number of alveoli which become abnormally large, and altered vascular development resulting in decreased arterial count. This occurs due to several factors during fetal and neonatal life which are injurious to the immature lung and alter the highly integrated morphogenic program of lung development. These injuries include fetal and neonatal infections, oxygen toxicity, ventilatory induced lung injury, nutritional deficiencies, and possibly genetic susceptibility.

The main clinical findings in infants with BPD are tachypnea and mild to severe chest retractions. Chest auscultation may reveal mild wheezing and scattered rales. Anteroposterior diameter of the chest may be increased, indicating lung hyperinflation. Hypercapnia is common.

Chest radiographs initially show diffuse haziness reflecting inflammation and edema. Areas of atelectasis alternating with areas of hyperinflation due to air trapping may be seen, as the disease evolves. Hyperinflation and even cyst formation is seen in infants with the most severe form of BPD.

Therapeutic modalities which have been shown to decrease the incidence of BPD include lung protection by early use of CPAP, the use of synchronized nasal intermittent positive pressure ventilation, vitamin A administration and the use of caffeine [35].

The management of BPD is mainly supportive. Oxygen supplementation is needed to prevent hypoxemia, most commonly given through a nasal cannula in the spontaneously breathing infant. Adequate nutritional support is important as the nutritional requirements of infants with BPD may be increased. Diuretics are frequently used in an attempt to decrease pulmonary edema and improve lung function, although their use is not supported by clinical trials [36]. Furosemide or the combination of chlorothiazides and spironolactone is most frequently used. For the same purpose, fluid administration is frequently restricted to 130–150 ml/kg/day by providing the infants with high-caloric formulas. Bronchodilators have been shown to decrease the airway resistance in some infants with BPD, but their routine use is not warranted [37]. The administration of postnatal systemic steroids decreases oxygen requirements and improves lung function in infants with established BPD, and facilitates their weaning from a respirator. However, because of a concern about long term effects associated with their use, including neurodevelopmental impairment, their routine use for this purpose is not recommend and should be reserved for infants with the most severe form of the disease [38]. Inhaled steroids may facilitate extubation, but they have not been shown to reduce the incidence of BPD [39].

Infants with BPD are at risk of developing pulmonary artery hypertension, which may progress to cor pulmonale [40]. Maintaining adequate oxygenation in infants with established BPD is important in the prevention and treatment of pulmonary hypertension and cor pulmonale. Regular cardiac evaluations should be done in infants with severe BPD, including echocardiograms and electrocardiograms.

Pulmonary function tests on infants with BPD have revealed decreased airway conductance, increased airway

resistance and increased residual lung volume/total lung volume ratio, compared to term and preterm infants without BPD [41]. They are more frequently hospitalized during the first 2 years of life, most commonly due to reactive airway disease, pneumonias and worsening BPD [42]. Bronchiolitis due to respiratory syncytial virus can be detrimental to these infants.

Very low birth weight (VLBW) infants with BPD are at greater risk of motor skill impairment, as well as cognitive function and language delay, than VLBW infants without BPD [43].

Apnea of Prematurity

Clinically significant apnea is defined as a cessation of breathing lasting for 20 s or more, or a respiratory pause of shorter duration which is associated with cyanosis, bradycardia or both. Apneas are most common in preterm infants. They are seen in 25 % of infants with birth weight less than 2,500 g and in more than 80 % of infants with birth weight less than 1,000 g [44]. Apneas in preterm infants are presumed to be caused by immaturity of respiratory control. Less commonly it is caused by a more serious condition, such as sepsis, seizures, hypoglycemia, intracranial hemorrhage, or maternal drug ingestion. Apnea in a term infant always requires a full evaluation to determine its cause.

Apnea of prematurity can be categorized as central, obstructive, or both (mixed apnea) [45].

Central apnea is thought to be due to immaturity of the respiratory center in the brainstem. Preterm infants have reduced ventilatory response to partial pressure of carbon dioxide, which improves progressively with advanced gestational age.

In obstructive apnea there is increased resistance to airflow in the upper airway due to hypotonia of the pharyngeal muscles, malpositioning of the head (especially flexion), or secretions in the upper airway. The diaphragm of the preterm infant may contract before the increase in tone in the muscles of the upper airway, which normally occurs during inspiration, predisposing the infant to obstructive apnea. As the infant with obstructive apnea initially continues to have chest wall movements, the apnea may not be detected by the usual cardiorespiratory monitors until the infant stops fighting for breath, or cyanosis or bradycardia has occurred.

All infants less than 35 weeks of gestation should have continuous monitoring of respiration and heart rate. If apnea occurs, it is important to identify and treat any possible underlying causes. Most commonly the apneas respond to tactile stimulation. Suctioning of the upper airway and repositioning is indicated when obstruction is the likely cause. More severe apneas may require bag and mask ventilation. Methylxanthines (aminophylline, theophylline and caffeine) increase central respiratory drive and diaphragmatic contractility. They can be given either intravenously or orally. CPAP reduces the number of apneic events with an obstructive component, probably by preventing the pharyngeal airway from collapsing during inspiration. Severe apneic episodes may require endotracheal intubation and mechanical ventilation. Fortunately, the frequency and severity of apneic episodes decrease with increasing age and are infrequent beyond 37 weeks postmenstrual age. Respiratory monitoring in preterm infants with a history of apnea should be continued until at least one week after the last apneic episode without methylxanthine therapy.

Preterm infants younger than 46 weeks postmenstrual age may exhibit life-threatening apnea after general anesthesia. They should therefore have cardio-respiratory monitoring for at least 12 h following anesthesia [46].

Pulmonary Air Leaks

Pulmonary air leak refers to the collection of gas outside the airway of the lungs, including pneumothorax, pneumomediastinum, pneumopericardium, pulmonary interstitial emphysema (PIE), pneumoperitoneum and air embolus. If the smallest conducting airways and alveoli become overdistended, air can escape into the interstitium of the lung resulting in PIE. It can expand further along the perivascular spaces into the mediastinum, through the visceral pleura resulting in pneumothorax, or rarely into the pericardium, peritoneum or subcutaneous tissues. When pneumothorax develops the lung on the affected side collapses to various degree and if the air is under pressure (tension pneumothorax) the mediastinum shifts to the other side, which may decrease venous return to the heart and thus impair cardiac output.

Spontaneous pneumothorax occurs immediately after birth in otherwise healthy infants after 1 % of vaginal deliveries and 1.5 % of Cesarean sections. The high negative intrapleural pressure required to inflate the lungs during the first breath results in rupture of the surface of one or both lungs. Although many of these infants are asymptomatic, some develop considerable respiratory distress. Resuscitation with positive-pressure ventilation increases the risk of pneumothorax. Other risk factors include surfactant deficiency, meconium aspiration and lung hypoplasia. Mechanical ventilation increases the risk of pneumothorax, especially when high inflation pressures are used. Surfactant administration markedly reduces the incidence of pulmonary air leak in ventilated infants with RDS.

Infants with tension pneumothorax frequently have sudden deterioration and exhibit signs of severe respiratory distress with cyanosis. Other clinical findings include asymmetrical chest expansion, asymmetrical breath sounds, signs

of poor peripheral perfusion and even weak peripheral pulses. The heart sounds may be shifted from the affected side and deviation of the trachea can be noted. Rapid diagnosis can be made by transillumination of the chest, but the diagnosis is confirmed by a chest radiograph [47].

Term infants who develop spontaneous pneumothorax can usually be managed by close observation and oxygen administration as needed until the pneumothorax resolves. However, infants with tension pneumothorax usually need to be managed without delay by aspiration or drainage of the air. This can be done by puncture with a needle in the second intercostal space in the midclavicular line or by insertion of a chest tube in the sixth intercostal space in the midaxillary line. Pneumomediastinum usually is of little clinical importance and does not need to be drained. Pneumopericardium usually causes life-threatening cardiac tamponade. It should be managed by needle aspiration via the subxiphoid route. If air accumulates, pericardial tube placement and drainage may be necessary.

PIE is most commonly seen in infants with RDS who are managed with mechanical ventilation or CPAP. Diffuse PIE usually results in lung overinflation, and if unilateral it causes deviation of the mediastinum to the other side and compression of the contralateral lung, which may result in the formation of atelectases. These infants should preferably be placed on the ipsilateral side, as it causes the heart and other mediastinal structures to press on the lung which may halter further overexpansion. Severe unilateral PIE can also be managed by selectively intubating the more normal lung. High frequency ventilation has been shown to be a successful means of ventilating infants with PIE [48].

Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia (CDH) occurs due to a defect in the diaphragm, which allows herniation of the abdominal contents into the thorax. The defect is on the left side in 85 % of cases, at the posterolateral lumbocostal triangle (Bochdalek's hernia). CDH occurs in approximately 1 of every 3,000 life births and is associated with considerable morbidity and mortality. If the herniation occurs early in fetal life it is associated with various degrees of pulmonary hypoplasia. The lung on the affected side is small, there is a reduction in the number and generations of bronchi, the alveolar septa are thickened and the architecture of the respiratory acini is abnormal. The number of pulmonary vessels is reduced, the media and adventitia of the arteries are thickened, and there is an increase in the medial muscle layer of pulmonary arterioles at the acinar level, which results in increased resistance to blood flow in the pulmonary circulation. This poses the infant with CDH at considerable risk for pulmonary hypertension. Pulmonary hypoplasia of a milder degree is usually also seen on the contralateral side.

Today, infants born with CHD have frequently been diagnosed prenatally by ultrasound. The observed/expected lung-to-head ratio, evaluated by fetal ultrasound, has been used to estimate the degree of pulmonary hypoplasia and has been shown to be a predictor of neonatal outcome [49]. In addition, the intrathoracic herniation of the liver is associated with worse prognosis [50].

Infants with CDH and pulmonary hypoplasia present with respiratory distress shortly after birth. The chest is barrel shaped and the abdomen is scaphoid. Breath sounds are absent on the affected side and the heart sounds are usually displaced. These infants have various degrees of arterial hypoxemia, hypercarbia and acidosis. Infants who have minimal or no pulmonary hypoplasia may be asymptomatic at birth, but develop respiratory distress later, when normal accumulation of air in the stomach and intestines progressively compresses the intrathoracic organs.

Upon delivery the infant with respiratory distress should be intubated without delay and a large (preferably 10 French) orogastric or nasogastric tube should be placed to decompress air from the stomach. Ventilation with a mask should be avoided as it may result in further distention of the stomach and intestines. Initial respiratory support should preferably be provided by a pressure regulated device and peak inspiratory pressures limited to 25 cm H_2O. The infant should be sedated, but paralysis avoided as it may decrease tidal volume and lung compliance in infants with CHD and most infants with CDH can be managed successfully without neuromuscular blockage [51, 52].

During mechanical ventilation preductal SO_2 should be monitored, as it indicates cerebral oxygenation. The goal should be to keep preductal $SO_2 \geq 85$ %, pCO_2 40–60 mmHg and pH > 7.25 [53, 54]. Low inflation pressures with rapid rates should be provided to avoid ventilatory induced lung injury. PIP should be limited to ≤25 cm H_2O. If inflating pressures of >25 cm H_2O are needed, high frequency ventilation (HFV) should be initiated. As CDH does not represent a recruitable lung disease and attempts to use high mean airway pressure are likely to cause pulmonary damage, mean airway pressures higher than 14–16 cm H_2O should be avoided [53].

If echocardiogram shows evidence of persistent pulmonary hypertension or if pre- to postductal SO_2 gradient is ≥10 % the management with iNO (20 ppm) should be considered [55]. However, iNO has not been shown to decrease mortality or the need for ECMO in CDH. Other pulmonary vasodilators which have been used in CDH include prostacyclin, dipyridamole and sildenafil. Infants with evidence of right sided heart failure due to high pulmonary vascular resistance can be managed with prostaglandin E1 (PGE1) infusion in order to maintain the patency of the ductus

arteriosus and thus decrease the strain on the right ventricle [53].

Some infants with CDH have decreased left ventricular (LV) size and/or function. This may aggravate pulmonary hypertension, as the result of increased venous pressure in the pulmonary circulation. Severe LV dysfunction may lead to dependence on the right ventricle for adequate systemic perfusion. In this situation, use of PGE1 to maintain ductal patency and thus enhance the right ventricular contribution to systemic blood flow may be helpful. Milrinone may also be of value by enhancing LV performance and decreasing LV afterload [55].

ECMO therapy should be considered for infants whose preductal SO_2 cannot been maintained ≥85 % in spite of optimal ventilatory and pharmacological support. However, infants with severe pulmonary hypoplasia incompatible with survival can obviously not be salvaged with ECMO therapy.

Surgical closure of the defect in the diaphragm is the definitive treatment of CDH. However, surgery should be delayed until cardiopulmonary stabilization has been achieved. There is no general consensus as to when this stability is achieved, but it may take several days after delivery.

Conclusion

Advances in respiratory management of the newborn over the past few decades have resulted in marked decrease in their mortality and morbidity, mainly in the preterm infant but also in infants born at term. These advances include the administration of pulmonary surfactant, prenatal use of corticosteroids, the introduction of nitric oxide for persistent pulmonary hypertension and ECMO therapy. Moreover, improvements in respiratory support have resulted in decreased ventilatory-induced lung injury. Further knowledge in pulmonary biology and the mechanism of lung injury is needed for continuing advances in respiratory management of the newborn infant. Guidelines for optimal oxygenation and ventilation targeting in the preterm infants need to be developed, as well as disease specific approach to ventilator management in the term and preterm infant. Ongoing search for new knowledge in this field holds promise for further advances in neonatal respiratory care and improved outcome of neonates with respiratory failure.

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Pulmonary Hypertension

15

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Abstract

Neonates, infants, and children may present to critical care settings primarily due to pulmonary hypertension, or pulmonary hypertension may complicate the course of another illness. In advanced pulmonary hypertension, progressive pulmonary vascular functional and structural changes ultimately cause increased pulmonary vascular impedance, increased right ventricular afterload, right ventricular failure, and death. In addition, in the setting of certain critical illnesses severe pulmonary hypertension can develop rapidly (i.e. pulmonary hypertensive crisis) or pulmonary vascular dysfunction can complicate the course, even in the absence of preexisting frank pulmonary hypertension. Management includes: the prevention and/or treatment of active pulmonary vasoconstriction, the support of right ventricular function, and treatment of the underlying disease, if possible. Most available therapies that target the pulmonary vasculature promote vascular relaxation by augmenting or inhibiting factors, or mediators of their downstream signaling cascades, that originate in the pulmonary vascular endothelium. These pathways include: nitric-oxide-cGMP, prostacyclin, and endothelin-1. This chapter will provide a brief overview of the disease processes associated with pulmonary hypertension, review the key pathophysiologic principles, and describe a general therapeutic approach, with an emphasis on the critical care setting.

Introduction

Pulmonary hypertension (PH) is defined as a mean pulmonary artery pressure (PAP) of greater than or equal to 25 mmHg. This simple definition belies the complexity and variety of pathophysiologic situations that can cause PH in critically ill pediatric patients. Moreover, pulmonary vascular dysfunction can complicate the course of patients before the definition of PH is satisfied. This chapter will provide a brief overview of the disease processes associated with PH, review the key pathophysiologic principles, and describe a general therapeutic approach, with an emphasis on the critical care setting.

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Clinical Classification and Etiology

Over the past 40 years, clinical classification schemes have evolved in order to keep pace with the expanding number of disease processes identified to be associated with PH. The initial classification endorsed by the World Health Organization in 1973 divided PH into only two categories – primary and secondary PH. The most recent classification, which followed the 5th World Symposium on PH in 2013, divided PH into 5 groups, with 28 subgroups (Table 15.1) [1].

The prevalence of PH in pediatric patients is not known precisely. A French registry estimated the prevalence of PH to be 3.7 cases/million [2]. In that cohort, the majority (60 %) had idiopathic PH, 24 % had PH associated with congenital heart disease, and 10 % had familial PH [2]. An earlier report from the UK Pulmonary Hypertension Service for Children from 2001 to 2006 described 216 children with PH [3]. In that cohort, 28 % of the patients had idiopathic PH, 31 % had Eisenmenger physiology, 30 % had postoperative PH, 19 %

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Table 15.1 Clinical classification of pulmonary hypertension[1]

1. Pulmonary arterial hypertension (PAH)
1.1 Idiopathic PAH
1.2 Heritable
1.2.1 BMPR2
1.2.2 ALK1, ENG, SMAD9, CAV1, KCNK3
1.2.3 Unknown
1.3 Drug- and toxin-induced
1.4 Associated with
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart diseases
1.4.5 Schistosomiasis
1′. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
1″. Persistent pulmonary hypertension of the newborn (PPHN)
2. Pulmonary hypertension owing to left heart disease
2.1 Systolic dysfunction
2.2 Diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
3. Pulmonary hypertension associated with lung disease and/or hypoxemia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental abnormalities
4. Chronic thromboembolic pulmonary hypertension (CTEPH)
5. Pulmonary hypertension with unclear multifactorial mechanisms
5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Other: tumoral obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

[1]Adapted from Simonneau et al. [1]. With permission Elsevier

had PH associated with lung disease, 9 % had PH associated with miscellaneous disorders including HIV, bone marrow transplant and metabolic disease, 6 % had connective tissue disease, and 5 % had PH associated with complex unoperated or palliated congenital heart disease [3].

In the neonatal population, persistent pulmonary hypertension of the newborn (PPHN) warrants particular attention. The incidence of PPHN has been estimated to be approximately 2 per 1,000 live births [4]. PPHN may occur as a primary disorder of the fetal pulmonary circulation, or may be secondary to pathologic processes that cause a maladaptive transition from the fetal to neonatal circulation, such as sepsis, meconium aspiration or surfactant deficiency, or diseases that result in abnormalities of lung development, such as congenital diaphragmatic hernia [5]. Furthermore, PH is also associated with chronic lung disorders, including bronchopulmonary dysplasia [6–9].

It is important to recognize that patients may have significant pulmonary vascular disease without resting PAPs that meet the definition of PH [10]. For example, patients with congenital cardiac defects resulting in either increased pulmonary blood flow or impaired pulmonary venous drainage are prone to episodes of acute reactive pulmonary vasoconstriction, even when baseline PAPs are normal, that can result in catastrophic cardiopulmonary collapse, particularly in the postoperative period after exposure to cardiopulmonary bypass [11, 12]. In addition, certain disease processes can create pulmonary vascular disease in patients without preexisting abnormalities. For example, acute lung injury (ALI) is associated with pulmonary vascular endothelial injury, that can lead to vascular obstruction from intravascular thrombi, segmental atelectasis, and/or increased hypoxic pulmonary vasoconstriction [13, 14]. In some patients this can progress to PH and right ventricular failure [13–16]. In a

cohort of 23 children with ALI, Katz and colleagues found that PAP, pulmonary vascular resistance (PVR), and intrapulmonary shunt fractions were higher in non-survivors than in survivors [17]. More recently, Bull and colleagues evaluated the transpulmonary gradient (PAP – pulmonary capillary wedge pressure) and the PVR index in 475 and 470 (respectively) adult patients with ALI, and found that pulmonary vascular dysfunction was common and independently associated with poor outcome [18].

Diagnosis

Invasive and noninvasive techniques are used in order to diagnose, classify, and manage PH. Indwelling pulmonary artery catheters provide the most direct information, allowing for measurements of vascular pressures and cardiac output, and calculations of PVR. However, these catheters are used infrequently in critically ill pediatric patients, owing to size limitations and a lack of evidence that justifies their routine use.

Standard noninvasive studies include ECG and transthoracic echocardiography. The chief finding of interest on an ECG is evidence of right ventricular hypertrophy, although studies of patients with known PH have demonstrated that ECG alone lacks adequate sensitivity and specificity [19, 20].

The important data that may be obtained by echocardiography are: an estimate of systolic pulmonary arterial pressure (sPAP), right and left ventricular function, and cardiac anatomy, including determinations of chamber sizes, valvular function, and intracardiac shunts. In general, the sPAP is considered equivalent to the right ventricular systolic pressure (RVSP), unless there is right ventricular outflow tract obstruction or pulmonary valve stenosis. With the use of Doppler echocardiography, RVSP is estimated by determining the velocity of flow across the tricuspid valve during systole (tricuspid regurgitation jet, TR jet). A modification of the Bernoulli equation is used to estimate the RVSP, as follows: $\text{RVSP} = 4v^2 + \text{RAP}$, where v is the velocity of the TR jet in meters per second, and RAP is the right atrial pressure that is ether standardized or estimated by echocardiography. Multiple studies have validated estimates of sPAP determined by echocardiography using right-heart catheterization as confirmation [21–29]. In the absence of a measurable TR jet, parameters related to right ventricular outflow patterns and time intervals could be assessed by Doppler echocardiography with demonstrated accuracy compared to right-heart catheterization [30–33]. Recently, Arkles and colleagues found that the shape of the right ventricular Doppler envelope predicted hemodynamics and right heart function in adult PH patients [34]. The same group in an earlier study demonstrated that another echocardiographic estimate of right heart function, the tricuspid annular plane systolic excursion (TAPSE), was reflective of RV function when compared to right heart catheterization, and predicted survival in a cohort of 63 adult PH patients [35].

Cardiac catheterization remains the "gold standard" for the diagnosis of pulmonary hypertension. In addition to measuring PAP and PVR, cardiac catheterization can assess for intracardiac and extracardiac shunts, evaluate the pulmonary vascular anatomy (such as assessments of pulmonary venous abnormalities), and measure intracardiac pressures and cardiac output. Furthermore, pulmonary vascular reactivity testing is essential in selecting appropriate therapy. Indeed, children who are responsive to acute vasodilator testing (evoked by short acting agents such as inhaled nitric oxide (iNO) or iloprost, and intravenous epoprostenol or adenosine) which is defined as a ≥20 % decrease in PAP without a decrease in cardiac output, have been shown to have improved survival [36]. In addition, responsiveness to acute vasodilator testing predicts a favorable response to long-term therapies, such as calcium channel blockers [37, 38]. Conversely, calcium channel blockers may be deleterious for patients not responsive to vasodilator therapy, which exemplifies the value of this information [39, 40]. However, the timing of cardiac catheterization is often less clear. Indeed, catheterization may not be safe in critically ill patients suffering from severe acute PH.

Other diagnostic modalities include V/Q scan, CT scan, and MRI. Thromboembolic disease may present with pulmonary hypertension, and can be evaluated by V/Q scan. Several studies found that V/Q scanning was highly sensitive and specific in differentiating between idiopathic pulmonary hypertension and thromboembolic disease [41–43]. Contrast enhanced CT scan and/or MRI can help identify causes of pulmonary hypertension. Thromboembolic disease may be visualized by both modalities [44]. In addition, both imaging techniques can help identify other pulmonary pathology, such as interstitial disease, masses or vasculitis [45]. Findings on CT scan, such as pulmonary artery size, may contribute to the diagnosis of pulmonary hypertension, but do not replace Doppler echocardiography [46–49]. MRI can better delineate the cardiac anatomy, particularly chamber sizes and wall thickness, and MRI measurements can detect PH [50–52]. However, like CT, it is not clear that MRI offers significant advantages for diagnosis compared to Doppler echocardiography.

Pathophysiology

The pathophysiology of PH is multifactorial, complex, and incompletely understood. Various etiologies are associated with different particular mechanisms of disease, and a unifying construct has not been identified. However, several pathways common to a number of etiologies have been elucidated.

Hemodynamics and Morphology

From a hemodynamic standpoint, the morbidity and mortality associated with PH relates to increased right ventricular afterload. Over some period of time, compensatory mechanisms fail leading to right heart failure and death. It is important to note that the tempo of this clinical sequence varies across etiologies and individual patients. For example, right ventricular failure can develop rapidly in an infant following cardiac surgery (i.e. postoperative pulmonary hypertensive crisis) or may progress over years in other patients (e.g. Eisenmenger's).

Although right ventricular failure is a common potential endpoint for patients with PH, the location of the disease within the pulmonary vasculature depends upon the particular etiology. This is important when considering available therapies, since therapies appropriate for one group of patients may be deleterious for another. For example, iNO may be effective for patients suffering from acute pulmonary arteriolar constriction (e.g. pulmonary arterial hypertension (PAH); or PH owing to lung diseases and/or hypoxia), but may be entirely ineffective or even harmful in patients with pulmonary veno-occlusive disease or left heart failure [53–55].

Among the various PH groups, the mechanisms that result in increased right ventricular afterload are best understood in PAH. However, left heart disease is a common cause of PH, at least in adults [56]. In these patients, elevations in PAP relate to the transmission of elevated left atrial pressures. PVR may be normal. Although subsets of patients with left heart disease develop PAH, the associated mechanisms are less well understood and specific therapies for these patients have not been adequately studied [57–60]. Likewise, the pulmonary vascular changes associated with pulmonary veno-occlusive disease, pulmonary capillary hemangiomatosis, and congenital cardiac defects associated with pulmonary venous obstruction are less well studied, but the initial elevations in PAP relate to the backward transmission of pressure across the pulmonary vasculature, a situation that is not likely to benefit from pharmacologic pulmonary arteriolar dilation [61–63].

In PAH, increased right ventricular afterload relates to increased PVR and decreased compliance [64, 65]. Traditionally, hemodynamic assessments focused on measuring PAP and calculating PVR in PH patients, but more recent data have demonstrated value in measuring pulmonary vascular impedance, which combines resistance and compliance [66–68]. Increased PVR and decreased compliance in PAH relates to several basic mechanisms: increased pulmonary vascular reactivity, sustained pulmonary vasoconstriction, vascular remodeling, and luminal obstruction, due to *in situ* thrombosis and/or obstructive neointimal and plexiform lesions. In 1958, Heath and Edwards first described the histopathology of pulmonary vascular changes associated with congenital cardiac defects, and devised a six grade classification [69]. In their classification, changes progress from medial hypertrophy (Grade I) to intimal hyperplasia (Grade II), lumen occlusion (Grade III), arterial dilatation (Grade IV), angiomatoid formation (Grade V) and fibrinoid necrosis (Grade VI). Rabinovitch and colleagues followed with a morphometric classification system, based on lung biopsies taken from patients (aged 2 days to 30 years, with a median age of 1 year) with congenital cardiac defects [70]. This morphometric analysis showed progression of disturbed arterial growth and remodeling of the pulmonary vascular bed that correlated with the aberrant hemodynamic state of the pulmonary circulation. These changes were characterized by: (i) abnormal extension of vascular smooth muscle into small peripheral pulmonary arteries and mild medial hypertrophy of normally muscular arteries (Grade A), (ii) severe medial hypertrophy of normally muscular arteries (Grade B) and (ii) decreased pulmonary arterial number (Grade C) (Fig. 15.1). These vascular changes tend to progress in a stepwise fashion, and in severe disease obliterate portions of the pulmonary circulation at the level of the distal precapillary resistance arterioles. It is recognized that this sequence represents a pathologic framework, but that significant heterogeneity exists in terms of the precise pathology of PAH [71]. Furthermore, the degree to which these changes are reversible remains unclear, but likely depends in part upon the etiology, and may be influenced by age [72]. For example, in a seminal study, Rabinovitch and colleagues demonstrated that age at surgery, lung morphometric analysis, and the Heath-Edwards system grade predicted the reversibility of structural and functional pulmonary vascular changes secondary to congenital cardiac defects with increased pulmonary blood flow after surgical repair [73]. In addition, it must be remembered that even early reversible pulmonary vascular disease can contribute to morbidity and mortality. An important study by Celermajer and colleagues, for example, demonstrated that children with increased pulmonary blood flow due to intracardiac shunting had a selective impairment of endothelium-dependent pulmonary vascular relaxation, before their baseline PAP or PVR increased significantly [10].

In addition, extravascular forces also influence PAP and pulmonary vascular impedance. The relationship between intravascular pressures and alveolar pressures are well described [74, 75]. Pulmonary vessels are termed extra-alveolar, corner, or intra-alveolar. Extra-alveolar and corner vessels increase their size with lung expansion, due to radial traction placed on their walls by the lung parenchyma. Intra-alveolar vessels, however, are directly associated with alveoli and thus are subject to compression with alveolar expansion. This results in the classic U-shaped curve describing the relationship between PVR and lung inflation, wherein PVR is lowest at functional residual capacity, but increased with under- and over-inflation of the lung (Fig. 15.2). West further

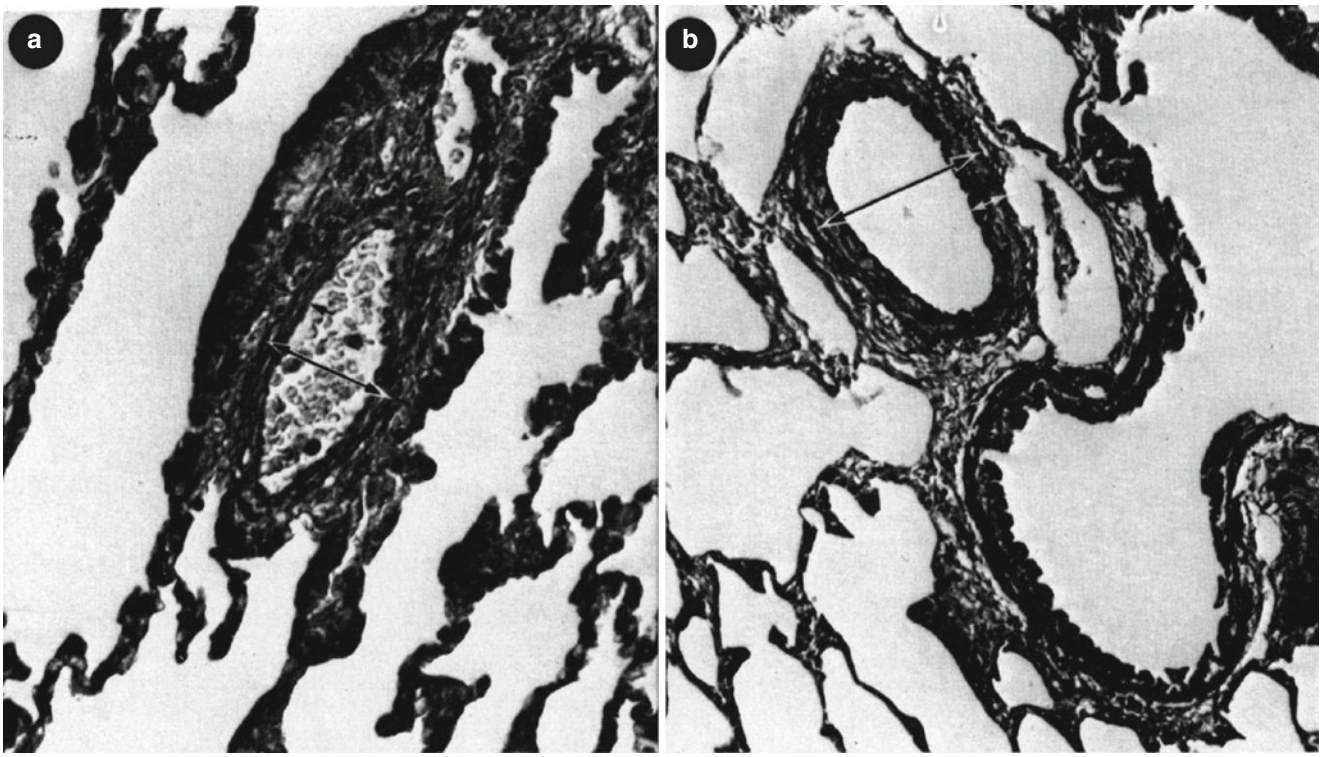


Fig. 15.1 Examples of morphometric analysis done on lung biopsies taken from a patient with a small ventricular septal defect (**a**) and a patient with an atrioventricular septal defect and pulmonary hypertension (**b**). A cross section from arteries at the same level are shown (Elastic Van Geison stain, magnification × 100). The wall thickness is increased in the patient with pulmonary hypertension (**b**). *Arrows* indicate wall thickness and external diameter (Reprinted from Rabinovitch et al. [70]. With permission from Wolter Kluwers Health.)

characterized this relationship by dividing the lung into three theoretical zones, which move down the lung from the apex to the base, in an upright subject. These zones are based on the relationship between pulmonary artery pressure (PAP), or inflow pressure, alveolar pressure (P_{av}), and pulmonary venous pressure (P_{ven}), or outflow pressure. In theory, no blood flows to zone I because P_{av} exceeds PAP, or $P_{av} > PAP > P_{ven}$. In this zone, intra-alveolar vessels are collapsed. Clinically, zone I conditions are negligible in a healthy lung, as pulmonary blood flow does occur at the apex. The fact that extra-alveolar and corner vessels are patent in this zone may help maintain blood flow. In Zone II, PAP exceeds P_{av} and blood flow occurs independent of outflow pressures, or $PAP > P_{av} > P_{ven}$. In this zone, blood flow increases down the lung, since PAP, but not P_{av}, is influenced by gravity. In Zone III, blood flow is dictated by the normal relationship of PAP to P_{ven}, or inflow pressure minus outflow pressure. In this zone, blood flow does not change dramatically down the lung as it does in zone II because gravity affects PAP and P_{ven} equally, or $PAP > P_{ven} > P_{av}$. Subsequently, an additional zone, zone IV, has been described where pulmonary blood flow decreases at the extreme base of the lung. This is due to the impact of the weight of the lung on the extra-alveolar and corner vessels, which causes compression thereby increasing resistance to flow; furthermore, the decrease in ventilation that occurs at the base results in areas of relative hypoxia with resultant hypoxic pulmonary vasoconstriction.

Under normal conditions, pulmonary blood flow is largely determined by zone III conditions. It is important to stress that these zones are conceptual and that in disease states a number of factors in addition to gravity influence V/Q matching; in addition, critically ill patients are rarely upright, but rather are supine or prone [76]. Particularly pertinent to pediatric critical care are the effects of positive pressure ventilation with high levels of peak end expiratory pressure. Increased alveolar pressure, may expand zone II and allow zone I conditions to be realized, resulting in mismatching of ventilation and perfusion and intrapulmonary shunting with hypoxia and hypercapnia. Likewise, pathology such as pneumothorax, hemothorax, pleural effusion, pneumonia and pulmonary edema, along with other conditions, can increase zone IV conditions within the lung. Finally, hypotension from multiple etiologies, such as hemorrhage, can expand zone I and zone II conditions.

Pulmonary Vascular Endothelium

It is now accepted that increased pulmonary vasoconstriction and impaired relaxation in PH is mediated in large part by

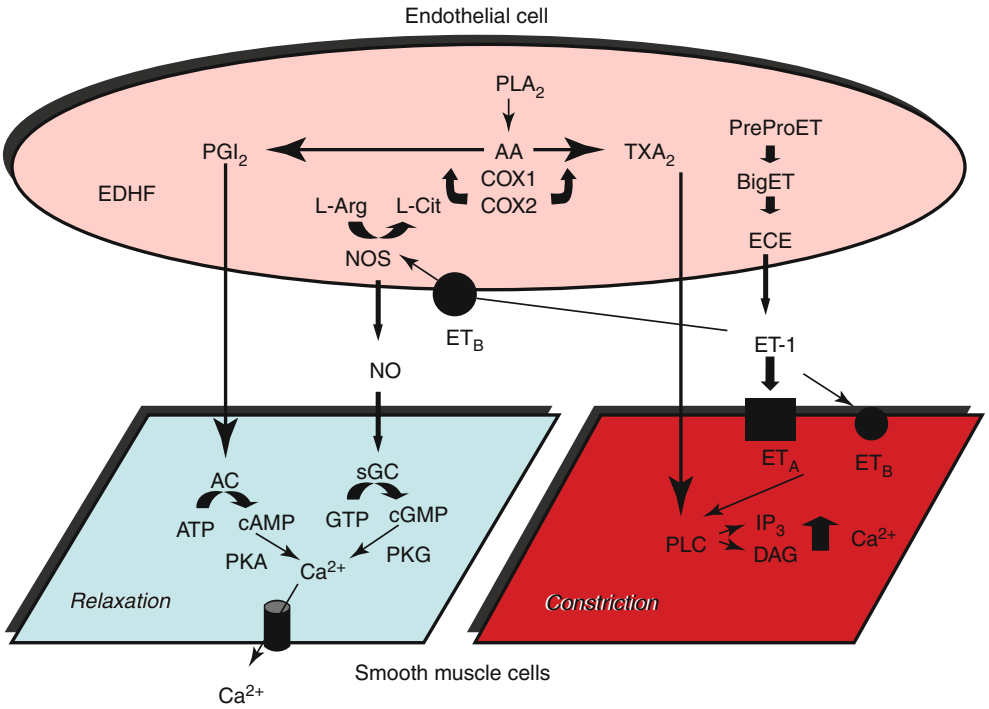


Fig. 15.2 A schematic of some endothelial derived factors. These factors may cause decreased (relaxation) and/or increased (constriction) smooth muscle cell contraction. *PLA2* phospholipase A2, *PGI2* prostaglandin I2, *AA* arachidonic acid, *TXA2* thromboxane A2, *ECE* endothelin converting enzyme, *L-Arg* L-arginine, *L-Cit* L-citrulline, *NOS* nitric oxide synthase, *ET-1* endothelin-1, *ETA* endothelin A receptor, *ETB* endothelin B receptor, *NO* nitric oxide, *sGC* soluble guanylate cyclase, *GTP* guanosine-5′-triphosphate, *cGMP* guanosine-3′-5′cyclic monophosphate, *GMP* guanosine monophosphate, *AC* adenylate cyclase, *ATP* adenosine-5′-triphosphate, *cAMP* adenosine-3′-5′-monophosphate, *PDE* phosphodiesterase (type 5 shown), *PLC* phospholipase C, *IP3* inositol 1,4,5-trisphosphate, *DAG* diacylglycerol, *Ca2+* calcium

aberrant endothelial function, wherein endogenous vasodilators, such as nitric oxide (NO) and prostacyclin (PGI_2), are decreased while endogenous vasoconstrictors, such as endothelin (ET-1) and serotonin (5-HT), are increased (Fig. 15.2) [77–82]. Indeed, the majority of approved therapies for PH target these endothelial-derived factors or their signaling pathways in some way (Fig. 15.3).

NO is produced in the vascular endothelium by the enzyme endothelial NO synthase (eNOS), from the precursor L-arginine. Once formed, NO diffuses into the adjacent smooth muscle cell and activates soluble guanylate cyclase (sGC), producing cGMP. cGMP results in smooth muscle cell relaxation through protein kinase G (PKG). cGMP is broken down by a family of phosphodiesterases (PDE), with PDE5 being prominent in the pulmonary vasculature (Fig. 15.2).

Arachidonic acid metabolism within vascular endothelial cells, results in the production of PGI_2 and thromboxane (TXA_2). PGI_2 activates adenylate cyclase, resulting in increased cAMP production, activation of protein kinase A, and subsequent vasodilation, whereas TXA_2 results in vasoconstriction via phospholipase C signaling (Fig. 15.2). PGI_2 also binds to platelet receptors, which inhibits their activation.

ET-1 is a 21 amino acid polypeptide also produced by vascular endothelial cells [83]. The vasoactive properties of ET-1 are complex [84–88]. However, its most striking property is its sustained hypertensive action. The hemodynamic effects of ET-1 are mediated by at least two distinct receptor populations, ET_A and ET_B [89, 90]. The ET_A receptors are located on vascular smooth muscle cells, and mediate vasoconstriction, whereas the ET_B receptors are located on endothelial and smooth muscle cells, and thus may mediate both vasodilation and vasoconstriction, respectively (Fig. 15.2). In addition, ET_B receptors are involved in the clearance of ET-1.

An important area of active research is focused on understanding the mechanisms responsible for endothelial injury or dysfunction in PH. Some important mechanisms include: alterations in mechanical forces (such as increased pulmonary blood flow associated with congenital cardiac defects, or altered flow velocities that are associated with areas of luminal narrowing) that result in increased vascular wall shear stress, hypoxia, oxidative stress, and inflammation [91–99]. Additional factors that contribute to endothelial injury in some patients include, infection, such as HIV and Schistosomiasis, as well as injury from drugs or toxins [100–102].

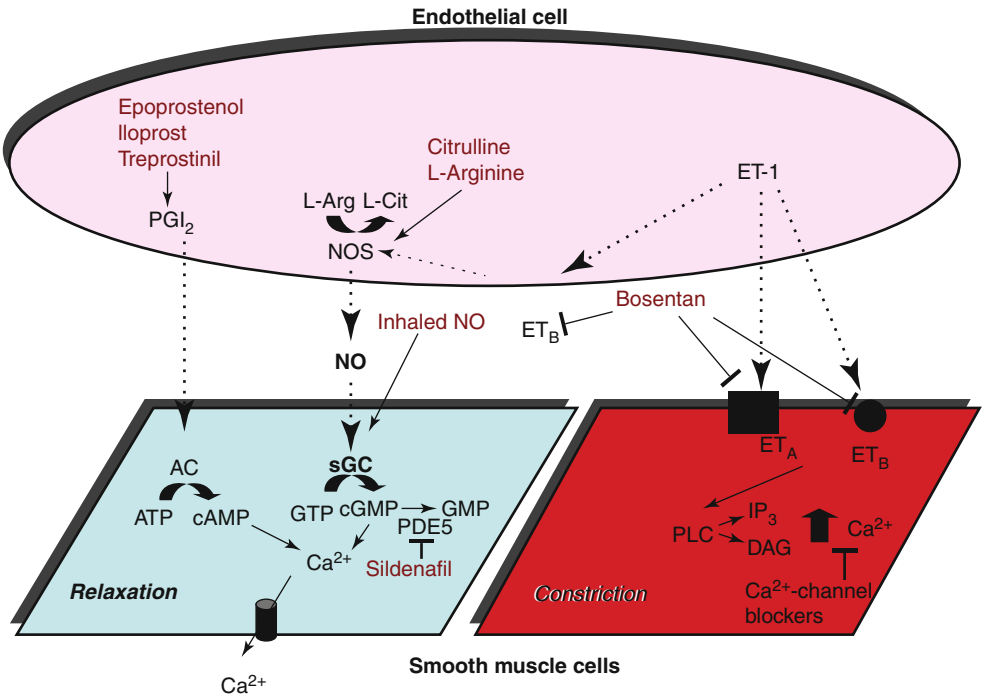


Fig. 15.3 A schematic of the sites of action of some endothelial and smooth muscle cell based therapies. *Arrows* indicate activation and (*T*) indicate inhibition

Moreover, it is known that endothelial derived factors, such as NO, PGI_2, and ET-1, are integral to processes beyond the regulation of vascular smooth muscle cell tone. Nitric oxide and PGI_2 are key regulators of vascular homeostasis, having antithrombotic and antiproliferative properties, in addition to their effects on vascular tone. Conversely, the mitogenic properties of ET-1 are well described. Indeed, endothelial injury or dysfunction likely contributes to alterations in inflammatory cascades, growth factors, and transcriptional factors that are increasingly recognized as key mediators of the vascular remodeling associated with PH [99].

Pulmonary Vascular Smooth Muscle

Considerable efforts have been made to understand the processes responsible for smooth muscle cell hypertrophy and proliferation that accompany PH. It is clear that a complex interplay exists between endothelial and smooth muscle cells. Some known mechanisms include: increased pericyte differentiation, smooth muscle cell migration, endothelial cell transdifferentiation, smooth muscle cell proliferation, smooth muscle cell hypertrophy, and inflammation [103, 104]. The extracellular matrix and matrix metalloproteinases (MMPs) are known to participate in these processes, with a cascade that involves the release of mitogens, such as basic fibroblast growth factor [105–107]. Multiple putative mechanisms and mediators are currently under investigation, many of which involve abnormalities in apoptosis with some sharing features with neoplastic processes [108]. In addition, genetic abnormalities participate in the development of PH in some patients, most prominently, mutations in bone morphogenetic protein receptor 2 (BMPR2) [109–114].

Management Strategies and Therapeutic Options

The basic elements of PH management include: the prevention and/or treatment of active pulmonary vasoconstriction, the support of right ventricle function and, when possible, treatment of the underlying disease. The ultimate treatment would involve the regression of advanced pulmonary vascular structural remodeling, but to date this remains an unattained goal.

In the critical care setting, avoidance, recognition and treatment of pulmonary hypertensive crises are paramount. Pulmonary hypertensive crises are most commonly observed in susceptible patients after cardiac surgery, but can occur in a number of settings. These life-threatening events involve: acute elevations in pulmonary vascular impedance, that cause an increase in right ventricular afterload, right ventricular ischemia, and decreased cardiac output [115, 116]. Decreased cardiac output results from the associated increase in right ventricular end diastolic volume that shifts the intraventricular septum to the left, decreasing left ventricular end diastolic volume and stroke volume. Decreased cardiac output results in decreased systemic oxygen delivery and metabolic acidosis. In addition, decreased pulmonary blood flow increases dead space ventilation. Distention of the pulmonary

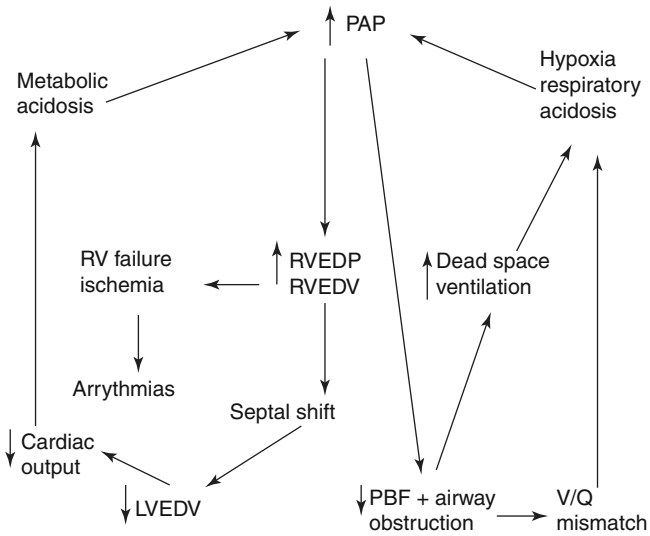


Fig. 15.4 A schematic of a pulmonary hypertensive crisis. An acute increase in pulmonary arterial pressure (*PAP*) results in a decrease in pulmonary blood flow (*PBF*) and airway obstruction due to distention of pulmonary arteries proximal to the maximally constricted resistance arterioles and perivascular edema. This results in an increase in dead space ventilation and ventilation-perfusion (*V/Q*) mismatch, both of which contribute to respiratory acidosis. In addition, right ventricular end-diastolic pressure (*RVEDP*) and volume (*RVEDV*) increase, which can result in failure of the right ventricle (*RV*) and movement of the intraventricular septum leftward, with compromise of left ventricular filling (decreased left ventricular end-diastolic volume (*LVEDV*)). This can impair cardiac output, resulting in metabolic acidosis. The resultant hypoxia (via hypoxic pulmonary vasoconstriction) and respiratory and metabolic acidosis can further increase PAP, causing a downward cycle

arteries and perivascular edema produce large and small airway obstruction, respectively, which further impairs ventilation-perfusion matching and decreases lung compliance. In fact, the decrease in lung compliance can be so dramatic that chest wall movement is impaired, even with manual ventilation. A cycle of worsening hypoxemia, hypercapnia, and acidosis (metabolic and/or respiratory) that results in further increases pulmonary vascular impedance develops that ultimately ends with right heart failure and death if left untreated (Fig. 15.4) [117–121].

Prevention and/or Treatment of Active Pulmonary Vasoconstriction

Increased pulmonary vascular reactivity is an early feature of PH, which manifests clinically as augmented pulmonary vasoconstriction in response to such stimuli as hypoxia, acidosis, catecholamine-mediated α_1-adrenergic stimulation associated with pain and/or agitation, and increases in intrathoracic pressure [121–123].

In critical care settings, acute PH is often first treated with pain control, sedation, oxygenation, and alkalinization. Indeed, recently published clinical practice guidelines for the hemodynamic support of pediatric and neonatal septic shock, specifically addressed the risk of elevated PAP/PVR and right heart failure in neonates with sepsis, and the potential need for metabolic and respiratory alkalinization as a part of the initial resuscitative strategy [124]. Decreasing oxygen tension and decreases in pH elicit pulmonary vasoconstriction. Alveolar hypoxia constricts pulmonary arterioles, diverting blood flow away from hypoxic lung segments, toward well-oxygenated segments, thus enhancing ventilation-perfusion matching. This response to hypoxia is unique to the pulmonary vasculature. Indeed, in all other vascular beds hypoxia is a potent vasodilator. The exact mechanism of hypoxic pulmonary vasoconstriction remains incompletely understood, but likely involves changes in the local concentration of reactive oxygen species that in turn regulate voltage-gated potassium channels and calcium channels [125]. Acidosis potentiates hypoxic pulmonary vasoconstriction, while alkalosis reduces it [126]. The exact mechanism of pH-mediated pulmonary vascular reactivity also remains incompletely understood, but appears to be independent of PaCO2. Recent data suggest that potassium channels play an important role in mediating these responses as well [127].

Vasodilator Therapy

The most widely used therapies for PH work by altering one of three endothelial signaling cascades: NO-cGMP, PGI_2, and ET-1. Figure 15.3 is a simplified depiction of the various sites of action of the therapies. In the critical care setting, augmentation of NO-cGMP signaling is most common, but the use of PGI_2 analogs is increasing. For the treatment of chronic PH, combination therapy is often required, and in fact may also be necessary in severe PH in the critical care setting [128–132]. Calcium channel blockers have demonstrated efficacy in the chronic treatment of subsets of PH patients, although their use may be decreasing [37, 40]. However, in the acute care setting the effects on the systemic circulation are of great concern, particularly in the face of right heart failure, and thus they are rarely used [133].

NO-cGMP Cascade

Inhaled NO (iNO) is the best-studied and most widely used agent for acute selective pulmonary vasodilation. When delivered by inhalation, NO diffuses across the alveolus into the smooth muscle of the accompanying capillary, resulting in relaxation. NO then diffuses into the blood vessel where it is rapidly inactivated by its interaction with hemoglobin. In this way, the effects of iNO are relatively confined to the pulmonary circulation and to ventilated areas of the lung, thus optimizing VQ matching. In large trials, iNO was found

to decrease the need for extracorporeal life support in neonates with PPHN and hypoxic respiratory failure, and these data led to its FDA approval [134–136]. Despite this initial indication, iNO is used to treat many other forms of PH and for diagnostic purposes. For example, several studies have investigated the use of iNO in pediatric patients undergoing cardiac surgery [12, 137–140]. These studies indicated that iNO was effective in lowering PAP and PVR in the postoperative period, but the data were less clear about the impact on outcome [141]. Likewise, investigators have examined the utility of iNO in the particular situations of bidirectional cavopulmonary connections and after Fontan completion [142–144]. In these patients, iNO decreased central venous pressure and transpulmonary gradient, and increased oxygen saturations. In addition, the pulmonary vascular response to iNO has been studied as a part of the assessment for operability in patients with PH associated with congenital heart disease [145–148]. These studies found that the combination of 100 % oxygen and iNO (80 ppm) produced maximal pulmonary vasodilation and was more predictive than either treatment alone for postoperative outcome [145–148].

Sildenafil is a PDE5 inhibitor and, as such, its mechanism of action is to augment NO-cGMP signaling by inhibiting the degradation of cGMP. Increased cGMP results in pulmonary vascular relaxation. It should be noted, however, that sildenafil has both pulmonary and systemic effects. In addition, the effects of PDE5 inhibition may not be restricted to the vasculature. For example, a recent study found that PDE5 was upregulated in the hypertrophied right ventricle and that PDE5 inhibition improved contractility [149]. Several studies have demonstrated the efficacy of sildenafil for the treatment of chronic PH [150–154]. Despite limited data, the use of sildenafil in infants and children with PH after cardiac surgery is increasing. Three small studies found that enteral sildenafil facilitated weaning from iNO in pediatric patients with congenital heart disease undergoing therapy for postoperative PH [155–157]. Two studies examined the effects of intravenous sildenafil in pediatric patients after cardiac surgery [158, 159]. Both studies found that intravenous sildenafil decreased PAP and PVR either to a greater extent than iNO or synergistically, but that its use was associated with increased intrapulmonary shunting and decreased systemic arterial pressures.

The administration of additional substrate for NOS with arginine and citrulline is another approach that has been taken to augment the NO-cGMP cascade, with some success [160–167].

Prostanoids

Higenbottam and colleagues, first described the long-term use of intravenous PGI_2 for the treatment of PH almost 30years ago [168]. Despite the many recent advances in therapy, intravenous PGI_2, epoprostenol, remains the best-proven and most effective therapy for chronic PH [169–173]. Complications associated with long-term epoprostenol are well known and include: thrombosis and infection secondary to the required indwelling central venous catheter, the need for dose escalation over time, and life threatening rebound PH with abrupt discontinuation of the infusion.

Given the success of chronic intravenous epoprostenol therapy, recent efforts have focused on developing additional agents and delivery approaches, in large part in order to address the complications and limitations associated with chronic intravenous infusions. In order to achieve selective pulmonary vascular relaxation, various investigations have focused on delivering prostanoids via the inhalational route [174–176]. This route (in large part due to the potential for selective pulmonary vascular relaxation) is particularly useful in the intensive care setting. Iloprost is a PGI_2 analog that is FDA approved for administration by nebulization. Ivy and colleagues studied iloprost in 22 children with PH [177]. They found that inhaled iloprost decreased PAP to a degree equivalent to iNO with oxygen. Likewise, Rimensberger and colleagues administered inhaled iloprost and iNO, alone and in combination, to 15 children with PH secondary to congenital cardiac defects [178]. Both agents decreased the PVR:SVR ratio to a similar degree, and there was no added benefit from a combination of the treatments. Furthermore, in an interesting study by Limsuwan and colleagues done in Thailand, which has relatively less access to iNO, inhaled iloprost decreased mean PAP and increased systemic saturations without decreasing systemic blood pressure in eight children suffering from acute increases in PAP after repair of congenital heart disease [179].

Other dosing strategies for prostanoids include subcutaneous and oral routes of administration, although these are less likely to be useful in critically ill children [180–185]. In children, an important impediment to the use of subcutaneous treprostinil relates to pain at the site of injection, but nonetheless it has been used successfully in these patients [186, 187].

Endothelin-1

Unlike augmentation of the NO-cGMP and prostanoid cascades, inhibition of ET-1 signaling does not reliably cause acute pulmonary vascular relaxation, and thus ET receptor antagonists are considered chronic therapies. However, in a small study that included seven infants that had undergone surgical repair of left-to-right intracardiac shunts, Schulze-Neick and colleagues demonstrated that an intravenous infusion of a selective ET_A-receptor antagonist resulted in an acute decrease in PVR [188]. Notably, the addition of iNO

had no effect, and the decrease in PVR correlated with left atrial ET-1 levels. But, currently, intravenous ET receptor antagonists are restricted to experimental settings.

Presently, the most common ET receptor antagonist is bosentan, an oral dual ET receptor antagonist. A number of studies have demonstrated the efficacy of bosentan in patients with chronic PAH, including children [189–192]. Bosentan is a sulfonamide-based agent metabolized by cytochrome P450 enzymes and thus monitoring liver function is important due to potential hepatic toxicity [193, 194]. Newer agents include selective ET_A-receptor antagonists [195–198].

The Support of Right Ventricular Function

Mortality from PH is most directly related to right ventricular function. The therapies outlined above may improve right ventricular function to the extent that they decrease right ventricular afterload, although emerging data suggest that some of these therapies, such as PDE5 inhibition and ET-1 receptor antagonism, may also enhance or impair (respectively) contractility of the hypertrophied right ventricle [149, 199]. However, in addition to afterload reduction, other therapies that support the right ventricle may be necessary, especially in acute care settings.

Under conditions of increased afterload, the contractility of right ventricular cardiomyocytes increases initially, due to changes in sarcomere length-tension relationships, increased Ca^{+2} sensitivity, and alterations in force-frequency relationships [200, 201]. In addition, the time course over which right ventricular afterload increases with the state of the right ventricle (in particular, right ventricular mass) together influence the degree to which the right ventricle can compensate [202]. For example, patients with Eisenmenger's syndrome tolerate elevated right ventricular afterload far better than patients with normal right ventricles who suffer an acute pulmonary embolism [200, 203].

Nonetheless, over some period of time (acutely or chronically) compensatory mechanisms fail, leading to elevations in right ventricular end-diastolic volume and decreased output. Due to ventricular interdependence, increases in right ventricular end-diastolic volume result directly in decreased left ventricular filling and decreased systemic output [204]. In fact, diastolic ventricular interactions, with decreases in left ventricular end-diastolic volumes, have been demonstrated to be more closely related to stroke volume than PAP in patients with PAH [205]. It is also important to recognize that right and left ventricular contractility are directly related. The ventricles share muscle fibers, the interventricular septum, and the pericardial space. Based on studies that used electrically isolated right heart preparations and experimental aortic constriction, it is estimated that 20–40 % of right ventricular systolic pressure is due to left ventricular contraction [206–208]. In addition, right coronary artery perfusion is dependent, in large part, on the pressure gradient between the aortic root and right ventricle.

Taken together, then, the principles of right ventricular support are: a reduction in right ventricular afterload (i.e. a reduction in pulmonary vascular impedance), optimization of right ventricular volume, augmentation of right ventricular contractility, and maintenance of left ventricular contractility and systemic vascular resistance. Importantly, this strategy requires adequate left ventricular function. The physiology associated with PH due to left heart failure, is quite different. Left heart failure is associated with elevations in left ventricular end-diastolic volume and pressure, the reverse situation of right heart failure due to PAH. Moreover, in this situation decreased right ventricular afterload and/or increased systemic vascular resistance could result in clinical deterioration, with pulmonary edema or impaired cardiac output [53, 54, 209]. Interestingly, however, sildenafil has been shown to increase cardiac output in patients with PH secondary to left heart failure, presumably due to reductions in pulmonary and systemic vascular resistance [210, 211].

The optimization of right ventricular volume presents a significant clinical challenge, as the proper management is dependent on the particular situation [212–217]. Although volume loading may be necessary in some situations, excessive volume may provoke adverse diastolic ventricular interactions. Management aimed at decreasing right ventricular volume (e.g. diuretics) may be necessary [217, 218].

Inotropes are often necessary in order to augment right ventricular contractility, however it remains unclear if one agent is superior. Although dopamine has been shown to increase cardiac output in patients with PH, Liet and colleagues found that dopamine increased the PVR to systemic vascular resistance ratio in preterm infants with a widely patent ductus arteriosus [219, 220]. Based on animal studies, epinephrine may have a superior hemodynamic profile in the setting of PH compared to dopamine, including a decrease in the PVR to systemic vascular resistance ratio, but direct clinical evidence is sparse [221]. Dobutamine, at low doses, may result in a reduction in PVR, while increasing right ventricular contractility. Several clinical studies have demonstrated the efficacy of dobutamine in adult patients with PH [222–224]. Likewise, milrinone, a PDE3 inhibitor and inodilator that augments ventricular contractility while decreasing PVR and systemic vascular resistance, has been shown to improve right ventricular output in adult patients with PH [225–227]. The decrease in systemic vascular resistance may not be desirable and thus may need to be addressed by the addition of a vasopressor. Finally, the drug levosimendan, which is a Ca^{2+} sensitizing agent and PDE3 inhibitor, holds great promise. Levosimendan has been shown to decrease PVR and improve right ventricular output in adult patients

with RV failure secondary to a number of conditions including PH [228–232].

The role of vasopressors is to increase systemic vascular resistance in order to augment right ventricular output through an elevation in left ventricular systolic pressure, and to maintain right coronary perfusion. Norepinephrine has been validated as a useful agent in a number of animal studies [233, 234]. Tourneux and colleagues demonstrated that norepinephrine increased left ventricular output, systemic arterial pressure, and pulmonary blood flow, while decreasing the pulmonary to systemic pressure ratio in 18 newborns with PPHN [235]. Phenylephrine has been shown to increase right coronary blood flow in the setting of increased right ventricular pressures, but may also increase PVR [236, 237]. Vasopressin, a systemic vasoconstrictor and pulmonary vasodilator, has been advocated in the treatment of right ventricular failure secondary to PH, with several positive clinical studies [238–243].

Finally, atrial septostomy as a part of management for chronic pulmonary hypertension has been advocated in order to allow for decompression of the right ventricle due to right-to-left shunting [231, 244–249]. Severe hypoxemia with this approach remains a concern. Recently, Labombarda and colleagues described favorable results with the placement of a Potts anastomosis (descending aorta to left pulmonary artery) in two children with severe idiopathic PH, thereby directing desaturated blood to the lower body [250].

Treatment of Underlying Disease

The ability to impact the course of PH by treating associated conditions is highly variable. Early repair of congenital cardiac defects represents the most successful effort to alter the natural history of PH [73, 122, 251, 252]. Likewise, PH related to treatable left heart disease would be expected to resolve in most cases, depending on the timing of the repair. However, treatment for other associated conditions may not decrease the incidence of PH. For example, PH can develop with Schistosomiasis and HIV infection despite treatment [253, 254]. The reversal of PH associated with portal hypertension after liver transplant has been described, but not in large series [255, 256]. Likewise, the reversal of PH associated with systemic lupus erythematosus after hematopoietic stem cell transplantation has been described, but only as case reports [257]. The use of steroids has been successful in the treatment of some patients with autoimmune disease, mixed connective tissue disease, POEMS syndrome, Langerhans' cell granulomatosis, and sarcoidosis [133, 258–261]. Advances in the management of sickle cell disease may decrease the incidence of associated PH, but definitive studies are lacking [262].

Subsets of newborns with PPHN are often treatable, and can ultimately survive without PH [263]. Several reports have described the reversal of PH after tonsillectomy or adenoidectomy for the treatment of obstructive sleep apnea [264, 265, 266]. In addition, PH related to high altitude can be reversed when patients move to sea level [267]. Home oxygen therapy is a relatively common treatment for pediatric patients with PH or at risk for developing PH. But, the data are conflicting about whether oxygen therapy alters the disease course, likely due to differences between the diseases that are studied [268, 269]. Finally, an increasing number of metabolic conditions have been found to be associated with PH. For example, the association between thyroid disorders and PH is now well established, and in fact therapy has been shown to reverse PH in these patients [270].

Future Directions

Right heart failure due to elevated pulmonary vascular impedance is the ultimate cause of mortality in most patients with PH. The majority of patients with advanced disease do not respond to acute pulmonary vasodilators, and yet most available therapies either augment pathways that cause vasodilation or inhibit pathways that cause vasoconstriction. Taken together it can be seen that an approach aimed at promoting the regression of structural pulmonary vascular remodeling may be a fundamentally more effective paradigm for patients with PH not associated with treatable conditions or with advanced PH. For critically ill patients with impending right heart failure, novel therapies may yet promote acute pulmonary vascular relaxation in patients that do not respond to the currently available treatments, by targeting new pathways within endothelial and/or smooth muscle cells.

Novel therapies in various stages of development include: direct sGC activators, eNOS couplers, antioxidants, cell-based therapy, vasoactive intestinal peptide, adrenomedullin, Rho-kinase inhibitors, tyrosine kinase inhibitors, statins, peroxisome proliferator–activated receptor agonists, elastase inhibitors, epidermal growth factor receptor inhibitors, and dichloroacetate.

Conclusions

Neonates, infants, and children may present to critical care settings primarily due to PH, or PH may complicate the course of another illness. A basic understanding of pulmonary vascular biology, the pathobiology and pathophysiology of PH, and the therapeutic approach is essential for intensive care physicians caring for these vulnerable patients. Early attention to right heart function is absolutely essential.

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Neuromuscular Respiratory Failure

16

R. Paul Boesch and Hemant Sawnani

Abstract

A number of acute and chronic disorders, congenital and acquired, can affect muscular function, control of breathing, and the mechanics of respiration. Consequently, the leading cause of death among children afflicted with a neuromuscular disorder (NMD) is respiratory insufficiency. Even with excellent chronic management, the lives of these children may be punctuated by episodes of acute respiratory failure necessitating management in the pediatric intensive care unit (PICU). As long term survivorship with these disorders is increasing, there is an expectation of recovery to baseline functional status following acute crises. This requires the critical care specialist to have a broad understanding of the implications of neuromuscular disease and its management, that are unique and characteristic to this group. This chapter comprehensively details the anatomic and physiological disturbances particular to neuromuscular respiratory failure. Interactions between respiratory muscles, the chest wall, and the lung are highlighted. The management approach for this group of patients is then presented with a basis in the available evidence and the underlying pathophysiology. This includes secretion clearance, feeding and nutrition, non-invasive and invasive ventilation, extubation strategies, decision making regarding tracheostomy and palliative care. The significant defining features and treatment options for the major neuromuscular disorders that the critical care specialist encounters are also presented.

Keywords

Neuromuscular disease • Muscular dystrophy • Respiratory muscle • Chest wall • Pediatrics • Critical care • Noninvasive ventilation • Airway clearance

Introduction

A number of acute and chronic disorders, congenital and acquired, can affect muscular function, control of breathing, and the mechanics of respiration. Consequently, the leading cause of death among children afflicted with a neuromuscular disorder (NMD) is respiratory insufficiency. Respiratory failure may present either acutely, as a result of pneumonia, or may develop more insidiously as a result of progressive ventilatory decompensation. Even with excellent chronic management, the lives of these children may be punctuated by episodes of acute respiratory failure necessitating management in the pediatric intensive care unit (PICU). As long term survivorship with these disorders is increasing, there is an

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expectation of recovery to baseline functional status following acute crises [1–3]. Though there are significant defining features of each disorder, there are common approaches to management that can aid the critical care specialist in meeting this expectation. The physiological disturbances particular to neuromuscular respiratory failure are unique and characteristic of this group and require an approach that reflects an understanding of these deficits. Broadly, NMD may be classified into five major groups: muscular dystrophies, congenital and metabolic myopathies, disorders of the neuromuscular junction, peripheral neuropathies, and anterior horn cell disease (spinal muscular atrophies) (Table 16.1).

General Anatomic and Physiologic Considerations

The function of the respiratory pump is compromised in children with NMD and may deteriorate progressively over time.

Respiratory Muscle Function

The diaphragm is the primary muscle of respiration. During normal quiet breathing the dome of the (adult) diaphragm may descend 1–2 cm, and with forceful inspiration and exhalation may undergo up to 10 cm of total excursion. Contraction of the diaphragm expands the lungs with a piston action but also elevates the lower ribs (along its zone of apposition) and increases the abdominal pressure. The diaphragm is innervated by the phrenic nerve which originates from spinal segments C3-C5 and is under both voluntary and autonomic control [4]. Injury to the phrenic nerve sufficient to cause severe paresis or paralysis results in paradoxical motion of the diaphragm on inspiration and also impairs maintenance of inflation of the basal segments of the lung. Inward movement of abdomen on inspiration is the cardinal sign of diaphragm paralysis. With diaphragmatic paralysis, there is a marked additional reduction in vital capacity when moving from erect to supine, as the supine position facilitates the cephalad movement of the abdominal contents when negative pleural pressure is created by contraction of inspiratory muscles of the neck and chest wall [5]. Diaphragm function is affected disproportionately to other inspiratory muscles in amyotrophic lateral sclerosis (ALS), spinal muscle atrophy (SMA), limb-girdle dystrophy, and Pompe disease [6]. Isolated diaphragm dysfunction can be caused by phrenic nerve injury during cardiothoracic surgery, birth injury, etc. During tidal breathing the diaphragm is responsible for two-thirds of the inspired tidal volume, however the intercostal and accessory muscles contribute to a substantial portion of the inspiratory capacity [7, 8].

While the diaphragm is the primary muscle of respiration, the intercostal muscles and accessory muscles of respiration provide a significant contribution. The external intercostal and interchondral portion of internal intercostal muscles are inspiratory in nature and receive their innervation from the 1st to 12th thoracic nerve roots. The main accessory muscles of respiration include the scalene and sternocleidomastoid muscles. The action of inspiratory muscles elevates the ribs and expands the chest wall. The external intercostals act on the upper two-thirds of the ribcage while the accessory muscles elevate the uppermost ribs and the sternum. They also support the chest wall against the negative pressures developed during tidal breathing and significantly augment generation of large tidal volumes during exercise, sigh breaths, and coughing. Activation of inspiratory muscles also provides braking during the first phase of exhalation. Exhalation is generally a result of the elastic recoil of the lung, however expiratory muscles are utilized for forced exhalation, such as during exercise, speech, and coughing or when there is increased airway resistance (such as due to asthma, bronchiolitis, or tracheobronchomalacia). The internal intercostals, triangularis sterni, and abdominal muscles make up the expiratory muscles of respiration [4, 9]. Increased use of inspiratory rib cage muscles and use of expiratory muscles can be associated with a sensation of dyspnea and increased work of breathing [10].

Less well appreciated muscles of respiration include those of the upper airway. They serve to maintain airway patency, which is particularly important during sleep and periods of high respiratory demand. Upper airway stability may be compromised in children with NMD resulting in obstructive sleep apnea [11]. This is most prominent during REM sleep when there is a marked reduction in tone in all muscles except the diaphragm (Fig. 16.1). More dramatically, upper airway instability is observed in severe forms of SMA 1 where an infant may have difficulty maintaining a patent airway even while awake due to such a neuropathic airway.

The active force generated by muscle contraction is a function of muscle length, stimulation of muscle fibers, and velocity of fiber shortening. A muscle's maximal force is generated at its resting length. At increased lung volumes, expiratory muscle force increases and inspiratory muscle force decreases, while at low lung volumes inspiratory force increases and expiratory force decreases. Force generation increases with increases in stimulation frequency up to a plateau. Neuromuscular diseases affect respiratory muscle force via dystrophic changes in the muscles as an intrinsic defect, or due to wasting and atrophy from decreased stimulation from lower motor neurons. This decrease in stimulation can occur from atrophy of the motor neurons or disorders of the neuromuscular junction.

Table 16.1 Major neuromuscular disorders in children

Disease	Mode of inheritance	Gene location
Muscular dystrophies		
Duchenne MD	XLR	Xp21
Becker MD	XLR	Xp21
Limb girdle MD	AR, AD	17q12–q21, 13q12, 15q, 2p, 5q, unknown
Congenital MD	AR	6q, 9q31–q33, unknown
Distal MD	AR, AD	2p12–p14, unknown
Emery-Dreifuss MD	XLR	Xq28
Facioscapulohumeral MD	AD	4q35
Congenital and metabolic myopathies	AD	unknown
Central core disease		
Minicore disease	AR	unknown
Nemaline rod myopathy	AR, AD	1q21–q23, unknown
Centronuclear myopathy	AR unknown	unknown
Glycogenoses	Typically do not affect respiratory muscles (exception: Pompe's disease-acid maltase deficiency), but may induce exercise intolerance	
Lipid disorders		
Muscle carnitine deficiency	AR	
Systemic carnitine deficiency	AR	
Carnitine palmitoyl transferase deficiency	AR	
Mitochondrial disorders	Sporadic	
Kearn Sayre syndrome		
Leber hereditary optic neuropathy Maternal	Maternal	
MELAS Maternal	Maternal	
MERRF Maternal	Maternal	
Ion channel disorders	AD, AR	
Myotonia congenita		
Neuromuscular junction		
Myasthenia	unknown	
Hereditary peripheral neuropathies		
Charcot-Marie-Tooth AD	AD, AR	
Refsum AR	AR	
Deierine-Sottas AR	AR	
Spinal muscular atrophies		5q11–q13
Type I (Werdnig-Hoffman disease) AR	AR	
Type II (intermediate severity) AR	AR	
Type III (Kugelberg-Welander disease)	AR, AD unknown	

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MD muscular dystrophy, *XLR* X-linked recessive, *AD* autosomal dominant, *AR* autosomal recessive, *MELAS* mitochondrial encephalomyopathy with lactic acidoses and stroke-like episodes, *MERRF* myoclonus epilepsy and ragged-red fibers

Chest Wall Function

The thorax consists of the vertebral column, ribs, and sternum. The superior ribs are elevated anteriorly by the scalenes and therefore undergo "pump handle" motion which increases the anterior-posterior diameter of the ribcage. The middle to lower ribs undergo "bucket handle" motion with inspiration, flexing on their articulations with the vertebral column and sternum. This results in an increase in the transverse diameter of the thorax. Ribs 11 and 12 have no sternal connection and therefore undergo "caliper" motion, opening on inspiration to increase the transverse diameter. The natural tendency of the chest wall to is to recoil outwards. This counterbalances elastic recoil of the lungs inward.

Functional residual capacity (FRC) is the lung volume at which there is equilibrium between the outward recoil of the chest wall and the inward recoil of the lungs, without any respiratory muscle contraction. As compared to adults, infants have more compliant chest walls and less compliant lungs which require them to actively maintain FRC via laryngeal braking and by inspiring prior to reaching full exhalation. The FRC of infants is 15 % of VC compared to 35 %



Fig. 16.1 Dynamic inspiratory pharyngeal collapse. View with flexible bronchoscope positioned just above the hypopharynx, below the soft palate. Note the inward collapse of the lateral and posterior pharyngeal walls over the inspiratory cycle (**a**–**c**). The pharyngeal airway becomes completely obstructed due to hypotonia of pharyngeal strap muscles, even without collapse of the tongue base

in adults. Rib motion is also decreased in infants due to their relatively greater horizontal orientation. These factors place infants at a mechanical disadvantage and more susceptible to respiratory fatigue and acute respiratory failure at times of increased load on the respiratory system. This scenario is greatly exaggerated in premature infants. After 6 months of age, chest wall compliance progressively decreases. Body position also affects chest well compliance. Chest wall compliance is 30 % greater seated as compared to supine, resulting in a greater contribution from the diaphragm for tidal volume generation. Chest wall compliance is even further decreased in the prone position.

Interactions Between Respiratory Muscles, Chest Wall, and Lungs in NMD

In addition to respiratory muscle weakness, neuromuscular diseases are associated with intrinsic changes in chest wall and lung dynamics. This is evident as loss of vital capacity out of proportion to the decrease predicted by respiratory muscle weakness alone. Chest wall function becomes progressively diminished in children with NMD [5]. Chest wall compliance is reduced in older NMD patients independent of scoliosis and has been attributed to fibrotic changes of the dystrophic chest wall muscles as well as to shortening and stiffening of the un-stretched tissues [12, 13]. Low tidal volume breathing over extended periods of time does not allow costovertebral or costosternal joints to move through their full range of motion and ankylosis develops at these locations. Rib motion can also be further impaired by changing angulation of the ribs to a more down-sloping orientation and by scoliosis (Figs. 16.2 and 16.3). Overall chest wall compliance may be decreased to two-thirds of normal in chronic NMD. Lung compliance also progressively decreases. This does not appear to be due to increased alveolar surface tension, and is independent of atelectasis [14]. Though not experimentally demonstrated, this decreased lung compliance has been attributed to altered elastic properties of lung parenchyma from persistent limited range of activity/stretching over time. Increased elastic recoil of the lung, unopposed by the weaker chest wall, results in a lower FRC in patients with NMD of any type. Over a wide range of neuromuscular diseases, FRC decreases to ~80 % of predicted (with a normal residual volume, decreased total lung capacity, and markedly decreased vital capacity) [15, 16].

Measurement of Respiratory Muscle Function

Evidence of decline in pulmonary function may be seen very early in congenital NMD. On routine spirometry this is most evident by reduced vital capacity that further decreases as weakness progresses [17, 18]. Forced expiratory volume in 1 s (FEV_1) declines proportionately to vital capacity which describes a restrictive defect as expected from the muscle weakness, chest wall dysfunction and decrease in lung compliance described earlier. Decrease in vital capacity can be linked to important outcomes such as frequency of chest infections, nocturnal ventilation, daytime respiratory failure, and mortality [19–22]. In a study of older children with NMD, sleep disordered breathing-onset was predicted by inspiratory vital capacity <60 % and nocturnal hypercapnic hypoventilation by inspiratory vital capacity <40 % [20]. A vital capacity of 20 % is associated with awake carbon dioxide retention in patients with Duchenne muscular dystrophy (DMD) [21]. Phillips et al. reported a median life expectancy in DMD of 3 years once vital capacity dropped to below 1 L [22].

As neuromuscular diseases are characterized by both inspiratory and expiratory muscle weakness, maximal inspiratory and expiratory pressures can be measured. Both of

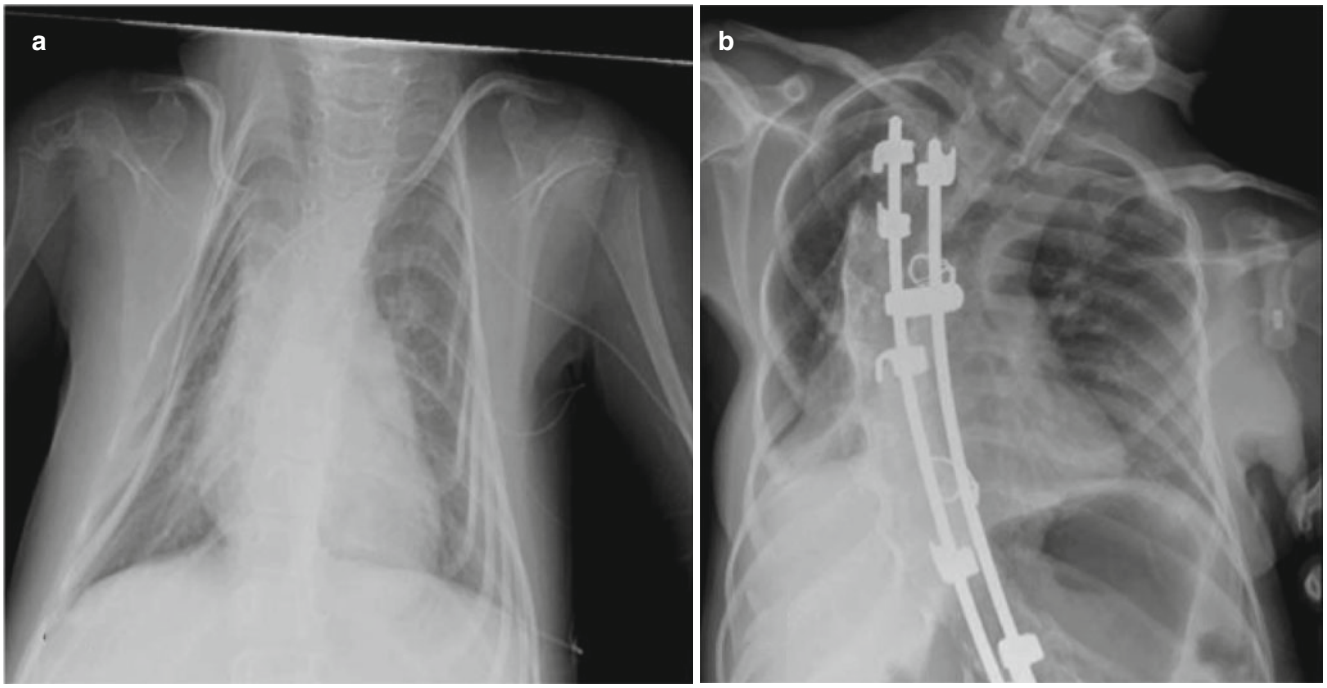


Fig. 16.2 Chest wall dysfunction in children with neuromuscular disease. (**a**) A 4 year old with spinal muscle atrophy type 1 demonstrating thin, down-sloping ribs and poor lung volumes. (**b**) Adolescent with severe scoliosis due to central nuclear myopathy. Note that even after spinal fusion there is persistent distortion to each hemi-thorax with wide separation of ribs on the right and crowding on the left. The ribs have also become progressively misshapen and do not move together well. Note chronic atelectasis in right lung base

these tests require volitional generation of pressure against a closed valve. Maximal inspiratory pressure (MIP) is measured from low lung volume and maximal expiratory pressure (MEP) from high lung volume. While there are normal ranges for each, the coefficient of variation is also quite high. A decreased MIP is a marker of respiratory impairment, while decreased MEP can correlate to poor cough clearance [20].

Inability to clear airway secretions is a significant cause of morbidity and mortality in patients with NMD. During a cough, deep inspiration gets air behind secretions, places expiratory muscle fibers at an advantageous position for force generation, and utilizes the elastic recoil of the lung to generate high expiratory flows. In addition, partial lower airway collapse from forceful exhalation increases air flow velocity and shear forces to propel secretions out of the airways. Children with neuromuscular disease have impairment in generating deep inspiration (decreased vital capacity) and in expiratory muscle strength (MEP), though the ability to generate supramaximal flows during a cough are not directly measured by standard spirometry or MEP. Impaired bulbar function prevents the build-up of intrathoracic pressure by glottic closure prior to coughing. Cough peak flows can be measured by a maximal inspiration, followed by a cough into a peak flow meter. When the cough peak flow falls below 160 L/min (normal >300 L/min), the cough is no longer effective enough to provide adequate mucus clearance [23]. When the PCF is 160–270 L/min, it is likely to fall below 160 L/min when viral illnesses occur [24]. Decreased cough peak flow correlates to other pulmonary function test values. Gauld and Boynton found that the likelihood of PCF <270 l/min rises when FVC <2.1 L and FEV_1 <2.1 L/s [25]. Chaudri et al. found a correlation between inability to generate high maximal expiratory flow spikes with coughing and lower VC, MIP, and MEP but there was great overlap between those with adequate and impaired cough [26]. The fact that they found that poor spike generation was independently associated with increased risk of mortality suggests that cough peak flow could have additional predictive ability compared to spirometry.

A means of describing the tendency of the diaphragm to fatigue is the tension-time index. As respiratory muscle fatigue is defined as the inability to sustain force against a constant load, the tension-time index is the product of two ratios: the ratio of diaphragmatic pressure to maximal transdiaphragmatic pressure (Pdi/Pdi max) and the ratio of the inspiratory time to total respiratory cycle time (Ti/Ttot) [27]. If the transdiaphragmatic pressure per breath is of a greater proportion of the maximum possible or if the time of demand of the diaphragm (longer Ti) is increased, the tension-time index will increase. A higher tension-time index reflects an increased probability that the diaphragm will fatigue. Measurement of the tension-time index requires

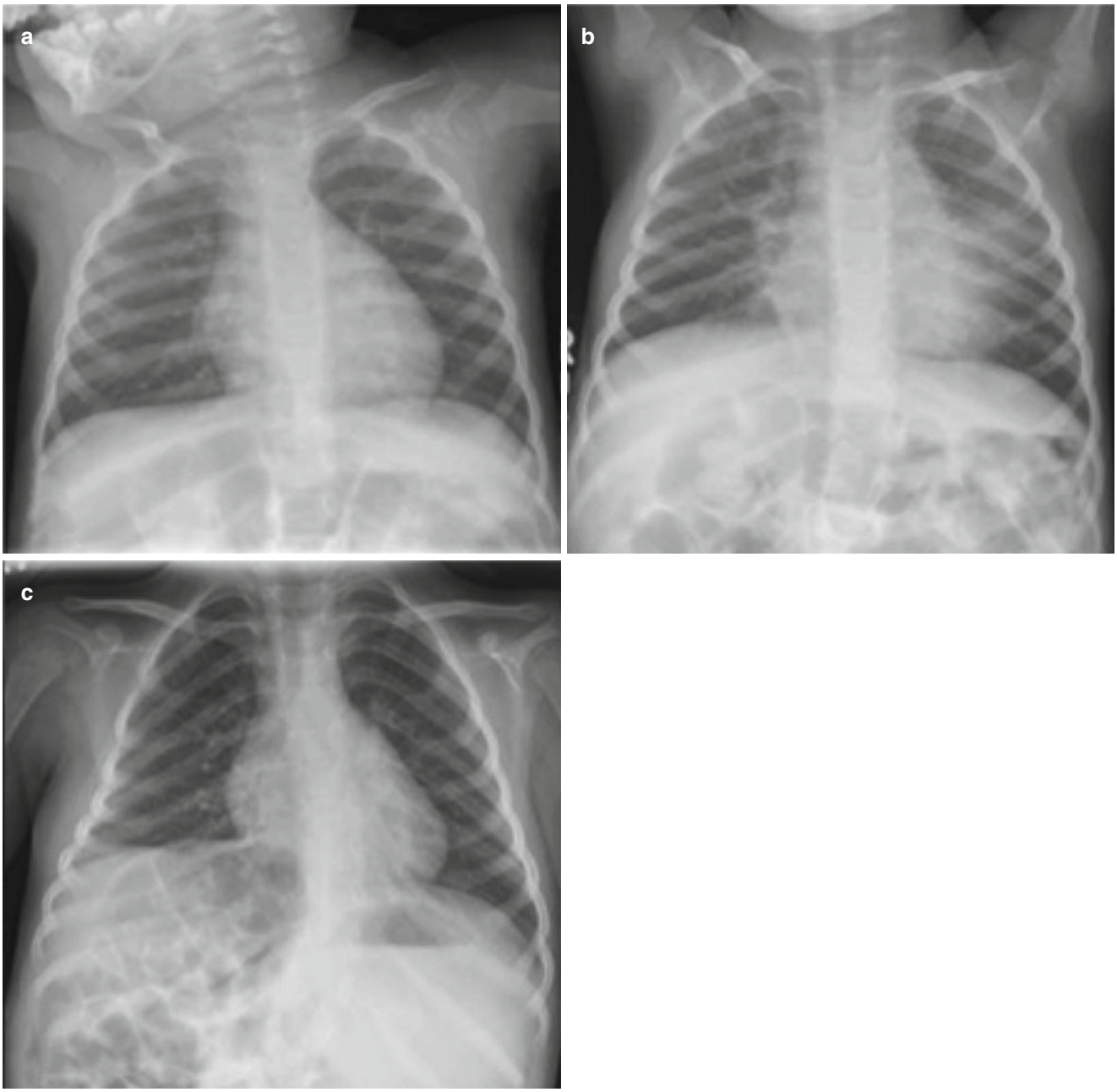


Fig. 16.3 Progression of chest wall changes in NMD. Child with Spinal Muscle Atrophy type 2 at age 2 (**a**), age 4 (**b**), and age 5 (**c**). Note increasingly down-sloping ribs. Polysomnography was normal at age 2 and 4, but showed alveolar hypoventilation requiring nocturnal BiPAP at age 5

measurement of the transdiaphragmatic pressure with an esophageal or gastric catheter. An analogous non-invasive index has been described and evaluated in a population of children with NMD [28, 29]. The tension-time index of the respiratory muscles (TTmus) indicates the likelihood of fatigue of all respiratory muscles. Mulreany et al. evaluated TTmus among a population of children with NMD (DMD, prune belly syndrome, spinal muscle atropy, and muscular dystrophy) and controls and found a significant elevation in NMD patients, almost entirely due to an increase in the ratio of mean to maximal inspiratory pressure [29].

As respiratory muscle weakness progresses nocturnal hypoventilation commonly ensues. Children with NMD may not have the typical daytime symptoms of sleep disordered breathing [30, 31]. Nocturnal hypoxemia and hypercapnea also negatively impact daytime respiratory function. Furthermore, due to decreased upper airway tone, children with NMD are at risk for obstructive sleep apnea. For these

reasons overnight polysomnography is recommended when there are symptoms of sleep disordered breathing or at least annually when vital capacity is decreased or when DMD patients are no longer ambulatory [32, 33]. Figure 16.4 summarizes the downstream effects of neuromuscular weakness and the interrelated mechanisms leading to respiratory failure.

The most common types of NMD that affect children, requiring ICU management are elaborated on in the subsequent section.

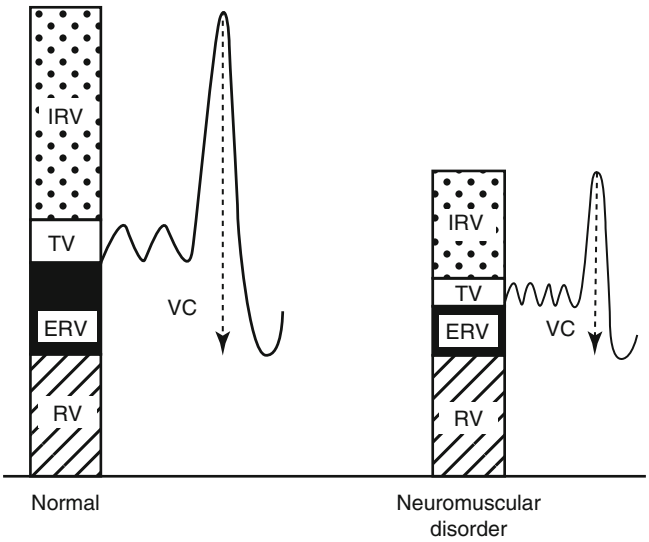


Fig. 16.4 Downstream effects of respiratory muscle weakness leading to respiratory insufficiency. Treatment strategies to resolve respiratory failure must take into account each of these mechanisms

Neuropathies

Spinal Muscular Atrophy

Childhood SMAs are the second most common cause of mortality from a recessive genetic disorder after cystic fibrosis. SMA is characterized by degeneration of the alpha motor neuron and proximal muscle weakness and atrophy. Diagnosis is based on clinical features, presence of normal creatine kinase serum levels, and electromyographic and muscle biopsy patterns [34]. The SMAs are classified into three categories according to severity and age of onset of disease (Table 16.1). In terms of prevalence, Type I SMA (Werdnig-Hoffmann disease) is the most commonly occurring form with a prevalence of 1:20,000 live births [35]. The onset of symptoms is almost always within the first 6 months of age, and often heralded by history of decreased fetal movements. Infants will have a weak cry and be floppy at birth, or develop floppiness over time. There may be associated feeding and respiratory difficulties. SMA is suggested as infants tend to adopt a frog-like position when supine, and fasciculations are observed in the tongue or other skeletal muscles. On the other hand, combined, SMA types II and III together affect 1:24,000 live births [36]. Type II is considered an intermediate form in which the onset is typically between 6 and 12 months, with children having attained the ability to sit. Type III SMA (Kugelberg-Welander disease) usually becomes manifest during the second or third years of life. Survival is usually into the third decade due to a slower rate of progression. Typical complaints include frequent falls, waddling gait, and positive Gower's sequence when trying to

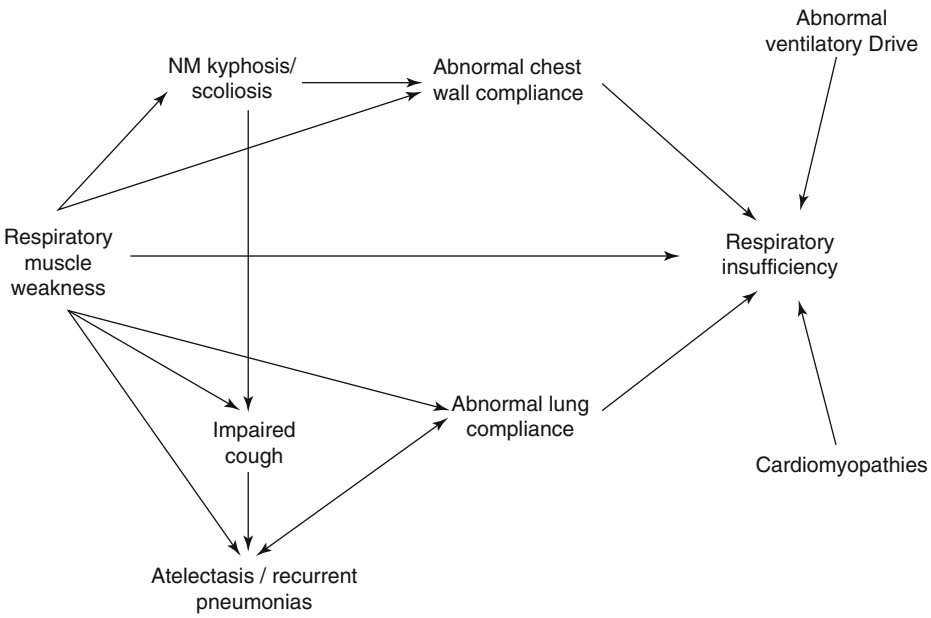


Fig. 16.5 Inter-relationship of the pathophysiology contributing to respiratory failure in children with neuromuscular disease

get up from the floor. The proximal limbs are usually more severely affected and fasciculations can be easily observed. Of note is the relentless progression of skeletal deformity in the non-ambulatory child, with the developments of scoliosis, kyphosis, and equinovarus feet deformities if postural support is inadequate. Intercurrent illnesses may prompt sudden deterioration of muscular weakness, at which time fasciculations may become prominent. Treatment is usually supportive (musculo-skeletal, respiratory and nutritional) with the goal of preventing the development of complications. Regular physiotherapy is administered to prevent contractures, and postural support is essential for slowing the onset and progression of kyphoscoliosis. The intrusion of the thoracic spine into a (usually right) hemithorax can cause airway compression; thoracic deformity leads to loss of diaphragm mechanical advantage. The combination of these factors hampers adequate airway clearance and ventilation, with increase in the frequency of acute respiratory decompensation. In a large natural history of SMA study, Zerres described survival probabilities at ages 2, 4, 10, and 20 years were 32 %, 18 %, 8 %, and 0 %, respectively, in SMA type I, and 100 %, 100 %, 98 %, and 77 % in patients with SMA type II [37].

Spinal Cord Injury

Blunt cervical spine injury complicates 1.2 % of pediatric trauma admissions but the morbidity and mortality are high [38]. Infants and toddlers are most often injured by motor vehicle accidents or falls, while adolescents are most injured by motor vehicle accidents or sports [39, 40]. Respiratory complications drive most of the morbidity and mortality associated with spinal cord injury and include atelectasis, pneumonia, and respiratory failure [41]. Respiratory complications may occur in 40–70 % of spinal cord injured patients [42, 43]. The incidence of respiratory failure is greater the higher the level of injury and with complete disruption. Cervical spinal cord injury from C1-C4 will result in paralysis of the diaphragm, scalenes, external intercostal muscles, and all the expiratory muscles, while lesions below C5 will primarily affect only the intercostals and expiratory muscles. Loss of sternocleidomastoid and trapezius muscle function is rare. Both the loss of effective inspiratory capacity and effective cough clearance contribute to respiratory decline. Paradoxical abdominal breathing with inspiratory collapse of the flaccid chest wall will indicate diaphragmatic function and loss of intercostal activity, but it is essential to be vigilant for other subtle signs of impending respiratory failure. These may be present in the absence of abdominal paradox and hypoxemia, and include tachypnea, tachycardia, and decreasing vital capacity. Loss of sympathetic tone results in increased bronchial mucus secretion and bronchospasm which further contribute to respiratory insufficiency. Management should be geared towards (1) early recognition of respiratory insufficiency and use of positive pressure support, (2) prevention of aspiration, (3) prevention and treatment of atelectasis, (4) and clearance of airway secretions [41, 44]. Intrapulmonary percussive ventilation can help maintain lung recruitment and there is some evidence that mechanical ventilation with high tidal volumes (18–20 ml/kg) prevents the development of atelectasis [44, 45]. Overall, patients who do not develop atelectasis or pneumonia wean from ventilation more successfully.

Guillain-Barré Syndrome

Guillain-Barré Syndrome (GBS) is an autoimmune inflammatory polyneuropathy of rapid onset which frequently follows an infectious or inflammatory process by days to weeks. It is the most common cause of acute flaccid paralysis in infants and children [46, 47]. The season of greatest prevalence is the fall and winter, temporally related to the respiratory virus season in the US. T-cell activation, with the production of antibodies directed against peripheral nerves may follow infections with Epstein–Barr virus or *Campylobacter jejuni*, immunization, or surgery. Most cases in children are classified as Acute Inflammatory Demyelinating Polyneuropathy (AIDP), characterized by decreased nerve conduction velocities and amplitudes, delayed distal nerve latency, and nerve conduction blocks. The less common axonal form of GBS, Acute Motor Axonal Neuropathy (AMAN), is characterized by lack of electrophysiologic evidence of demyelination and has been associated with preceding *Campylobacter jejeuni* infection and anti-ganglioside antibodies [46]. Cerebrospinal fluid protein is generally elevated in both forms, with little or no pleocytosis. In a 16 year retrospective review of 23 patients, Hung, et al., found a biphasic age distribution with no patients under 1 year old. Fourteen of their 23 patients were 1–10 years old and nine were 13–17 years old [46].

The evolution of symptoms usually progresses over 1–2 weeks. Sensory and motor weakness or pain develops in limb muscles first and has a characteristic ascending pattern with lower extremity involvement preceding upper extremity involvement. Clinical characteristics of GBS are similar in adults and children, although proximal distribution of weakness is less common in children, and cranial nerve involvement, distal paresthesia and neuropathic pain are more common [47]. Bulbar muscle weakness is common in pediatric patients with GBS. A retrospective study of 56 pediatric GBS patients reported by Lee, et al. found facial palsy in 15 children (26.8 %), ophthalmoplegia in 12 (21.4 %), and dysphagia in 15 (26.8 %) [47]. Respiratory failure is reported

more commonly in studies including adults and children (20–30 %) than in studies of children alone over the course of the disease (4–14 %) [46–48].

Therapy is supportive including monitoring of pulmonary function and vital signs, good nutrition and skin care, provision of DVT prophylaxis and pain control. Plasmapheresis or intravenous gammaglobulin (IVIG) given at 0.4 mg/kg/dose for 5 days is the most effective intervention. Intravenous gammaglobulin is felt to shorten the time to first improvement and decrease the hospitalization time [48]. Systemic corticosteroids have not been shown to be helpful.

Guillain-Barré Syndrome in children has a shorter course and is associated with a more complete recovery than GBS in adult patients. Functional outcomes are good at 1–2 years post onset and are not clearly different between ADIP and AMAN type. Those with a greater maximum disability score may have less complete recovery [47, 49].

Diseases of the Neuromuscular Junction

Myasthenia Gravis

Myasthenia gravis (MG) is the most common defect of neuromuscular transmission and is an autoimmune process characterized by the development of antibodies to the postsynaptic acetylcholine receptor. Fluctuating weakness occurs, primarily in muscles innervated by cranial nerves, but also skeletal and respiratory muscles [50]. In adults there is a biphasic age distribution, occurring most often in women 20–40 years old, or older men and women. In pre-pubertal patients there is an even male–female distribution [51]. In children there are three types of myasthenia syndromes: neonatal MG, congenital MG, and juvenile MG. Neonatal MG is transient and self-limited, congenital MG includes inherited disorders of neuromuscular transmission, and juvenile MG is pathogenetically similar to adult MG. Myasthenia gravis is often associated with other autoimmune disorders, thyroid disease, rheumatoid arthritis, and systemic lupus erythematosus [52]. Common presenting symptoms usually include ptosis, diplopia, dysarthria, dysphagia, and weakness in proximal limb muscles, but respiratory muscles weakness and failure may occur ("myasthenic crisis"). Diagnosis can be confirmed with use of a short-acting anticholinesterase (e.g. edrophonium), electromyography, or assaying for anti-acetylcholine receptor antibodies (present in 80–90 % of adult and 50–74 % of juvenile cases) [51, 53].

Treatment is symptomatic with a longer acting anticholinesterase (pyridostigmine). Other immune modulating therapies (steroids, azathioprine, cyclosporin A, cyclophosphamide) may be used in resistant cases. Plasmapheresis and/or intravenous immunoglobulin can acutely and temporarily decrease antibody titers in a myasthenic crisis or in preparation for surgery. Thymectomy is an established treatment and results in a high remission rate. In young children the additional risk of immunosuppression following thymectomy needs to be considered, especially given the higher spontaneous remission rate in this age group.

Caution should be used in selection of pharmacologic agents for patients with myasthenia because of the potential for worsening weakness. Paralyzing agents and anesthetics, certain antibiotics and a long list of other drugs have been associated with either precipitating a myasthenic crisis or worsening underlying disease [54].

Botulism

There are five forms of botulism including food-borne, wound, infantile, aerosolized, and iatrogenic. Infantile is the most common and develops following the ingestion of spores of *Clostridium botulinum*, which colonize the gut and then the toxin is absorbed into the blood stream. The botulinum toxin binds irreversibly to the presynaptic motor terminals causing irreversible blockade of synaptic vesicle release, inhibiting motor activity. Neither the sensory system nor cognitive function is affected. Presenting symptoms of infantile botulism include: constipation, lethargy, bulbar weakness, with weak cry, poor feeding, and failure to thrive [55]. In food-borne disease, symptoms usually begin 12–36 h following ingestion of toxin-contaminated food. With increased therapeutic use of botulinum toxin for muscle spasticity, sialorrhea, hyperhidrosis and other indications, there have been reported cases of iatrogenic botulism [56]. These cases are few and are generally limited to dysphagia and dysarthria but severe cases have been reported as well and one trial was discontinued early due to adverse events [56–58]. Diagnosis can often be suspected by history and physical findings, and confirmed by identification of organism in the stool and by characteristic EMG findings [59]. Treatment of botulism is supportive, identifying the cause and removing the source of spores or toxin. Mechanical ventilation may be required for several weeks and full recovery of function may take a few months. Infants may exhibit subtle sleep apnea and hypoventilation and failure to recognize the problem and intervene may lead to death from respiratory failure. A human-derived antitoxin (Botulism Immune Globulin Intravenous) is available for treatment of infant botulism which reduces morbidity and length of hospitalization [59]. It is most effective when administered early in the course, since it works only on circulating toxin, not on that which is already bound to the nerve terminal. There are two equine-derived antitoxins for treatment of foodborne and wound botulism: a trivalent form consisting of antibodies to types A, B, and E, and a bivalent form with antibodies to types A and B only.

Myopathies

DMD

Muscular dystrophies are a group of genetically determined progressive disorders which primarily affect the striated muscle, without involvement of the central nervous system, spinal cord, anterior horn cells, peripheral nerves, or neuromuscular junctions (Table 16.1). The inheritance of muscular dystrophies may vary from X-linked, such as in Duchenne or Becker muscular dystrophies, to autosomal recessive or dominant, such in congenital or limb-girdle muscular dystrophies.

Duchenne Muscular Dystrophy (DMD), the most common neuromuscular disease of childhood, is a progressive sex-linked disorder characterized by the production of abnormal dystrophin in muscle. DMD has an estimated occurrence of 1 in 3,500 male births and is allelic with Becker muscular dystrophy, since both are due to deletions or mutations in the X chromosome (Xp21) [60]. The diagnosis of DMD is usually confirmed by muscle biopsy or by identification of an Xp21 mutation or deletion. Elevation of serum creatine kinase may be marked, especially during the early phases of the disease during which extensive skeletal muscle loss occurs.

Owing to insidious nature of onset, DMD is usually recognized around the time the child starts walking with delayed gait, abnormal gait (waddling), or difficulty in climbing stairs [61]. Progressive difficulty in getting up from the floor is notable, with one or more components of the Gower's sequence. Lower limbs are initially affected, with arm weakness appearing later in the disease. Muscle pain and muscle enlargement, particularly of the calves, are more common than macroglossia which will be present in 1/3 of the patients with DMD. Intellectual impairment with a mean loss of 20 I.Q. points compared to a control population is believed to represent a true manifestation of the dystrophin gene abnormality [62].

Although some patients may retain their muscle bulk through replacement by fat and connective tissue, significant muscular atrophy and wasting will develop in others. Progression of weakness occurs at variable rates, with loss of ambulation occurring between 7 and 12 years of age [63]. Further, the loss of ambulation brings on progression or appearance of skeletal deformities. Hip and knee flexor contractures result from wheel chair dependence. The use of steroids in patients with DMD has led to stabilization of their muscle strength, prolonged their ambulation time, and delayed their wheel chair dependence. The prolonged ambulation has also contributed to reduced frequency of scoliosis in these patients.

Clinically, this myopathy is manifest with relentless and progressive muscle weakness and debilitation, and is universally fatal. Onset of respiratory insufficiency is mostly subtle. With progressive loss of respiratory muscle strength, there is increased respiratory morbidity from impaired cough, atelectasis and pneumonia, diurnal respiratory failure, and finally chronic respiratory failure. Respiratory failure appears to be the cause of death in majority of these patients although time to death is variable [64]. The respiratory problems of DMD are traditionally related to the restrictive defect caused by diaphragmatic, intercostal, and accessory respiratory muscle weakness. In addition, these patients develop dilated [65, 66]. In stronger patients, the mortality appears to be most often from associated cardiomyopathy, while weaker patients succumb to respiratory failure [67]. Most DMD patients will die during their second or third decade of life, usually following a respiratory infection [68, 69].

Myotonic Dystrophy

Myotonic Dystrophy or dystrophia myotonica (DM) is a genetically diverse group of muscular dystrophy affecting both children and adults, inherited in an autosomal dominant manner. It is characterized by progressive myopathy, myotonia, and multi-organ involvement. Myotonia, or delay in relaxation of muscle contraction, is a hallmark feature of DM and can be elicited upon physical examination as grip myotonia or by thenar percussion. In addition to myotonia, patients develop progressive muscle weakness and wasting. Involvement of the respiratory musculature often develops as a late stage of disease and is life threatening [70]. Respiratory and cardiac involvements contribute to the majority of mortality associated with DM.

Two genetic forms of DM have been described. The most common form is DM1 (Steinert's disease). DM2 bears a different molecular signature from DM1. DM1 and DM2 each arise from expansion of a nucleotide repeat sequence–on chromosome 19 for DM1 (19q13.3) and chromosome 3 for DM2 (3q21.3). The combined prevalence of the myotonic dystrophies was estimated at 1 in 8,000 before identification of the distinct genetic mutations. DM1 has different sub-types, depending on the age of presentation. Congenital DM1 is the most severe form, and babies are born with global muscular weakness and hypotonia, bulbar weakness, difficulty feeding, early respiratory failure and developmental delays [71]. The childhood-onset DM1 is very atypical, in that its presentation is usually with scholastic difficulties rather than progressive muscular weakness symptoms [72, 73]. These children are usually diagnosed after a parent is diagnosed with adult-onset DM1. With progression, these children develop the symptoms akin to severe, Adult-onset DM1 form. In the latter, symptoms appear between the second and fourth decades of life, and

progression is slow. Myotonia may be misinterpreted to be stiffness, with delays in diagnostic consideration. Mortality in late stages of this group is due to severe muscle weakness, respiratory insufficiency, dysarthria and dysphagia [74]. Muscle weakness progresses in face, neck, and distal extremities with muscle wasting. Atrophy in the facial muscles with ptosis contributes to development of characteristic myopathic facies. Patients with DM1 are predisposed to sudden cardiac death due to fibrosis in the SA node and conduction pathways [74, 75]. Patients may have associated prolonged PR interval or QRS complex, atrial fibrillation or atrial flutter, and serial cardiac monitoring is needed with placement of pace makers as needed [76]. Patients with DM2 may present in many different was, from severe disability and early cardiac death at 40 years in its more severe form, to mild proximal weakness that is hardly recognizable. Cardinal features of DM1, such as myotonia, may be absent in patients with DM2. Onset of weakness is delayed, with a favorable clinical course and normal life expectancy [77, 78] although severe variants have been described [77, 79].

Anesthesia challenges are greater in patients with DM1 due to global muscle weakness, with risk of delayed recovery being most notable. This also results in an increased frequency of recurrent pneumonia in DM1. The progression of restrictive lung defects due to muscle weakness and development of thoracic contractures has been shown to have a direct and independent effect on cardiac events. Kaminsky et al. demonstrated that severe restrictive pulmonary defect (total lung capacity <65 % predicted) in DM1 increases the risk of sudden death 15-fold [80]. Probability of death was only 1 % in patients free of severe restrictive lung disease, while that of patients with severe restrictive lung disease was 17 % at 2 years and 39 % at 5 years. It was also demonstrated that restrictive lung disease increased the probability of cardiac event to 23 and 36 % at 1 and 2 years respectively. Sleep apnea in DM1 has been observed to be both, central and obstructive in origin [81–83]. Lazarus et al. confirmed the frequent coexistence of electrical disorders of the heart and sleep apnea in patients with DM1 [84]. The observation of a high density of episodes of sleep apnea in this population prompted the recommendation that sleep disordered breathing should be aggressively assessed for, since sleep apnea represents a potential precipitant of profound bradycardia, tachyarrhythmias, or both.

Although overall mortality in DM is increased to roughly seven times that of the general population, and typically occurs in the fourth to fifth decade of life. The two most common causes of death in DM are respiratory and cardiovascular disease, and these patients are best served with high index of suspicion to diagnose the disease, and repeated appropriate cardiac and pulmonary evaluations.

Pompe Disease

Pompe disease (also known as glycogen storage disorder type 2 and acid maltase deficiency) is an autosomal recessive disease with a prevalence range of 1 in 40,000 to 1 in 600,000 [85]. The gene defect results in poor activity of acid α-glucosidase which allows accumulation of glycogen in lysosomes in various tissues, most prominently skeletal muscle. The diagnosis is made by demonstration of decreased acid α-glucosidase activity in skin fibroblasts and confirmed by genetics. The degree of weakness correlates roughly to the amount of enzyme activity. The infantile form is severe and presents early with respiratory failure and cardiomyopathy with death before age two if untreated. Later onset forms (early childhood-adult) are highly variable in presentation, severity, and rate of progression. Proximal muscle weakness is usually greater than peripheral and lower extremities more than upper. For this reason presenting symptoms may consist of poor tolerance of exercise or falling.

Respiratory muscle weakness is common and may not correlate well with skeletal muscle weakness. Diaphragmatic weakness is usually out of proportion to other respiratory muscles which results in greater inspiratory dysfunction than expiratory. Because of the disproportionate diaphragmatic weakness REM-related hypoventilation is very common and may be present even in ambulatory patients. The disease course is progressive though the rate and pattern of progression is highly variable. In a prospective cohort of 92 juvenile and adult patients with Pompe disease, van der Beek et al. found an average rate of loss of respiratory function of ~1.2 % per year for vital capacity and 3.8 % per year for MIP and MEP [86]. They found that respiratory symptoms were poor predictors of measured respiratory dysfunction. Respiratory decline was associated with male gender, greater time since symptom onset, and scores of skeletal muscle strength (though the correlation between respiratory dysfunction and skeletal muscle weakness was only moderate with a $\rho = 0.55$). They found a subgroup of rapid deteriorators who had no predictive characteristics. Patients with Pompe disease will commonly need positive pressure support, even in health, but more so with any acute illness. Anesthetic agents and muscle relaxants will have prolonged effect and may contribute to persisting respiratory failure after anesthesia. Mechanical augmentation of cough clearance can help prevent or resolve respiratory failure during respiratory infections. Recombinant acid α-glucosidase infusions have significantly improved survival and function in patients with Pompe disease but offer no cure. In general the impact is greater when started earlier with stabilization in respiratory decline, improvement in cardiomyopathy, and increased physical function observed [87, 88].

Critical Illness Polyneuropathy and Myopathy

Iatrogenic polymyopathy and polyneuropathy can result from the treatment of critical illness and can manifest as severe muscle weakness, quadriparesis, decreased or absent deep tendon reflexes, and failure to wean from mechanical ventilation. Risk factors for critical illness polyneuropathy and myopathy (CIPNM) include critical illness, sepsis, multi-organ failure, status asthmaticus, organ transplantation, hyperglycemia, treatment with corticosteroids, and prolonged neuromuscular blockade. This complication is much more common and well described in adults. Clinically muscle wasting is present in one-third and affects the lower limbs more so than the upper limbs [89]. Creatine kinase is usually normal, and nerve conduction studies and electromyography may show both motor and sensory axonal dysfunction in upper and lower extremities. In patients with failure to wean from mechanical ventilation, peripheral muscle weakness, and diminished reflexes, electrophysiologic studies may help differentiate between myopathy, demyelinating polyneuropathy (GBS, chronic inflammatory demyelinating polyneuropathy), axonal polyneuropathy (CIPNM, axonal GBS), and neuromuscular transmission deficits (myasthenia gravis, Lambert-Eaton myasthenia syndrome) [90]. Muscle biopsy may demonstrate myosin thick filament loss or abnormal variation in muscle fiber size, angulation, and vacuolization [91, 92]. A theoretical pathophysiologic model is of a distal axonopathy due to disturbance of microcirculation, with enhancement of denervation by neuromuscular blockade, and steroid-induced myosin loss [93]. A prospective study of 830 pediatric ICU admissions identified 14 patients (1.7 %) who developed generalized muscle weakness though the incidence was higher (5.1 %) in children >10 years old [91]. Twelve of the 14 patients required mechanical ventilation for more than 5 days. The majority of those affected had received solid organ or bone marrow transplants and had been treated with corticosteroids and neuromuscular blockade. There were three deaths (one due to profound muscle weakness) and significant muscle weakness persisted for at least 3 months in 8 of the 9 children available for long term follow-up. The only current treatment for CIPNM is prevention of systemic inflammatory response syndrome, judicious use of neuromuscular blockade, avoidance of high-dose corticosteroids, prevention of hyperglycemia with intensive insulin therapy, and rehabilitation [94].

Management Approach

As detailed previously, the major physiologic disturbances that lead to respiratory failure in children with children with NMD include: respiratory muscle fatigability, poor cough clearance, chest wall dysfunction, low lung volumes, and poor airway protection from aspiration. It stands to reason that these disturbances guide the therapeutic approach.

Secretion Clearance

Respiratory failure from acute pulmonary infections is the most common cause of death of neuromuscular patients and as a rule they will struggle to clear secretions from their airways. They are susceptible to atelectasis and have difficulty resolving it on their own. Mucociliary clearance is generally not affected by NMD other than due to damage to ciliated epithelium from chronic aspiration or acute infection. During acute respiratory infections assisted airway clearance, usually with devices that do not require patient cooperation or effort, is a required intervention. Aside from manual chest physiotherapy, there are two such devices commonly employed for assistance in mobilizing secretions to central airways to aid in clearance and resolution of atelectasis: high-frequency chest wall oscillation (HFCWO) and intrapulmonary percussive ventilation (IPPV).

Despite their common use and established efficacy in cystic fibrosis, HFCWO devices such as the Vest (Hill-Rom, St Paul, Minnesota, USA) or SmartVest (Electromed, New Prague, Minnesota, USA) have not been well studied in a NMD population. These devices wrap the chest (and some models, the abdomen) in a lifejacket-like garment that is inflated in order to transmit high-frequency oscillations to the chest wall. These micro-compressions are intended to create bursts of airflow to cause cephalad movement of airway secretions. This device requires the wearer to inspire deeply enough to get air behind secretions. A randomized controlled trial compared HFCWO to no treatment in stable adult patients with amyotrophic lateral sclerosis [95]. The authors found improvement in symptoms of breathlessness and night cough but not in spirometry, capnography, or oxygen saturation. In seven patients, aged 7–28 years, with quadriplegic cerebral palsy HFCWO therapy decreased the frequency of pneumonias in the year after introduction compared to the year prior [96]. There are no studied of HFCWO for acute crises in NMD patients.

IPPV (IPV-1C, Percussionaire Corp, Sandpoint, Idaho, USA) delivers high-flow, low volume bursts of positive pressure at 100–300 cycles/min though a mouthpiece, mask, or to a 15 mm (ETT/tracheostomy) adapter. The device supplies continuous nebulization of saline or medication, airway distention, lung expansion, and ventilation over the duration of treatment. Secretions are dislodged and migrated cephalad by the frequent impulses and steady egress of gas from the lungs. There is an inherent attractiveness to IPPV for neuromuscular patients as it provides deep lung inflation for recruitment and does not compromise ventilation during the treatment. The ability of IPPV to provide temporary

improvement in chest wall mechanics in 6 patients with kyphoscoliosis was demonstrated by Sinha and Bergofshy in 1972 [97]. After 5 min of IPPV treatment the study subjects had 70 % improvement in lung compliance and 50 % reduction in work of breathing which was sustained for 3 h. As part of a preventative program, patients randomized to receive IPPV over incentive spirometry experienced fewer hospitalizations for respiratory infections and fewer days of antibiotic use [98]. A cross-over study of eight chronically invasively ventilated patients with late-stage DMD demonstrated that the addition of IPPV to mechanically assisted cough resulted in greater mucus clearance in those with mucus hypersecretion [99]. In a randomized, controlled trial of IPPV compared to CPT in intubated and ventilated pediatric patients with atelectasis, IPPV demonstrated improvement in atelectasis and a shorter number of days of treatment [100]. There was no difference in static lung compliance between the two groups. There is a single case series of IPPV in neuromuscular patients with acute respiratory compromise [101]. Three of four patients with persistent opacities on chest radiographs despite manual chest physiotherapy and assisted cough had improvements in oxygen saturation and radiography within 48 h; the fourth improved more slowly.

Due to severe expiratory muscle weakness and poor cough clearance, assisted cough clearance is a fundamental component of both acute and chronic respiratory health maintenance in patients with NMD [1, 102]. Generating an effective cough requires deep inspiration (to get air behind secretions and load the elastic lung elements) and forceful exhalation (to create high velocity expiratory flow spikes) [26, 103]. In children with NMD this can be achieved through breath-stacking followed by coughs assisted by manual abdominal thrusts or with a mechanical in-exsufflator such as the CoughAssist machine (CA-3200, Phillips Healthcare, Andover, MA, USA). Mechanically-assisted cough can be performed via a mouthpiece, mask, or to a 15 mm (ETT/tracheostomy) adapter. This machine will manually or automatically cycle between positive pressure inhalations and negative pressure exhalations. Inspiratory and expiratory times (seconds) and pressures (cmH_2O) are set. Pressures often start low (+20/−20 cmH_2O) and are then titrated up to effect and comfort. At inspiratory pressures ≥+30 and expiratory pressures ≤−30, exsufflation flows exceed the 2.7 L/s thought needed for adequate mucus clearance [104]. Assisted cough cycles should always end with an inspiration so as not to leave the patient with alveolar de-recruitment.

Feeding and Nutrition

There are some important considerations regarding feeding and nutrition in patients with NMD. Children with NMD may struggle to eat effectively to maintain a positive energy balance, even given decreased energy needs. In patients with SMA type 1, gastrostomy placement is one of the management factors that have resulted in an improved life expectancy [1]. Of particular concern should be the possibility of aspiration. Dysphagia is common amongst congenital and acquired types of NMD that are associated with bulbar weakness or inability to support the head [47, 105, 106]. Risk for aspiration of gastroesophageal reflux is also substantial. Care should be taken to not provide stomach-distending therapies, such as non-invasive ventilation and mechanically-assisted cough while there is food or formula in the stomach. If a fundoplication has not already been performed then transpyloric feeding should be considered. Loss of abdominal muscle tone (narcotic use not-withstanding) will increase the likelihood of constipation. This problem should be anticipated and prevented as the associated loss of abdominal compliance will further restrict breathing in those who are dependent primarily on diaphragmatic excursion.

Non-invasive Ventilation

Patients with NMD commonly need positive pressure ventilatory support to prevent hypercapnia, stabilize oxygen saturations, and prevent atelectasis. They are often unable to appropriately increase their minute ventilation when needed in response to various catabolic stressors like fever, infection or stress of surgery. This may be true even in stronger patients who do not require respiratory support at a baseline. In almost all situations, non-invasive application of positive pressure support is preferred.

The interface most commonly used is a full-face or nasal mask secured firmly, but not tightly, with headgear. The full-face mask delivers higher ventilation pressures with lower leak, requires less patient cooperation, and permits mouth breathing. However, it is associated with reduced comfort, impedes communication, and limits oral intake. The nasal masks or nasal pillows need patent nasal passages and are generally better tolerated but suffer from a greater degree of pressure leak around the mask or from the mouth. This makes reliable monitoring of tidal volume difficult, and represents an important cause of failure [107]. Leaks typically increase with higher pressure delivery, and may also indicate low respiratory compliance or ventilation close to total lung capacity. Acceptance of the degree of leak varies widely, but generally, a leak of 5–25 % may be considered permissible if it allows for the balance between maintaining ventilation and oxygenation on one hand, and comfort (and subsequently the patient's tolerance and cooperation) on the other hand. Over tightening of nasal or full face masks to eliminate leak can lead to pressure necrosis of skin, typically over the nasal bridge. All NIV masks can contribute to aerophagia and gastric distention but more so a full face mask. One must be

careful to vent or decompress the stomach and to avoid simultaneous gastric feeding and NIV unless there is a functioning fundoplication to prevent reflux and vomiting. NMD patients may be too weak to remove a full face mask if they vomit and there is a risk for massive aspiration.

NIV can be delivered by multiple ICU and portable ventilators and in various modes. Basic principals include provision of the lowest PEEP or expiratory positive airway pressure (EPAP) to overcome upper airway obstruction and maintain alveolar recruitment and sufficient inspiratory pressure to produce effective tidal volumes to all lung regions in the face of what may be a stiff chest wall. Expiratory pressures may need to be increased temporarily to overcome significant atelectasis. All modes of NIV have been used to achieve significant physiological or clinical benefit with improvements in minute ventilation, respiratory rate, and arterial blood gases while unloading the respiratory muscles and relieving respiratory distress [108, 109]. Volume- and pressure-controlled modalities appear to reduce inspiratory workload better than pressure support ventilation [110]. Pressure support ventilation can ensure reliable ventilation while minimizing side effects and improving patient comfort. Generally, flow-triggered systems appear superior to pressure-triggered systems [111, 112]. Triggering may be very poor in NMD patients who are very young, very weak, or in those where there is substantial mask leak. These situations may require increasing the sensitivity of the ventilator to be triggered and increasing the back-up rate so the patient has little need to trigger the ventilator, allowing for unloading of respiratory muscles.

Invasive Mechanical Ventilation and Strategy for Extubation

Although non-invasive ventilation is generally preferred, children with NMD may require intubation for elective procedures or for acute respiratory failure. Weaning and extubation of children poses unique challenges and therefore any elective intubation should be carefully discussed with the patient (when appropriate) and their caregivers; decisions should be made in the context of their values. These children are at a greater risk of failure to extubate and the patient and family often already had extensive conversations (and formed strong opinions) regarding a desire to ever receive a tracheostomy [113–115]. Once placed, removal of a tracheostomy can be quite difficult, though not impossible. It is usually best to avoid intubation if at all possible, as NIV and very frequent aggressive airway clearance can usually support a child with NMD through an acute illness. Intubation for respiratory failure in patients with NMD often persists for weeks [116–118].

Table 16.2 Extubation criteria for unweanable ventilator-dependent patients

Afebrile and normal WBC count
Age 4 years or older
No ventilator-free breathing tolerance with 7-cm pressure support in ambient air on the basis of NMD
VC <20 % of normal
$PaCO_2$ ≤40 mmHg at peak inspiratory pressures <35 cmH_2O on full-setting assist/control mode at rate of 10–13 bpm
SpO_2 ≥95 % for 12 h or more in ambient air
All oxyhemoglobin desaturations <95 % reversed by mechanically-assisted cough and suctioning
Fully alert and cooperative, receiving no sedative medications
Chest radiograph abnormalities cleared or clearing
Air leak via upper airway sufficient for vocalization upon cuff deflation

Reprinted from Bach et al. [120]. With permission from American College of Chest Physicians
NMD neuromuscular disease, *VC* vital capacity

If intubation is required it is important to recognize that, unlike children with normal respiratory muscle strength, children with NMD do not tolerate extended periods of increased respiratory effort prior to or immediately following extubation; they are much more prone to respiratory muscle exhaustion. Due to diminished inspiratory capacity, children with NMD are often not able to resolve even a mild degree of atelectasis on their own and may therefore deteriorate back to respiratory failure. For this reason many recommend avoidance of extubation until atelectasis and hypoxemia are resolved. As a rule, children with NMD should be extubated to continuous BiPAP or other non-invasive ventilation. Non-invasive ventilation should not be reserved only for respiratory decline following extubation. Despite the fact that performance of airway clearance and mechanically assisted cough may cause transient desaturations, aggressive removal of lower airway secretions is essential and should be performed as it is a strong predictor of extubation success [119, 120].

In 2010 Bach et al. reported a protocol for extubation of unweanable patients with neuromuscular disease with a success rate of 91 % [120]. Patients with a cough peak flow >160 L/min had a higher success rate (100 %) than those with lower cough peak flow (80 %). Patient's prior experience with non-invasive ventilation and mechanically assisted cough were also significant predictors of success. Bach's criteria for extubation are listed in Table 16.2 and patients were extubated directly to NIV. NIV was delivered by a combination of mask or 15-mm angled mouthpiece (depending on bulbar weakness) and ventilation was achieved either in assist-control mode with rate of 10–14 or pressure control of at least 18 cmH_2O. Cough assist with abdominal thrusts on exhalation was performed as often as every 20 min to keep SaO_2 greater than 95 %. Non-invasive management is

extremely intensive and requires tight cooperation between ICU therapists and family caregivers to provide such a high frequency of airway clearance and cough assist and appropriate response to what may be subtle signs of compromise. Each stage of eventual return to respiratory baseline should be expected to be prolonged as compared to children without respiratory muscle weakness.

Tracheostomy

For patients with congenital muscular dystrophies and spinal muscle atrophy the decision making around placement of a tracheostomy is especially challenging. Despite aforementioned barriers to extubation, the majority of patients with even severe respiratory muscle weakness can be managed without tracheostomy. Bach et al. reported their retrospective experience of 56 SMA-1 patients with a history of respiratory failure prior to age 2 [121]. They compared the outcomes of three groups: 16 children with tracheostomy, 33 children with nocturnal NIV and cough assist plus tracheal intubation for acute infections, and seven children who died of respiratory failure after tracheal intubation or tracheostomy were rejected. Those children with tracheostomies had fewer hospitalizations before the age of 3 years, but this group also had more hospitalizations after the age of 5 years compared to those children using NIV. Fifteen of the children with tracheostomies required full mechanical ventilator support 24 h per day. Those using NIV had fewer hospitalizations after age 5 years and were more likely to be support-free during waking hours, though three of the 31 children in this group who survived beyond 13 months required virtually continuous NIV. The seven children in the third group died at 5–13 months of age when either the family rejected support or it was not offered. Soudon et al. reported similar outcomes for end-stage DMD patients who required >15 h of ventilation per day [122]. Sixteen were ventilated via tracheostomy and 26 non-invasively, both groups for a similar number of hours per day. Eight of the tracheostomized patients died compared to ten of the non-invasive patients. Over all the patients with tracheostomies experienced greater morbidity: tracheal injury, chronic mucus hypersecretion, frequent chest infections, and dysphagia. The patients without tracheostomy had more weight loss and need for gastrostomy. When the need for chronic respiratory support chronically exceeds nocturnal use, maintenance of support may become uncomfortable or intolerable, depending on personal preferences and the types of interfaces that can be utilized. Thus, the decision to place a tracheostomy tube is largely a preference-based decision in which patients and their families should decide between the advantages and disadvantages of invasive versus non-invasive respiratory support. It is only essential that the family understand the dynamic consequences of any therapeutic plan and that their medical providers partner with them to deliver it.

Palliative Care

Although survival with neuromuscular diseases continues to increase, survivorship is accompanied by tremendous amounts of disability, as well as cost, complexity and intensity of medical care [123]. Palliative care can be utilized to aid pediatric patients to cope with the strains of their chronic life-threatening illness, in the context of their current level of behavioral, cognitive, and emotional development. Patients and their families may mourn each and any change in status. The intensive intervention that is required to support a child with NMD through acute illness can be associated with pain, fear, discomfort, and breathlessness. Pediatric palliative care teams can provide support to patients and families for respite, symptom management, transition, and end-of-life care [124].

Conclusion

As a rule, congenital and acquired disorders that cause respiratory muscle weakness result in significant morbidity due to respiratory pump failure and inadequate secretion clearance. One should not underestimate the tendency for children with NMD to show only subtle signs of respiratory insufficiency only to suddenly decompensate into overt failure. Children with NMD for example are less likely than others to be able to resolve atelectasis on their own and they require a lower threshold for intervention and escalation of support. Despite these risks and challenges, longevity and function are continually improving, largely due to liberal use of non-invasive ventilation, assisted cough clearance, and adequate nutrition.

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Part II

The Cardiovascular System in Critical Illness and Injury

Applied Cardiovascular Physiology in the PICU

17

Katja M. Gist, Neil Spenceley, Bennett J. Sheridan, Graeme MacLaren, and Derek S. Wheeler

Abstract

Normal cellular function is critically dependent upon oxygen, as evidenced by the relative complexity of the organ systems that have evolved to transport oxygen from the surrounding environment to the cells – namely, the cardiac, respiratory, peripheral vascular, and hematopoietic systems. Cells do not have the means to store oxygen, and are therefore dependent upon a continuous supply that closely matches the changing metabolic needs that are necessary for normal metabolism and cellular function. If oxygen supply is not aligned with these metabolic requirements, hypoxia will ensue, eventually resulting in cellular injury and/or death. In addition to the body's compensatory mechanisms to augment oxygen delivery to the tissues, most of the management of critical illness is directed at restoring the normal balance between oxygen delivery and oxygen consumption. A thorough understanding of cardiovascular physiology, particularly as it applies to the management of the critically ill child in the Pediatric Intensive Care Unit (PICU) is therefore of utmost importance.

Keywords

Hemodynamics • Oxygen delivery • Venous return • Cardiac output • Neuroendocrine stress response • Shock • Mean circulatory filling pressure • Excitation-contraction coupling • Fetal circulation

Introduction

Normal cellular function is critically dependent upon oxygen, as evidenced by the relative complexity of the organ systems that have evolved to transport oxygen from the surrounding environment to the cells – namely, the cardiac, respiratory, peripheral vascular, and hematopoietic systems. Cells do not have the means to store oxygen and are therefore dependent upon a continuous supply that closely matches the changing metabolic needs that are necessary for normal metabolism and

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cellular function. If oxygen supply is not aligned with these metabolic requirements, hypoxia will ensue, eventually resulting in cellular injury and/or death. As early as 1872, Pflueger suggested that variables such as arterial oxygen content (CaO_2), arterial blood pressure, cardiac output, and respiratory rate are all incidental and subordinate to the needs of the cell. Several years later, Guyton followed that *The main goal of the circulation is to serve the needs of body tissues*, *ensuring optimal function and survival*. Physiology has changed little, if any, since the recognition of its important role centuries ago. However, over the years, by investigating the theoretical, animal, and human aspects of physiology, our understanding of this discipline has improved considerably. Advances in hemodynamic monitoring have further allowed physicians to apply this knowledge to the management of critical illness, to detect and manipulate the disturbed physiology in critically ill patients, and, most importantly, improve outcome. By substituting *circulation* with *physician*, Guyton's statement now describes the specific role of the bedside provider in the Pediatric Intensive Care Unit (PICU).

Avoiding hypoxia (through either inadequate oxygen delivery (DO_2) or excessive VO_2) is one of the most fundamental tenets of critical care medicine. Assessing whether DO_2 is sufficient at the bedside relies on more than just clinical acumen. Advanced hemodynamic monitoring is mandatory, but with our understanding of oxygen delivery becoming more complex there is a tendency to match this complexity from a technological standpoint. Detecting an obvious or evolving picture of abnormal physiology, and subsequently assessing the efficacy of intervention is fundamentally linked to our interpretation of DO_2 and VO_2. Neither of these variables can be routinely measured at the bedside, therefore resulting in the bedside providers reliance on indirect indicators of DO_2, VO_2, and oxygen extraction. When the basic physiological processes of DO_2 are interrupted or overwhelmed by disease, an imbalance between supply and demand occurs. In the critically ill child, this is the principle derangement, but inadequate utilization or a combination of these derangements is also recognized. Either way the end point is the same – hypoxia, organ dysfunction, morbidity, and eventually death. Cellular hypoxia will eventually have obvious consequences, and clinical evidence of a disturbance in this fragile physiological balance will reveal itself with time. Evolving hypoxia is subtler, yet early detection is desirable. Therefore, the successful understanding and application of physiology aims to detect faltering oxygen delivery early, provide oxygen to the cells commensurate with their demand, and facilitate its use prior to established hypoxia.

DO_2 is defined as the amount of oxygen transported to the tissues per minute:

$$DO_2 = CO \times CaO_2 = CO \times \begin{bmatrix} (1.36 \times Hb \times SaO_2) \\ + (0.003 \times PaO_2) \end{bmatrix} \quad (17.1)$$

where CO is the cardiac output (L/min), CaO_2 is the arterial oxygen content (mL O_2/dL blood), Hb is the hemoglobin concentration (g/dL), 1.36 is the amount of oxygen (mL) that 1 g of hemoglobin can carry (this constant varies from 1.34 to 1.39, depending upon how it is measured), and PaO_2 is the partial pressure of O_2 in the blood (mmHg). Importantly, oxygen delivery is not homogeneous throughout the body and its distribution is determined by central upstream (macro circulation) and peripheral downstream (microcirculation) factors. Although the process of oxygen utilization and cellular function occurs at the microcirculatory level, the most important component is providing an adequate gradient across the capillary beds to ensure a constant supply. Adequate DO_2 is facilitated by combining the arterial oxygen content (CaO_2) (a reflection of pulmonary function, hemoglobin concentration and its percentage saturation) with cardiac output (CO). Cardiac output is the most important element in DO_2, by quickly being able to compensate for a reduction in CaO_2 for whatever cause. The reverse is not necessarily true. The fundamental principles of cardiopulmonary resuscitation (CPR) support this contention, as chest compressions alone can deliver sufficient oxygen, even though effective ventilation with no chest compressions cannot, at least in adults [1, 2]. In this chapter, we will review the basic principles of cardiovascular physiology, specifically how these principles apply to the manipulation of both cardiac output and arterial oxygen content in the clinical setting.

Developmental Cardiac Anatomy

While a detailed discussion of cardiac development is beyond the scope of this chapter, we have provided a brief summary of the salient points. The critical period of cardiac development begins just prior to the third week in the growing embryo. During the third week, there is formation of the primary heart tube, and by 22 days the heart begins to beat. Cardiac looping begins by the fourth week, as does development of the vasculature (Fig. 17.1). The early right and left ventricles begin to form between the fourth and fifth weeks, along with the atrioventricular cushions and the pulmonary veins. During the fifth week, the right and left ventricles are formed, and growth of the pulmonary veins into the left atrium occurs. Formation of the aortic arches also begins at this time. Truncal septation and formation of the semilunar valves begins just prior to the 6th week of cardiac development, and by the 7th week, ventricular septation is complete. The patent foramen ovale (PFO) and patent ductus arteriosus (PDA) remain until birth (discussed below). By 8 weeks, there is complete development of the heart [3–5]. Neural crest and other cells contribute to cardiac formation, and abnormalities within these cells and signal transduction may lead to alterations in cardiac morphogenesis leading to the large variety of congenital cardiac defects [6]. Several excellent and detailed reviews on cardiac development, and the current knowledge of abnormal cardiac development have been published, and we refer the reader to these articles for additional details [3–9].

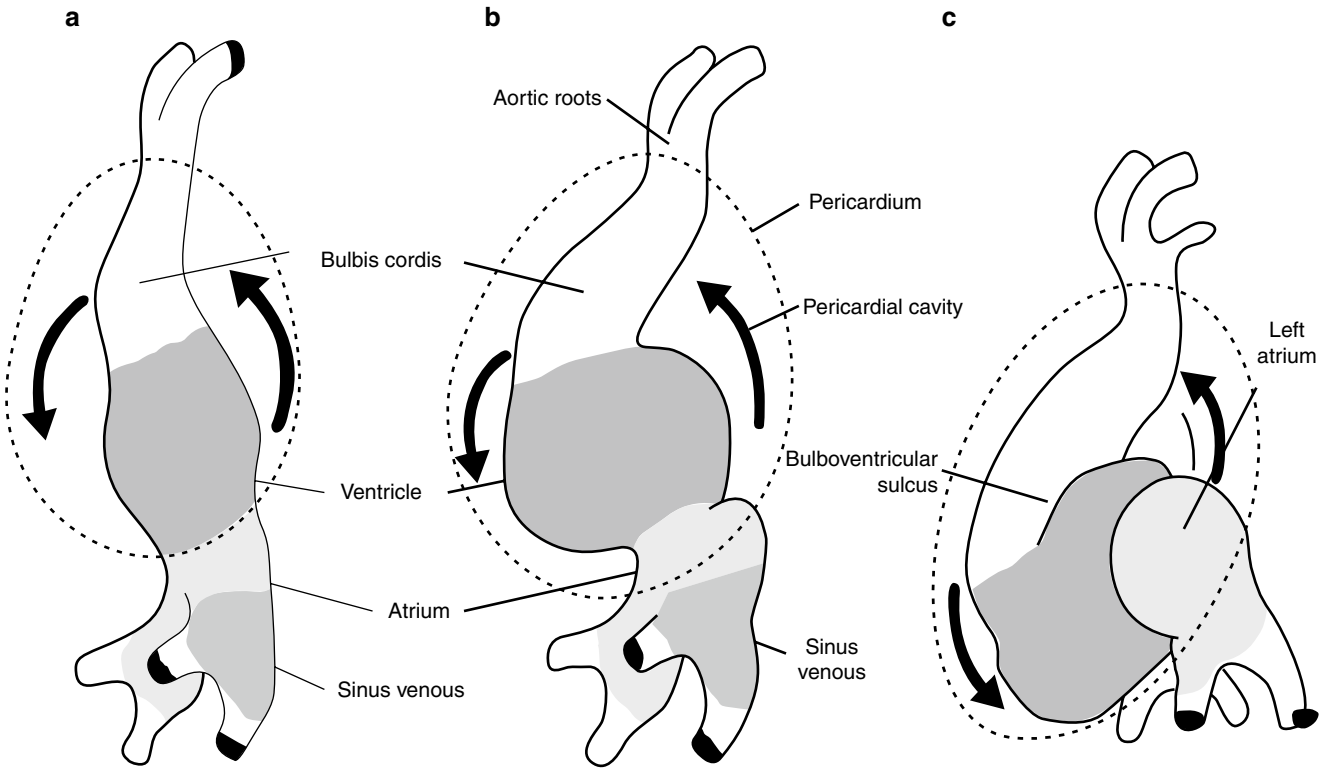


Fig. 17.1 Primitive heart tube is shown with the five embryologic structures that will form all future cardiac anatomy. From caudal to cranial, these structures are the (1) sinus venosus; (2) atrium; (3) ventricle; (4) bulbus cordis divided into a proximal (a) conus cordis and distal (b) truncus arteriosus; and (5) aortic sac. The progression from panels (**a**–**c**) illustrate the normal looping in which the heart tube rotates to the right to form the normal heart structures

Chambers of the Heart

The end result of normal cardiac development results in the formation of a heart that is composed of four chambers, two atria and two ventricles. The heart acts as a large pump connected to a network of blood vessels that carry blood with all of its metabolic substrates either toward or away from the peripheral tissues. The two ventricles function in series, with the right ventricle (RV) pumping blood to the pulmonary circulation, and the left ventricle (LV) pumping blood to the systemic circulation. The atrioventricular (AV) valves separate the atria from the ventricles, with the tricuspid valve separating the right atrium (RA) and RV. The left atrium (LA) and LV are separated by the mitral valve. The pulmonary and aortic valve are also known as semilunar valves and separate the RV and LV from the pulmonary artery and aorta, respectively. The atrial septum separates the atria, and *in utero*, there is a flap permitting right-to-left shunting across the PFO. The ventricular septum separates the right and left ventricles. Persistent defects in both the atrial and ventricular septum can occur, leading to persistent shunting beyond fetal life, which may bear consequences to the underlying hemodynamics and cardiac physiology.

The LV cavity is conical shaped during diastole (ventricular relaxation), and assumes a more spherical shape as the intraventricular pressure increases at the end of isovolumetric contraction. The oblique orientation of the fibers in the LV free wall and septum allow for the ringing or twisting that is required to eject blood [10]. The ventricular septum is an important component of the RV, and plays an important role in ventriculoventricular interactions (discussed below). Fiber orientation of the RV free wall and the septum play a significant role in determining ejection. The RV free wall contains predominantly transverse fibers, while the septum contains oblique fibers. While the LV fiber orientation allows for the twisting motion, the transverse fibers in the RV free wall generate a compressive force, allowing the ventricle to eject blood into the low resistance pulmonary vascular bed under normal conditions [10]. When the PVR is raised, the oblique fibers play a significant role in determining ventricular function [10–12].

Pericardium

The heart is surrounded by the pericardium that is composed of two layers, the visceral pericardium and the parietal pericardium. The visceral pericardium is in direct contact with the myocardium. The parietal pericardium is composed of several layers of elastic and collagen fibers and is separated from the visceral pericardium by a small amount of fluid creating a potential space (which normally contains a small amount of pericardial fluid). The pericardium encloses the

great arteries superiorly at the junction between the ascending aorta and the transverse aortic arch, the pulmonary artery just beyond its bifurcation, and the superior vena cava below the azygous vein. The inferior pericardial attachment includes a segment of the inferior vena cava and the posterior attachment includes the proximal pulmonary veins. The function of the pericardium is to prevent excessive motion of the heart within the chest. The pericardium also limits to some extent how much the heart itself can distend as it fills with blood (called "pericardial constraint") [13–19]. These concepts are discussed further in the chapters on cardiorespiratory interactions and diseases of the pericardium.

Coronary Circulation

The heart receives its blood supply from coronary arteries that originate from the left and right aortic sinuses. The left common coronary artery divides into the left anterior descending and the circumflex coronary artery. The right coronary supplies blood to a large portion of the right ventricle, and approximately 25–35 % to the left ventricle. From the origin of the right coronary artery at the aortic sinus, it travels in the atrioventricular groove toward the crux of the heart. About 75–85 % of the population have a right dominant coronary system [20], where the posterior descending coronary artery branches from the right coronary artery – in this case, the inferior portion of the interventricular septum receives its blood supply from the right coronary artery via the right posterior descending coronary artery, or PDA branch (not to be confused with a PDA, patent ductus arteriosus) [20, 21]. The coronary artery supplying the sinoatrial (SA) node branches off the right coronary artery in 60 % of the population and from the circumflex artery in 40 % of the population (this has no relation to whether the coronary artery is right dominant or not).

Peripheral Vasculature

The systemic vasculature is composed of concentric layers, which includes the intima, media and adventitia (from inside to outside). There are some portions of the vasculature that may be missing a layer. The intima contains the vascular endothelium that is responsible for the critical vascular metabolic processes. It also acts as a barrier to the movement of substances of varying permeability into the interstitial space. The larger arteries contain an internal elastic lamina that separates the intima from the media, and is composed of smooth muscle. The vasa vasorum are the intervening interface that contain nerves and perforating vessels that nourish the arteries themselves. The external elastic lamina separates the media from the adventitia, and contains vasa vasorum, nerves and connective tissue. As arteries become smaller, the quantity of elastic tissue decreases, with the arterioles having the least. Contraction of the smooth muscle decreases compliance, making it stiffer with an overall smaller luminal diameter. Capillaries are small, thin-walled vessels that lack all the components of the normal vasculature, except the endothelial cell layer. Their structure makes them ideal for transporting and receiving substances from the tissues that they supply. Veins differ from arteries in that they have thinner walls and larger luminal diameters. Veins also contain unidirectional valves that prevent blood from moving backward away from the heart.

From Fetus to Newborn: The Transitional Circulation

The fetal circulation differs significantly from the adult circulation. The placenta has an extremely large surface area resulting in a low vascular resistance. It receives deoxygenated blood from the fetal systemic organs, and returns oxygen rich blood to the fetal systemic arterial circulation. In addition, certain adaptations have occurred such that the most oxygenated blood is delivered to the myocardium and brain through preferential streaming and the presence of intracardiac and extracardiac shunts. Oxygenated and nutrient rich blood is transported from the placenta via an umbilical vein to the fetus. The deoxygenated blood is returned to the placenta via two umbilical arteries. The saturation of fetal blood is 80–90 %. Approximately 50 % of this blood enters the ductus venosus and enters the inferior vena cava (IVC). The remainder enters the liver through the hepatic veins. In the IVC, the more oxygenated blood is thought to stream separately from the extremely desaturated systemic venous blood that is returning from the lower portions of the body. The saturation of this desaturated blood ranges from 25 to 40 % (Fig. 17.2). A small tissue flap at the junction of the right atrium and IVC, known as the Eustachian valve, directs oxygenated blood across the PFO and into the LA. The blood then enters the LV and is ejected into the ascending aorta. The majority of the LV blood is delivered to the brain and coronary circulation. Desaturated blood (25–40 % saturated) returning to the heart via the superior vena cava (SVC) and the coronary sinus (20–30 % saturated), as well as that from the hepatic vessels is directed across the tricuspid valve and into the RV (Fig. 17.2). It is then ejected into the pulmonary artery. Because the lungs are collapsed and fluid filled, only about 8–12 % of the RV output enters the pulmonary circulation, with the remaining portion crossing the ductus arteriosus (DA) into the descending aorta. The lower half of the body is therefore supplied with relatively desaturated blood. As a result of intracardiac and extracardiac shunting in the fetus, the stroke volume of the LV is not equal to that of the RV. The RV receives about 65 % of the

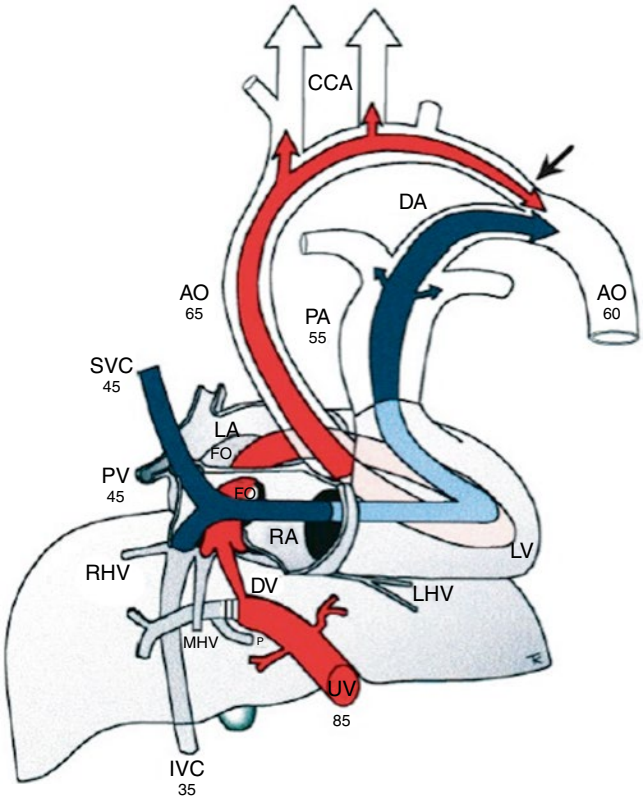


Fig. 17.2 Fetal circulation, including oxygen saturation values (in numbers). Red blood is directed through the ductus venosus (DV) across the inferior vena cave (*IVC*) through the patent foramen ovale (*FO*), left atrium (*LA*) and left ventricle (*LV*) and up the ascending aorta to join the deoxygenated blood (*blue*) in the descending aorta. Additional deoxygenated blood (*blue*) form the superior vena cava (*SVC*) and IVC flows through the right atrium, and is directed into the right ventricle (*RV*) via streaming and the Eustachian valve, then to the pulmonary artery (*PA*) and ductus arteriosus (*DA*). The aortic isthmus is represented by the *arrow*. *RHV* right hepatic vein, *LHV* left hepatic vein, *CCA* Common carotid artery, *AO* Aorta, *UV* umbilical vein, *MHV* middle hepatic vein, *PV* pulmonary vein. (Reprinted from Kiserud and Acharya [103]. With permission from John Wiley & Sons, Inc.)

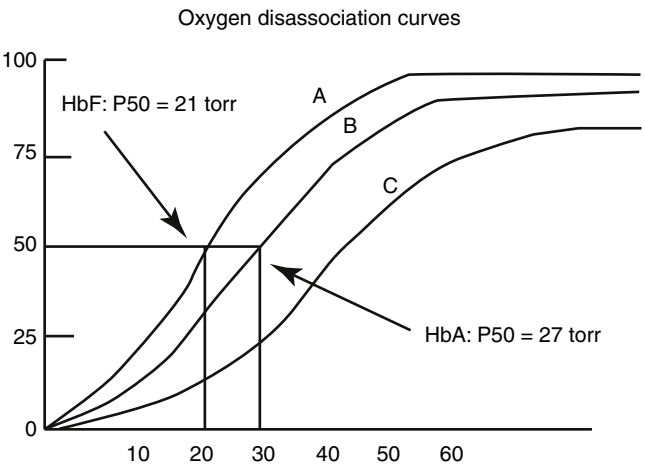


Fig. 17.3 Oxygen dissociation curve of fetal hemoglobin (*HbF*) (curve *A*) compared with adult haemoglobin (*HbA*) (curve *B*) as well as the rightward shift of the HbA curve (curve *C*) associated with several physiology processes, including 2,3-diphosphoglycerate

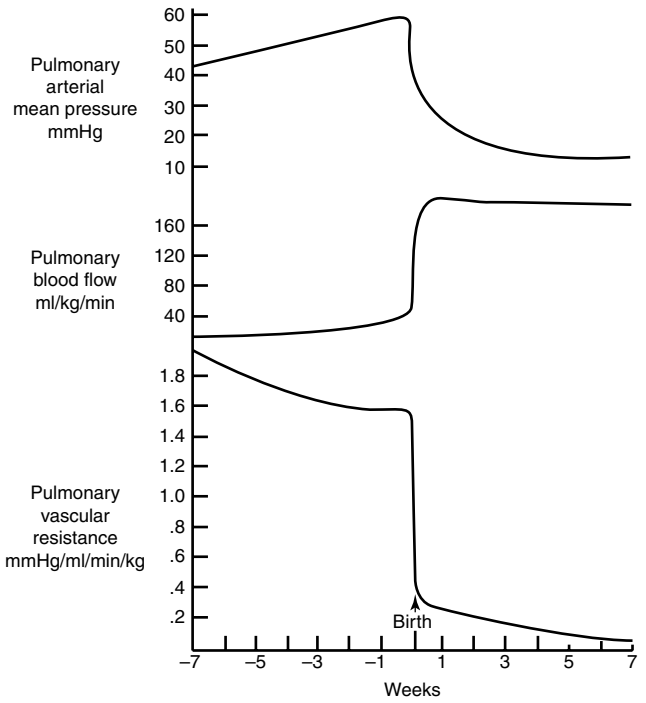


Fig. 17.4 Changes in pulmonary artery pressure, pulmonary blood flow and pulmonary vascular resistance during the terminal portion of pregnancy, birth and the first several weeks after birth

venous return and the LV about 35 %. Therefore, cardiac output in the fetus is described as combined ventricular output, where about 45 % is directed to the placental circulation and 8 % entering the pulmonary circulation.

Oxygen content is determined by the quantity of hemoglobin and its oxygen saturation. The fetal hemoglobin at term is high (approximately 16 g/dL), of which the largest proportion, is comprised of fetal hemoglobin (HbF). HbF has a lower concentration of 2,3-diphosphoglycerate, and thus shifts the oxy-hemoglobin saturation curve leftward resulting in a higher affinity for oxygen (Fig. 17.3). The partial pressure of oxygen at which fetal hemoglobin is approximately 50 % saturated (i.e., the P50) is 19 mmHg, compared to 27 mmHg in the adult. Despite the low partial pressure of oxygen (PO_2), the combined ventricular output, high hemoglobin concentration, and the presence of HbF help to maintain oxygen delivery in the fetus.

The changes in the central circulation after birth are primarily a result of external events, rather than changes in the circulation itself. There is a rapid and large decrease in pulmonary vascular resistance (PVR) with disruption of the umbilical-placental circulation. With this decrease in PVR, there is an increase in pulmonary blood flow and a concomitant decrease in pulmonary artery pressure (Fig. 17.4). Gas exchange is transferred from the placenta to the lungs, the fetal circulatory shunts close, and the LV output increases. Several factors are involved in the cessation of placental circulation at birth. The umbilical vessels are reactive and con-

strict in response to longitudinal stretch and an increased PO_2 in the blood. External clamping of the cord augments this process [22]. With the removal of the placenta, there is a dramatic fall in the flow through the ductus venosus and a significant fall in the venous return through the IVC. The ductus venosus closes passively between 3 and 10 days after birth. During late gestation, there is a gradual decline in pulmonary PVR. At birth, expansion of the lungs results in an abrupt and dramatic fall in PVR accompanied by an eight to tenfold increase in pulmonary blood flow. Studies in fetal lambs have demonstrated that mechanical expansion of the lungs with deoxygenated gas results in a massive fall in PVR [22]. The process is thought to be mediated by pulmonary stretch receptors resulting in reflex vasodilation and increased flow through the pulmonary vessels [22]. The increase in PO_2 also decreases the hypoxic pulmonary vasoconstriction, thereby further decreasing PVR. Because the pulmonary blood flow increases, and there is a decrease in IVC flow, there is an increase in pulmonary venous return to the left atrium, with a subsequent increase in left atrial pressure above the right atrial pressure. As a result, the flap of the foramen ovale is pushed against the atrial septum and the atrial shunt is effectively closed. Flap closure of the atrial septum can occur within minutes to hours after birth. Anatomical closure typically occurs weeks to years later with proliferation of tissue over the flap. Patency of the foramen ovale can persist for many years, but it is not usually hemodynamically significant. Atrial level shunts of any significance occur only in the setting of a deficiency of the primum septum, resulting in a secundum atrial septal defect, or when there is failure of fusion of the endocardial cushions leading to a primum atrial septal defect.

At the same time that PVR falls, the shunt at the ductus arteriosus (DA) becomes bidirectional and then all left to right. Closure of the DA occurs in 2 phases, the first being functional closure of the lumen by smooth muscle constriction, and the second being anatomic closure which occurs several days later by neo-intimal thickening and loss of the smooth muscle cells from the inner muscle media [23]. Smooth muscle constriction resulting in functional closure of the DA is secondary to an increase in arterial PO_2, a decrease in blood pressure within the DA lumen (due to the decrease in PVR) and a decrease in circulating prostaglandin E_2 (PGE_2). After delivery, there is loss of PGE_2 production and an increase in removal from the lung with a concomitant decrease in PGE_2 receptors in the ductal tissue [24].

Cardiac Contraction and Relaxation: From Cell to Function

Cardiac Myocyte

The cardiac myocytes are elongated specialized striated cells, with the sarcomere being the basic contractile unit of the muscle. The sarcomere contains all the myofibril contractile elements. Cardiac myocytes differ from regular striated muscle in that they have the ability to spontaneously depolarize – therefore, neural innervation is not required for the heart to contract. The heart also contains specialized cardiac conduction (pacemaker) cells with relatively few contractile elements. These specialized cells are localized to the sinoatrial (SA) node, the atrioventricular (AV) node, and the purkinje cells [25]. Cardiac myocytes increase in number and size with maturation of the heart. This maturation occurs mainly in fetal life and shortly after birth [26]. In the mature myocyte, contractile elements are organized into myofibrils that are arranged in rows parallel to the long axis of the cell, alternating with mitochondria. This is in contrast to the immature myocyte, where the arrangements of the contractile elements are more haphazard, and where there are overall less myofibrils [27–29].

Myocardial Bioenergetics

The mitochondria are the powerhouses of the cell, and their size and relative volume increase during development [30]. The process of energy conversion and utilization in the cell is complex. Energy, in the form of adenosine triphosphate (ATP) is derived from several sources. These energy sources differ in the fetus, neonate, and adult [31–33]. The fetus utilizes carbohydrates in the form of lactate (60 %), glucose (35 %), and pyruvate (5 %), whereas the adult heart consumes free fatty acids (90 %), with little energy derived from carbohydrate and amino acids. At birth, a glucagon surge occurs that switches the utilization of energy substrates from carbohydrates to fatty acids [34]. Nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$) are produced in the Krebs cycle and pass through the electron transport chain system, transferring electrons to oxygen. Oxidative phosphorylation takes place in the cristae of the mitochondria after a hydrogen ion gradient is established, thus producing ATP, which is then transported out of the mitochondria (Fig. 17.5). Defects within the mitochondria and its membrane are known to contribute to heart failure [35].

The adult heart consumes 8–15 mL O_2/min/100 g tissue at rest, which can increase to 70 ml O_2/min/100 g tissue with exercise [33]. These needs can only be met by aerobic metabolism. Myocardial oxygen consumption is directly proportional to wall tension generated by the ventricle, defined by the pressure volume area [36] and heart rate. Because myocardial wall stress is one of the determinants of oxygen consumption, it is important to have an understanding of Laplace's law [37, 38]. Laplace's law states that wall tension is directly proportional to the pressure generated within the ventricle and the radius of the ventricle, and inversely proportional to the thickness of the ventricular wall

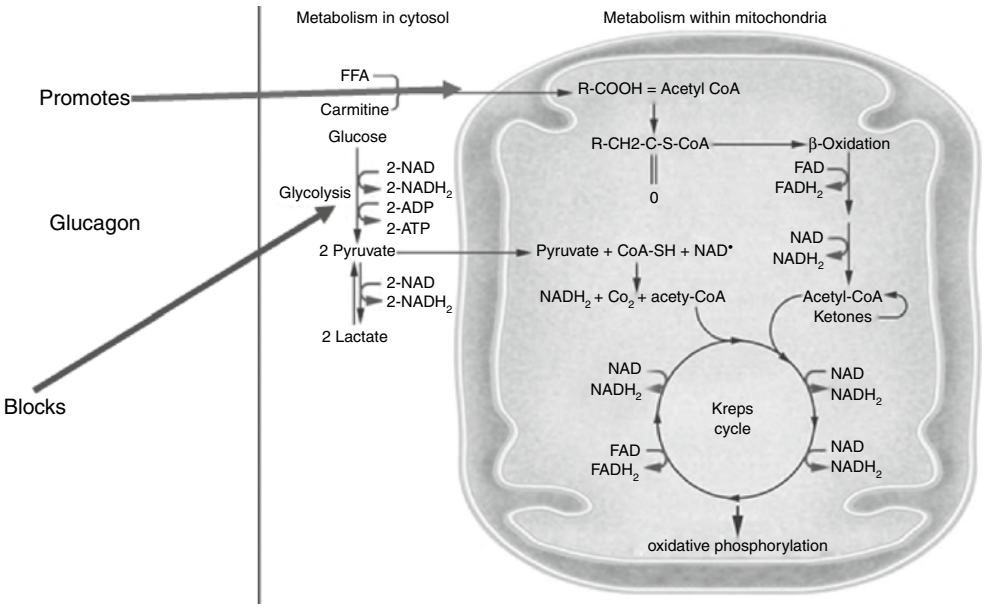


Fig. 17.5 Energy substrates for the generation of adenosine triphosphate in the cardiomyocyte come predominantly from glycolysis (fetus) and B oxidation of free fatty acids (adult). These energy sources create acetyl CoA, which then generates nicotinamide adenine dinucleotide (*NADH*) and flavin adenine dinucleotide ($FADH_2$) necessary for oxidative phosphorylation in the mitochondria. The glucagon surge shifts the cardiomyocytes into utilizing free fatty acids rather than glucose. *CoA* coenzyme-A, *NAD* nicotinamide adenine dinucleotide, *FAD* flavin adenine dinucleotide, *FFA* free fatty acids

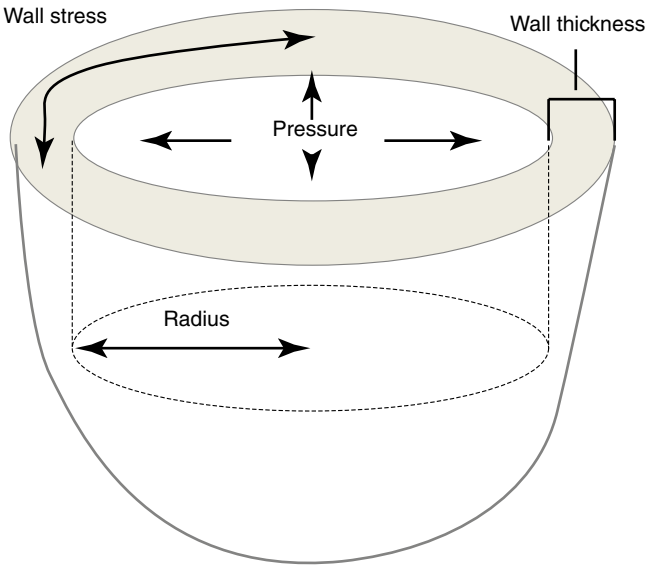


Fig. 17.6 Ventricle demonstrating the Law of Laplace. Wall stress increases the tension in the myocardium and reduces myocardial blood flow, counteracting myocardial shortening. Wall stress is directly proportional to the pressure generated within the ventricle and the radius of the ventricle, and indirectly proportional to wall thickness

(Fig. 17.6) [39, 40]. The ventricular pressure and wall stress change as blood is ejected from the ventricle from shortening to force generation. Certain conditions may lead to increased wall stress, and as a result, there is increased oxygen consumption. These conditions include certain disease states that result in a dilated ventricle (ventricular septal defect, dilated cardiomyopathy) or increased pressure within the ventricle (aortic stenosis) [40–44]. Cardiac hypertrophy is adaptive in some conditions to decrease wall tension, and those with hypertrophic cardiomyopathy have less wall stress [45, 46].

Excitation Contraction Coupling (ECC)

The sarcolemma (plasma membrane) contains the ion channels, ion pumps and exchangers that contribute to maintenance of the chemical gradient between the intracellular and extracellular spaces. The flux of ions across this membrane controls membrane depolarization and repolarization. Defects in specific ion channels cause arrhythmias that may result in sudden death – the discussion of these specific ion channel defects is beyond the scope of this chapter (see the accompanying Chap. 27 for additional information). Of the ions involved in contraction and relaxation of the heart, calcium is crucial for the process of excitation contraction coupling (ECC) [47]. ECC is the process from electrical excitation of the myocyte to contraction of the heart. Calcium is the activator of myofilaments that causes contraction of the heart, and is discussed below.

There are two major parts of ECC – namely, excitation and contraction. The immature myocardium is more dependent on the L-type calcium channels for normal ECC, whereas more mature myocardium depends upon calcium-induced calcium release (CICR). Excitation begins with generation of the normal action potential (Fig. 17.7) [47]. Cardiac myocytes have a resting membrane potential (**phase 4**) that is near the equilibrium potential of potassium (−90 mV). During the equilibrium phase, potassium channels are open, and fast sodium and slow (L-type) calcium channels are closed. This results in the net movement of potassium ions out of the cell (down the concentration gradient). Spontaneous depolarization occurs when the L-type calcium channels open to allow entry of calcium ions into the cell. Once a critical threshold voltage is reached (−70 mV), voltage gated fast sodium channels open, resulting in a rapid influx of sodium ions and subsequent rapid

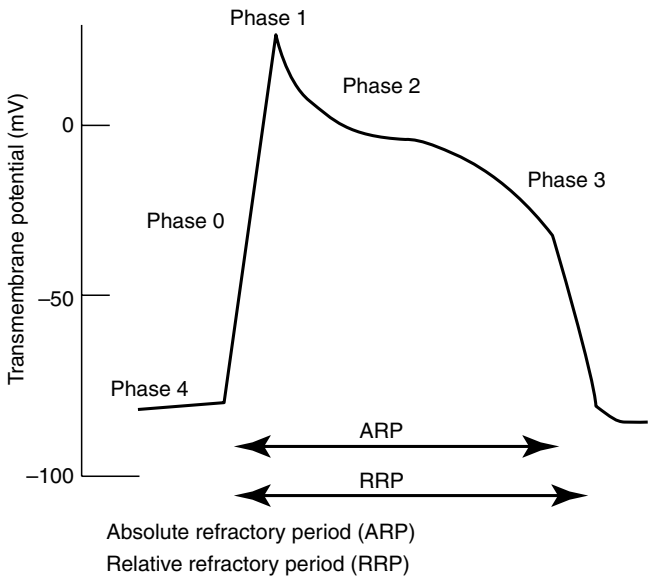


Fig. 17.7 Phases of the cardiomyocyte action potential. Diastolic depolarization occurs during *phase 4* until threshold is met, initiating *phase 0* depolarization (systole). *Phase 1* follows as an overshoot of the voltage within, followed by *phase 2* or the plateau phase when voltage remains slightly less than 0. *Phase 3* begins the return to resting maximal negative potential (–90 mV). During specific time periods within *phase 3* are the absolute refractory period (*ARP*) and the relative refractory period (*RRP*). Finally, onset of *phase 4* begins, when there is maximally negative potential within the cardiomyocyte (Reprinted from Gjesdal et al. [39]. With permission from Nature Publishing Group)

depolarization (**phase 0**). At the same time, potassium channels close, and the outward net movement of potassium ions decreases. The net effect is that the membrane potential of the cardiac myocyte approaches the equilibrium potential for sodium, which is approximately 10 mV. **Phase 1** of the action potential begins with inactivation of the fast sodium channels, and opening of a different type of potassium (K_{TO}) channel, resulting in transient hyperpolarization and an outward potassium current. The plateau phase of the cardiac action potential (**phase 2**) is sustained by a balance between the influx of calcium through L-type calcium channels (also known as dihydropyridine receptors, due to their sensitivity to the dihydropyridine class of calcium channel blockers), and outward movement of potassium through slow delayed rectifier potassium channels. This inward movement of calcium ions begins when the membrane potential is approximately –40 mV, and prolongs the action potential. This phase is absent in pacemaker cells, and distinguishes the action potential in the cardiac cell from that in skeletal and neuronal cells. It is during this phase that actin-myosin cross bridge formation occurs (discussed below). **Phase 3**, also known as rapid repolarization occurs as the L-type calcium and the slow delayed rectifier potassium channels close. Myocytes have a refractory period. There is an absolute refractory period, in which no amount of stimulation will evoke an action potential. This lasts from phase 0 to near completion of phase 2. The relative refractory period, lasting from phase 2 to phase 4 can result in depolarization and an action potential, if there is a stronger than usual stimulus.

The sodium-calcium exchanger functions to extrude calcium from the myocyte after each contraction in order maintain appropriate intracellular calcium content. The driving force for the maintenance of calcium is the sodium gradient between the intracellular and extracellular spaces and is maintained by ATP dependent sodium pumps. Calcium also enters the cell by way of the sodium-calcium exchanger. The inotropic effects of some cardiac glycosides are mediated by the sodium-calcium exchanger (e.g., digoxin). Inhibition of the sodium pump by cardiac glycosides will increase cytosolic sodium concentration. This sodium is extruded from the cell by the exchanger and therefore increases intracellular calcium concentrations, which is an important determinant of contractility. The ATP dependent calcium pump in the sarcolemma also removes calcium from the myocytes. Both calmodulin (calcium binding protein) and the binding of calcium stimulate the pump by increasing calcium sensitivity and thus velocity of contraction.

The sarcoplasmic reticulum (SR) is a tubular membrane that surrounds the myofibrils and regulates cytosolic calcium concentration through uptake, storage, and release. Neonatal cardiomyocytes are much more dependent on extracellular calcium influx for contraction because of the immaturity of the SR [48–53]. In the mature heart, the SR regulates the intracellular calcium concentration and is the most important source of activator calcium for binding to troponin C. The content of the SR is decreased and less organized in the immature heart, and thus age related changes in the SR structure and function is likely to affect myocardial function. These developmental differences further explain the extreme sensitivity of neonates to calcium channel antagonists [49]. Indeed, some authors have suggested that calcium chloride is an effective inotrope in neonates after cardiopulmonary bypass [54]. The uptake of calcium occurs in the longitudinal portion of the SR, which is connected to the junctional portion (responsible for storage and release) by anastomosing strands. This connection area within the SR is rich in ATP calcium pumps, which are encoded by the SR calcium ATPase (SERCA) 2a gene [55–57]. The calcium release channels (also known as the ryanodine receptor due to its ability to bind the plant alkaloid ryanodine) and sarcolemmal L-type calcium channels are grouped in functional clusters, also known as calcium release units with several binding proteins including calsequestrin, tricodin, and junction [58]. Calsequestrin is a low affinity calcium binding protein that stores large amounts of releasable calcium within the SR. Mutations in calsequestrin are linked to catecholaminergic polymorphic ventricular tachycardia [59]. Active transport of calcium into the SR by calcium pumps results in muscle relaxation. An intrinsic SR protein known as phospholamban

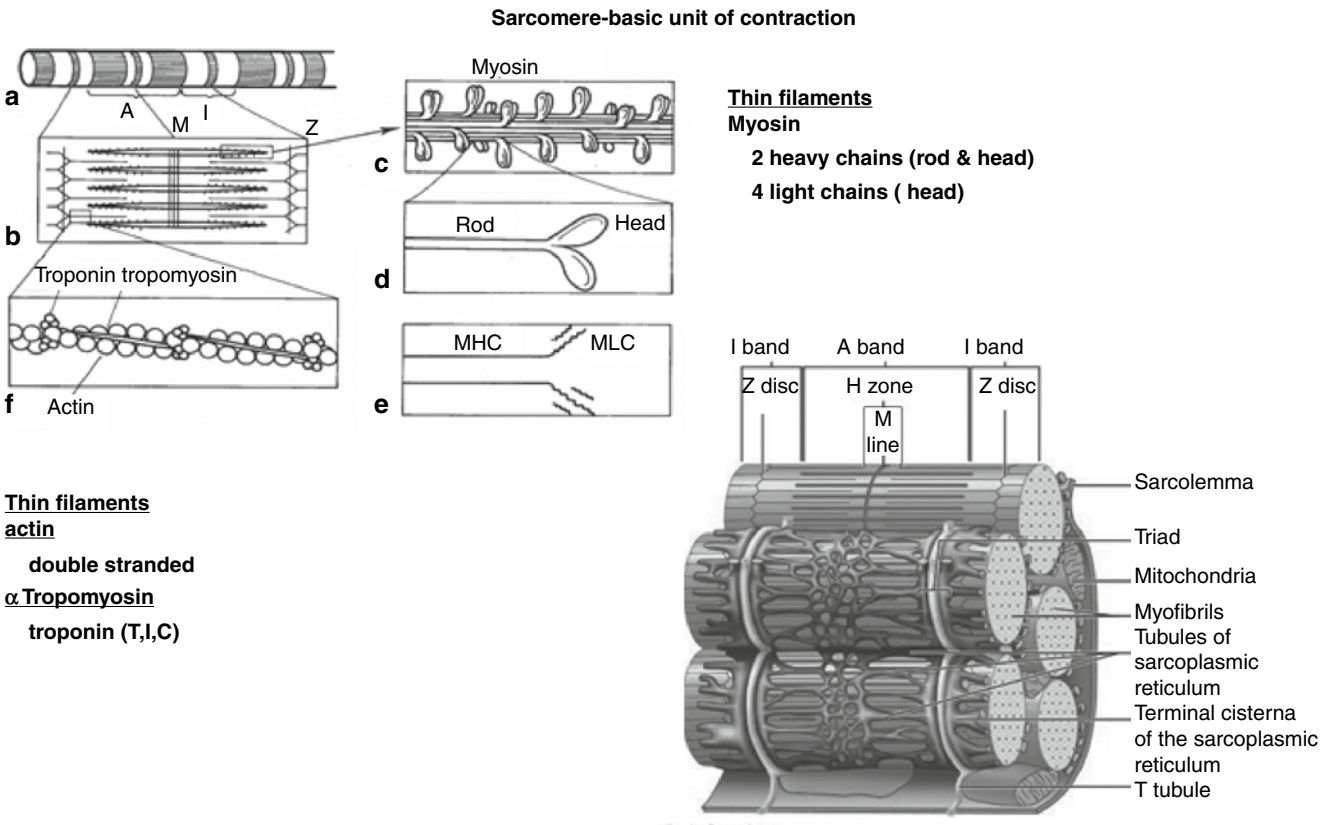


Fig. 17.8 Anatomy of the sarcomere, the basic unit of contraction (see text for full explanation). *MHC* myosin heavy chain, *MLC* myosin light chain

mediates regulation of the SR calcium pump activity [60]. Phospholamban is an important regulator of baseline calcium cycling and of contractility. It is a critical determinant of the cardiac response to sympathetic stimulation [60].

The sarcomere, the basic unit of the muscle, is composed of the myofibril contractile elements (Fig. 17.8). It is bound on both ends by z-discs, and composed of proteins that are organized into strands (filaments). The I band is composed of thin filaments (actin), as well as the troponin complex and tropomyosin. The Z disk bisects the I band. Thick filaments are polymers composed of myosin (and titin). The A band contains overlapping thick and thin filaments. The M band in the center of the A band consists of thick filaments cross-linked to titin by myosin binding protein C (Fig. 17.9) [50]. It is the mutations in the contractile proteins that can lead to clinical phenotypes of hypertrophic cardiomyopathy [61]. Myosin is the most abundant contractile protein. Its head contains ATPase activity that contributes to fiber shortening during contraction. Tropomyosin is composed of two helical chains that binds to troponin T at multiple sites along the major groove of the actin filament and modulates the interaction between actin and myosin. The troponin complex is composed of three separate proteins. Troponin T binds the complex to tropomyosin. Troponin I inhibits interactions between actin and myosin, and troponin C binds calcium. Together with tropomyosin, troponin complexes allow for changes in calcium sensitivity for the process of cross-bridge formation. Calcium induced changes in the actin binding affinity of Troponin I provide a molecular switch that identifies an increase in intracellular calcium and acts as a signal to induce contraction.

The final process of ECC resulting in cross bridge formation and subsequent muscle contraction is a complex interplay of proteins, beginning with initiation of the action potential in the sarcolemma for depolarization, followed by calcium-induced-calcium release from the SR (during phase 2 of the AP). Contraction is then initiated by binding to the amino acid terminal end of troponin C. Troponin C then undergoes a conformation change that increases its affinity for troponin I. Troponin I then moves from being tightly bound to actin in diastole to being tightly bound to troponin C. The inhibitory portion of troponin I moves away from actin. Tropomyosin shifts within the groove between the actin strands, which alters the actin-myosin interaction, and eventually allows for formation of tightly bound cross-bridges. Binding of ATP causes a conformational change in the actin-myosin interaction, resulting in displacement of actin toward the center of the sarcomere and subsequent contractile element shortening. The amount of force developed by the contracting myocyte is dependent upon the number of cross-bridges formed. This

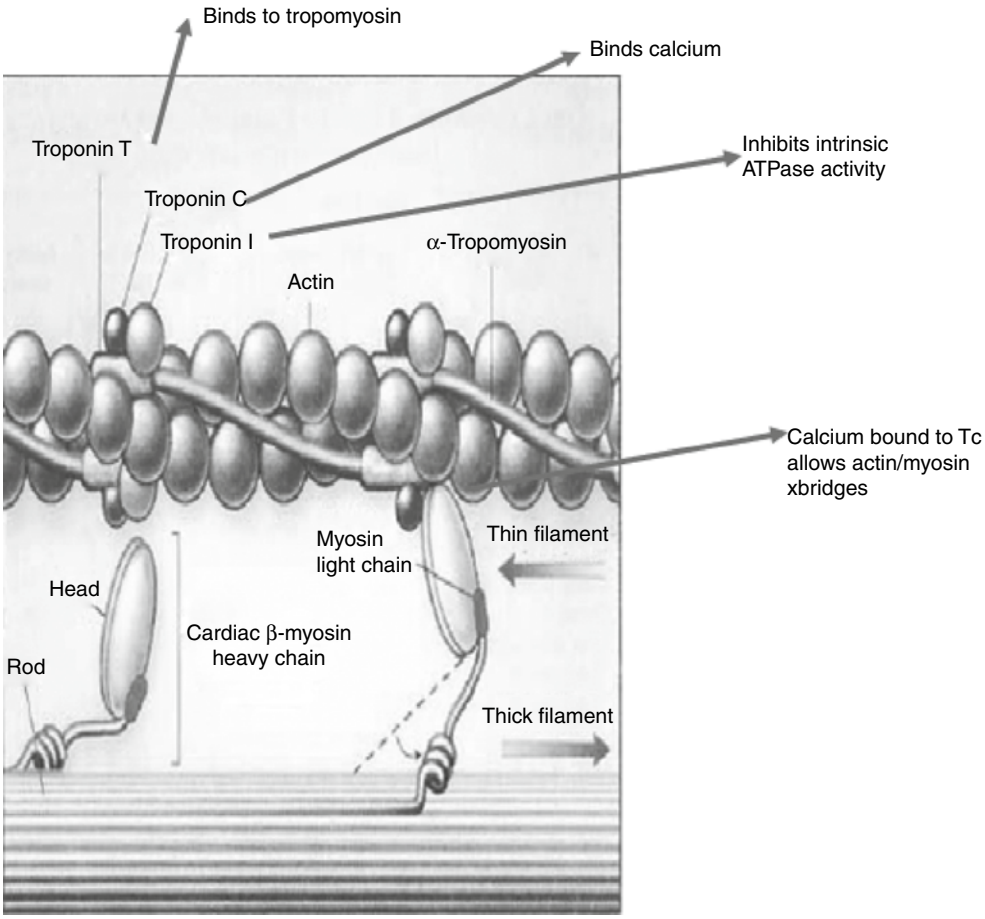


Fig. 17.9 Magnified view of the actin myosin cross-bridges and proteins necessary for the power stroke (cardiac cycle)

is in turn dependent upon the amount of calcium released by the SR, and on the intrinsic properties of the myofilaments [47, 50, 62]. As long as the calcium is available, this "ratcheting" process continues to occur. Towards the end of **Phase 2**, calcium is sequestered back into the sarcoplasmic reticulum by an ATP-dependent calcium pump (SERCA, or sarco-endoplasmic reticulum calcium-ATPase), as well as (to a much smaller extent) a sodium-calcium exchange pump. SERCA forms a complex with the inhibitory protein phospholamban. When phospholamban is phosphorylated (via protein kinase A-mediated pathways), it detaches from SERCA and accelerates calcium re-sequestration back into the sarcoplasmic reticulum. Once enough calcium has moved back into the sarcoplasmic reticulum, the troponin regulatory complex again blocks the actin-binding site, causing muscle relaxation. At the end of this cycle, a new molecule of ATP binds to the myosin head, displacing ADP, which restores the sarcomere back to its original length.

There are several receptor-signaling mechanisms that regulate cardiac contractility and the resistance in the systemic and pulmonary circulations. Adrenergic receptors (AR) are perhaps the most important and all share a common structural motif. These receptors are coupled to G proteins, which either activate or inhibit the enzyme adenylate cyclase to produce cyclic AMP (cAMP), triggering cAMP-dependent kinases to regulate the machinery important for excitation-contraction coupling discussed above. At this point, cross bridges break, and return to the actin and myosin filaments return to their resting state [47].

Determinants of Cardiac Output

The primary function of the heart is to pump deoxygenated blood to the lungs and oxygenated blood with nutrients and chemicals to the body for cellular function. While this is a rather crude definition of cardiac output (CO), it is the complex physiological interplay of the pump and the vasculature that ultimately determine CO. CO is described mathematically as the product of heart rate (HR) and stroke volume (SV), and is the total volume of blood pumped by the ventricle per minute.

$$CO = HR \times SV \tag{17.2}$$

Stroke volume is the difference between the end diastolic volume (EDV) and the end systolic volume and is dependent upon preload, afterload, and contractility.

$$SV = EDV - ESV \tag{17.3}$$

While CO affects hemodynamics, other factors including the circulating blood volume, respiratory mechanics, vascular diameter and resistance, and blood viscosity play a sig-

nificant role. Overall cardiac function is determined by the structure of the heart (normal vs. abnormal as in congenital heart disease), its rhythmicity, and its contractile function. Finally, myocardial function is determined by the contractile state of the heart, which is influenced by the intrinsic inotropic state, and the work it has to perform (preload and afterload). Blood pressure is the most commonly used measure of circulatory function, but the presence of a normal blood pressure does not necessarily imply adequacy of tissue oxygen delivery (DO_2).

Heart rate (HR) variability in the adult may have little impact on CO. In the neonate, the resting HR is approximately 145 beats per minute (BPM) while awake, and 120 BPM while asleep. Influences of the autonomic nervous system allow HR ranges to vary from 70 to 220 BPM in the neonatal population. Because the heart spends two-thirds of its time in diastole, CO is clearly dependent upon a coordinated HR with atrioventricular (AV) conduction, AV synchrony, and adequate diastolic filling time. The newborn has limited ability to modulate stroke volume, and is therefore mainly dependent on modifications in HR to alter CO. However, CO as a result of extreme tachycardia may become impaired due to insufficient filling time [63].

Stroke Volume

Stroke volume is dependent upon preload, afterload, and contractility. Each of these determinants is discussed further below.

Preload

Preload is analogous to the resting fiber length before contraction (in a single fiber) or the end diastolic volume. German physiologist Otto Frank examined the length-tension relationship in a frog ventricle preparation and noted that the peak ventricular pressure generated during a contraction increased as the end diastolic volume (EDV) is increased. Two decades later, Frank Starling related ventricular filling pressure or EDV to cardiac output in a series of highly influential papers. Using a canine heart-lung preparation, Starling noted that CO increased as EDV increased [64–66]. He noted that muscle fibers contract more vigorously when stretched beforehand, as long as they were not overstretched. Stretching of the muscle fibers before contraction results in optimal overlap of the actin and myosin muscle fibers, so that as LVEDV increases to a point corresponding to optimal overlap of actin and myosin fibers, stroke volume improves (i.e., the classic Frank-Starling relationship) [67]. Clinically, we have the ability to infer LV preload from measurement of the end diastolic pressure (EDP) by way of a Swan-Ganz catheter (e.g., wedge pressure), through intracardiac lines placed during cardiac surgery, or directly in the cardiac catheterization laboratory. Similarly, we can infer RV preload from measurement of central venous pressure (CVP) by way of a central venous line, intracardiac lines placed during cardiac surgery, or directly in the cardiac catheterization laboratory. Importantly, as discussed in the chapter on Hemodynamic Monitoring (and briefly mentioned below), pressure is NOT the same as volume, so the accuracy and validity of these measurements has been questioned. In addition, there are numerous conditions that can alter the pressure measurement without altering the volume.

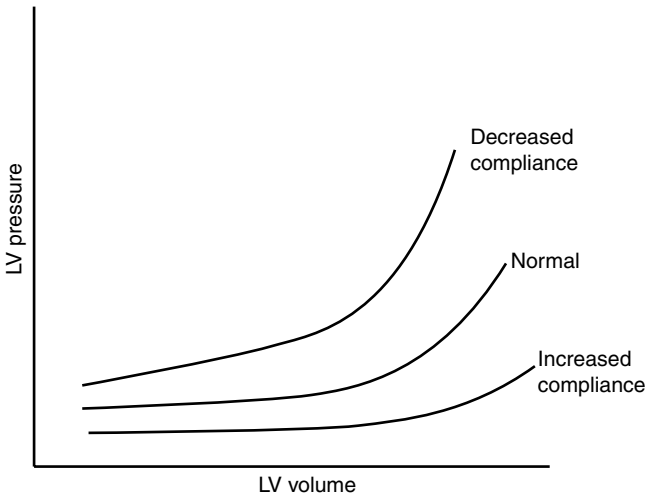


Fig. 17.10 Diastolic compliance curve of the ventricle. In the normal ventricle with adequate compliance, volume may be increased with minimal increase in pressure. However, at the steep end of the curve, small increases in volume lead to a steep increase in pressure. When the ventricle is non compliant, the curve is shifted to the left

Compliance is the relationship between pressure and volume, i.e. the ratio of change in volume per unit change in pressure. Therefore for a given EDV, the LVEDP will depend on the compliance of the ventricle. For a given preload, changes such as hypertrophy, structural abnormalities, and ischemia will increase the EDP and decrease compliance (Fig. 17.10). Because of the compliance of the ventricle, volume may be increased without a corresponding increase in pressure, until a steep increase in pressure is reached. The relationship between SV and EDV is linear, but because of the compliance of the ventricle, the relationship between EDP and SV is curvilinear (Fig. 17.11) [67]. Overall, decreased compliance leads to a higher EDP for any given preload, which may limit ventricular filling by impeding venous return to the heart (see later discussion on section "Venous Return").

The relationship between preload and contractility can be best understood by examining the pressure-volume loop (Fig. 17.12). **A** is the point at which left ventricular pressure falls below the left atrial pressure and the mitral valve opens. This results in filling of the ventricle during diastole. Point **B** is the pressure volume relationship at end diastole just before ventricular contraction occurs. At this point, the pressure in the atrium is lower than the pressure in the ventricle and the

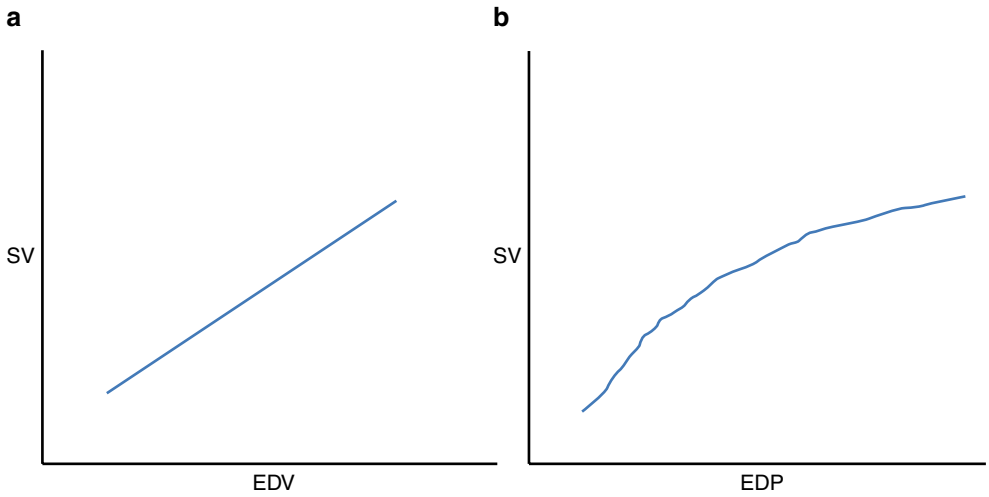


Fig. 17.11 Effect of Stroke volume on end diastolic volume and pressure. (**a**) There is a linear increase in stroke volume (*SV*) with increasing end diastolic volume (*EDV*). (**b**) The relationship between SV and end diastolic pressure (*EDP*) is curvilinear. Increase the EDP will initially result in an increase in SV, until the plateau because of the compliance relationship of the ventricle

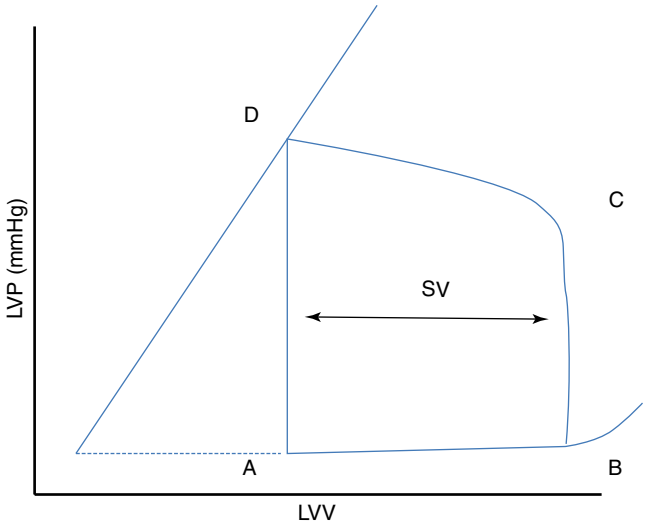


Fig. 17.12 Pressure-volume loop of the left ventricle. At point *A*, the mitral valve opens and ventricular diastole begins. During ventricular diastole, the volume of the left ventricle increases. When diastole ends (*B*), the mitral valve closes. Isovolemic contraction ensues and the aortic valve opens (*C*). Ventricular systole occurs and the volume of the ventricle decreases. The aortic valve then closes (point *D*), and isovolemic relaxation occurs. The area within the loop represents the cardiac work, and the stroke volume (*SV*) is shown. The line crossing point *D* represents the end systolic pressure volume relationship, and the line crossing point *B*, the end diastolic pressure volume relationship. The triangular area in front of the loop represents the potential energy, which is the elastance defined by potential work. Arterial elastance is the ratio of end-systolic pressure and stroke volume or a pressure of arterial load and is the slope of the line joining the end diastolic and end systolic points. *LVP* left ventricular pressure, *LVV* left ventricular volume

mitral valve closes. Point **C** is characterized by opening of the aortic valve (ventricular pressure is greater aortic pressure). The line between **B** and **C** corresponds to isovolumetric contraction. During this period, the ventricular pressure rises, with no change in volume. When the aortic valve opens (**C**), blood is ejected from the ventricle into the aorta (point **C** to **D**). While ventricular volume falls dramatically, there is very little change in pressure. When the ventricular pressure falls below aortic pressure, the aortic valve closes and isovolumetric relaxation ensues (line **DA**). At this point, there is a fall in ventricular pressure with volume remaining constant. Stroke or cardiac work represents the area of the loop, and the stroke volume is the difference between **AD** and **BC**. The ejection fraction is the ratio between stroke volume and end diastolic volume.

Situations exists where there will be physiologic changes that result in a change in the pressure-volume relationship. When preload increases and contractility remains the same, the SV will increase, and thus CO and the pressure-volume loop will extend to the right (i.e. the Frank-Starling law). However, excessive preloads can actually worsen SV if the EDP rises above a certain critical threshold (usually approximately 15–20 mmHg) (see later discussion on section "Venous Return"). Excessively high EDP can impair myocardial perfusion, with a subsequent loss of myocardial perfusion, and eventually contractility. In addition, increasing preload can lead to increased systemic and pulmonary venous pressure. This will lead to increased capillary permeability resulting in systemic and pulmonary edema.

As previously mentioned, neonates and infants have a relatively limited capacity to augment stroke volume compared to adults. First, neonates and infants have a relatively decreased left ventricular mass in comparison to adults [68, 69]. Second, the neonatal myocardium has relatively poor compliance compared to adults, due largely to an increased ratio of type I collagen (decreased elasticity) to type III collagen (increased elasticity) [70]. Of interest, the cardiac remodeling that occurs following an acute myocardial infarction (AMI) leads to a similar increased ratio of type I collagen to type III collagen, which may explain in part the decrease in myocardial function that occurs in adults following an AMI [71]. Similar changes have been observed in patients with dilated cardiomyopathy [72]. Third, the neonatal myocardium functions at a relatively high contractile state, even at baseline [73, 74]. Collectively, these developmental changes result in a relatively limited capacity to

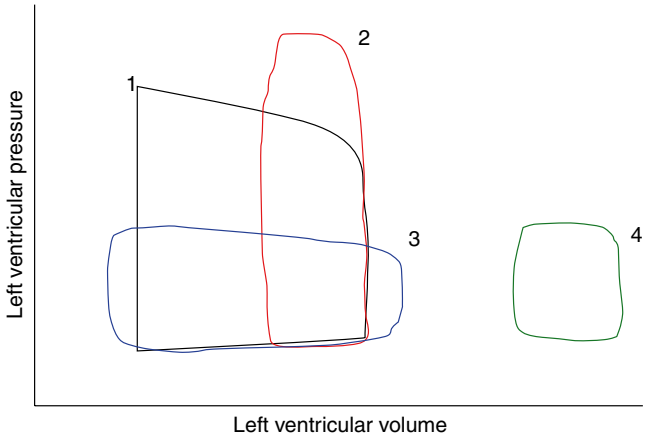


Fig. 17.13 Pressure volume loops for different conditions in which there are changes cardiac function, volume overload and pressure overload. *1* Normal, *2* aortic stenosis, *3* mitral regurgitation, *4* myocardial disease

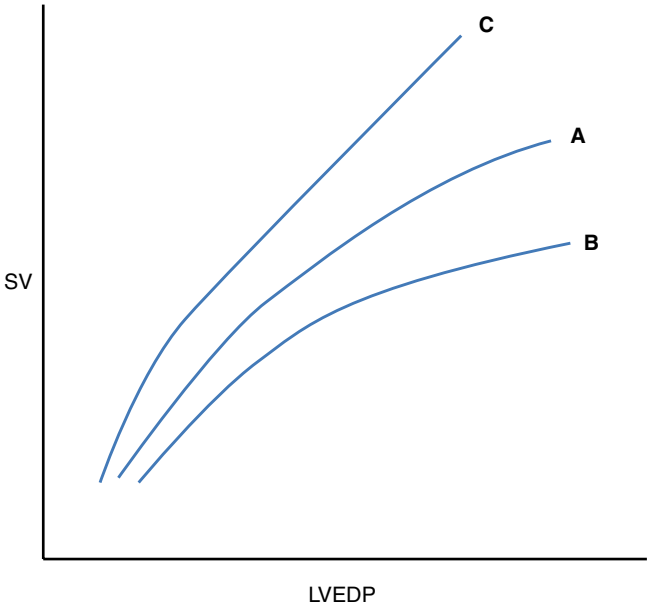


Fig. 17.14 Effect of changes in afterload on stroke volume. *SV* stroke volume, *LVEDP* left ventricular end diastolic pressure. Increased afterload (and decreased inotropy) shifts the curve down and to the right (from A to B). Decreased afterload (and increased inotropy) shifts the curve up and to the left (A to C)

increase SV, especially during stress [69, 74, 75]. In addition, for these reasons the neonatal heart also does not tolerate excessive preload as well as in adulthood [76]. Congenital abnormalities and myocardial dysfunction can therefore lead to changes in the pressure-volume relationship (Fig. 17.13).

As a further consequence of these changes, neonates and young infants are critically dependent upon an increase in heart rate (as opposed to an increase in SV) to generate increased CO during stress. Unfortunately, myocardial perfusion occurs to the greatest degree during diastole and depends directly upon the difference between diastolic blood pressure and left atrial pressure, and inversely with heart rate (as an indirect measure of diastolic filling time). As the heart rate increases, diastolic filling will eventually reach a point at which further increases in cardiac output are limited [77].

Contractility

The end-systolic pressure volume relationship (ESPVR) represents the contractility (Fig. 17.12). Given a constant state, a shift in the line upward to the y-axis (becoming steeper) indicates increased contractility, where the ejection fraction and SV are increased for a given end-diastolic pressure volume relationship (EDPVR). A shift in the line downward toward the x-axis (less steep) is consistent with decreased contractility, and thus SV and CO are reduced. The compensatory mechanisms of a child with a failing heart and decreased contractility would result in tachycardia, vasoconstriction, and fluid retention. The slope of the EDPVR is the reciprocal of ventricular compliance. An increase in the slope of the line toward the y-axis is secondary to decreased compliance. In a patient with a failing pump, the ventricle becomes less compliant with less contractility, and the slope of the ESPVR will decrease and EDPVR lines will increase resulting in a "clam shell" effect on the pressure-volume loop.

Afterload

Afterload is the dynamic resistance against which the ventricle has to contract. As afterload or aortic diastolic pressure increases, stroke volume decreases. A heart with normal function can tolerate increased aortic diastolic pressures fairly well. In the heart with decreased contractility, increases in afterload are poorly tolerated. The pressure at which the aortic valve opens is higher, as seen on a pressure-volume loop. As shown in Fig. 17.14, an increase in afterload will shift the Frank-Starling curve down and to the right. The basis for this is the force velocity relationship for cardiac myocytes. An increase in afterload will decrease the velocity of fiber shortening. Because the time available for ejection is limited, the decrease in fiber shortening velocity will reduce the rate of volume ejection, such that more blood is left in the ventricle at the end of systole. A decrease in afterload will shift the Frank-Starling curve up and to the left. Changes in afterload do not directly alter preload, but preload changes secondary to changes in afterload with a resultant increase in EDP. The increase in ESV is added to the venous return to the ventricle, and increases EDV. Medications causing vasodilation will result in decreased afterload, and in effect improved SV and cardiac output.

Venous Return

The physiologist Arthur Guyton proposed that the three most important factors that determined cardiac output are (i) the pumping action of the heart itself (i.e., contractility), (ii) the

resistance to blood flow through the peripheral circulation (i.e., afterload), and (iii) the degree of filling of the circulatory system with blood (i.e., preload) [78–80]. However, Guyton also emphasized that the venous circulation (as the major capacitance system of the circulatory system) played a much stronger role in determining the cardiac output than commonly envisioned. The heart does not store blood (only about 7 % of the total blood volume is stored within the heart at any given time) – therefore, the cardiac output is tightly coupled to the venous return (which depends, in turn, upon the peripheral venous circulation) [81–84]. In fact, almost 80 % of the total blood volume is contained within the systemic venous circulation (the vast majority of which is contained within the so-called "capacitance vessels," i.e., small veins and venules). Veins are about 30 times more compliant than arteries – therefore, changes in volume are not generally associated with significant changes in transmural pressure, making the venous circulation an ideal blood reservoir [85]. Therefore, changes in venous capacitance can have significant effects on the cardiac output, as will be discussed further below.

According to the Hagen-Poiseuille's Law (analogous to Ohm's Law of electrical current), fluid flow (Q) is related to the pressure gradient (P_1-P_2) divided by resistance (R):

$$Q = \left(P_1 - P_2\right) / R \tag{17.4}$$

Note that P_1 is the upstream pressure, whereas P_2 is the downstream pressure. Based on this important relationship, cardiac output and venous return can be easily determined. Cardiac output (i.e., flow out of the heart) is the determined by the difference in upstream pressure (mean arterial pressure, MAP) and downstream pressure (right atrial pressure, P_{RA}) divided by the systemic vascular resistance.

$$CO = \left(MAP - P_{RA}\right) / SVR \tag{17.5}$$

The flow out of the heart (cardiac output) must equal the flow into the heart (venous return). Venous return (VR) is therefore the difference in upstream pressure (mean circulatory filling pressure, P_{MS}) and downstream pressure (P_{RA}) divided by the resistance to flow through the venous circulation (R_V).

$$VR = \left(P_{MS} - P_{RA}\right) / R_V \tag{17.6}$$

Note that the resistance to flow in both of the above equations is further determined by the classic equation:

$$R = 8\eta l / \pi r^4 \tag{17.7}$$

where l is the length of the blood vessel, η is the viscosity of the blood, and r is the radius of the blood vessel. As the length of the blood vessel is relatively fixed, changes in the radius of the blood vessel with either vaso/venoconstriction or vaso/venodilation are the primary determinants of vascular resistance. However, the path of blood (and therefore the length through which the blood must travel) from the periphery to the heart can be altered by changes in perfusion of regional capillary beds. Blood viscosity usually does not play a major role in determining vascular resistance, except in the notable case of hemodilution due to the administration of large volumes of isotonic fluids during resuscitation [86–88].

Mean Circulatory Filling Pressure

The mean circulatory filling pressure (P_{MS}) may be a relatively new concept to many critical care providers, but the concept has been around since the late 1800's [89]. Conceptually, P_{MS} is the pressure of the circulatory system that would result if the heart stopped beating and all of the pressures within the circulatory system were allowed to equilibrate (i.e. the pressure in the circulatory system under static, "no-flow" conditions). It is the upstream pressure that essentially drives venous return (as shown in Eq. 17.6) and can be calculated as the stressed volume (V_S) over the mean compliance of the circulatory system (C_{CS}):

$$P_{MS} = V_S / C_{CS} \tag{17.8}$$

The unstressed volume of the circulatory system (V_0) is that volume of blood required to fill the entire circulatory system to capacity without any increase in the transmural pressure of the blood vessels [81, 83, 90]. Unstressed volume is analogous to functional residual capacity (FRC) in respiratory physiology. Stressed volume (V_S) is the amount of blood that, when added to the unstressed volume, results in an increase in transmural pressures of the blood vessels. Several authors have stated that if an animal was passively exsanguinated to cardiac standstill, the amount of blood lost would be the stressed volume (V_S), while the blood remaining within the vascular space would be the unstressed volume (V_0) [81, 83, 90]. Approximately 20–25 % of the total blood volume in humans is stressed volume [91]. Knowing that the total blood volume (V_t) is equal to stressed volume plus unstressed volume, PMS can be calculated.

$$V_t = V_0 + V_S \tag{17.9}$$

$$P_{MS} = \left(V_t - V_0\right) / C_{CS} \tag{17.10}$$

As the Eq. 17.10 suggests, PMS can be altered by either a change in the total blood volume (V_t) or by a change in the relative proportion of unstressed to stressed volume. For example, total blood volume can be increased through administration of packed red blood cells or intravenous fluids – this usually increases both V_t and V_S, without altering V_0. Conversely, an increase in vasomotor tone (as a compensatory mechanism to shock – see below) or administration of vasoactive medications (e.g., epinephrine, norepinephrine,

dopamine) will alter the ratio of V_S to V_0 without causing significant changes in compliance [92–98]. Indeed, after an acute loss of approximately 20 % of the blood volume (equivalent to the stressed volume [91]), P_{MS} would fall to zero (which effectively eliminates the driving pressure for venous return, and hence, cardiac output!), since by definition, the unstressed volume does not increase transmural pressure. Note that this degree of blood loss corresponds to Class II hemorrhagic shock [99], which is characterized by tachycardia, hypotension, and decreased perfusion of the brain and kidneys. Luckily, the body's exquisite compensatory mechanisms increase sympathetic tone and release of endogenous catecholamines, which decreases unstressed volume, increases stressed volume, and returns P_{MS} to normal levels.

Venous Resistance (R_V)

The total cross-sectional area of the venous system is very large, due to the extensive network of blood vessels that traverse the regional vascular beds. Overall resistance is therefore quite small. However, increases sympathetic tone, release of endogenous catecholamines, or administration of vasoactive medications can impact the resistance of blood passing through the venous system (i.e., R_V). In addition, the extensive network of capillaries, venules, and veins throughout the venous system are frequently divided into short and long time constant (τ) beds (Krogh's and Caldini's so-called two compartment model) [81, 83, 91, 93, 100, 101]. Recall that a time constant is equal to the product of resistance (i.e., pressure/flow) and compliance (i.e., volume/pressure), which is also equal to the volume of the vascular bed divided by the flow going through it. For example, the splanchnic and cutaneous (skin) beds have short time constants (large volume, low flow), while the renal and musculature beds have a long time constant (small volume, rapid flow). The fraction of blood between these two vascular beds can be shifted by changes in sympathetic tone (it helps that the splanchnic and cutaneous circulation is richly innervated), release of endogenous catecholamines, or administration of vasoactive medications.

Right Atrial Pressure (P_{RA})

Further inspection of the Eqs. 17.6 and 17.7 reveals that the downstream pressure in both equations is right atrial pressure (P_{RA}). In other words, if the right atrial pressure is equal to the mean circulatory filling pressure (P_{MS}), there is no venous return – and hence, cardiac output will fall to zero. Guyton constructed a series of venous return curves to demonstrate this point – that is, the rate of venous return is dependent upon both the mean circulatory filling pressure and right atrial pressure (Fig. 17.15) [78]. Guyton further combined the cardiac function curve with the venous return curve in a single diagram, in order to display the various

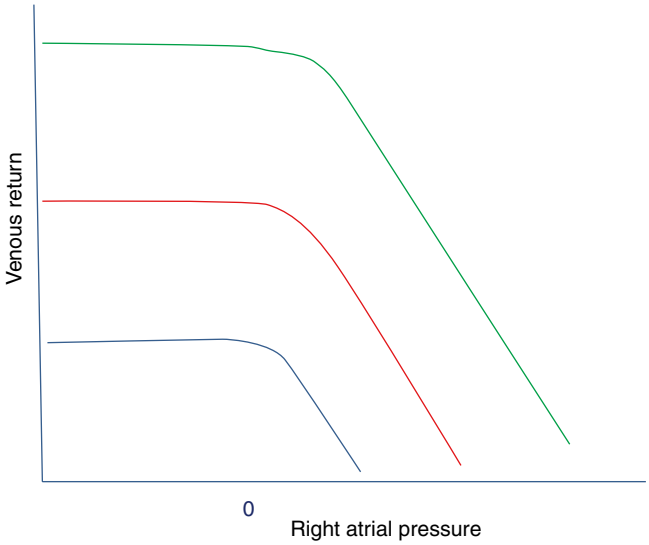


Fig. 17.15 Relationship between right atrial pressure, mean circulatory filling pressure, and venous return. The *blue*, *red*, and *green graphs* represent different mean circulatory filling pressures. Note that the x-intercept is equal to P_{MS}, while the slope of the curve is equal to $1/R_V$

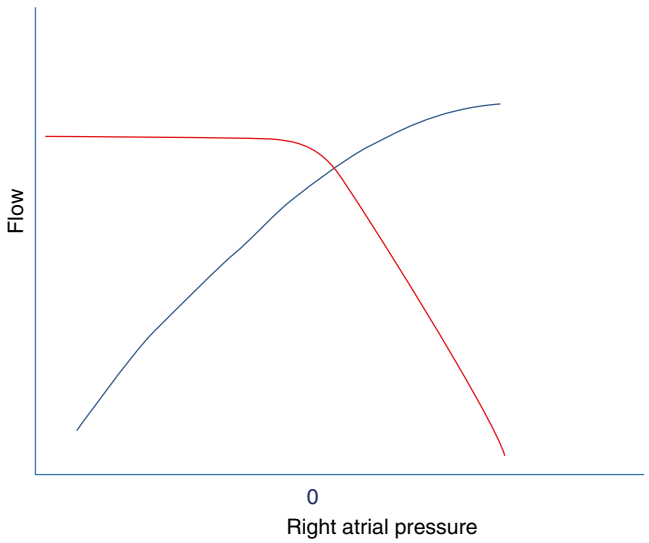


Fig. 17.16 Combination of Cardiac Output (*blue*) and Venous Return (*red*) curves

relationships between right atrial pressure, mean circulatory filling pressure, venous return, and cardiac output [79, 80, 82]. As shown in Fig. 17.16, the intersection of the venous return and cardiac function cures corresponds to a right atrial pressure of approximately 0 mmHg. The venous return and cardiac output curves can be used to explain the physiology of changes in hemodynamics in the PICU setting. An in-depth review of the different clinical situations encountered is beyond the scope of this review, so the reader is referred to several excellent recent reviews on this particular subject [81–84, 90, 91].

Control of Circulation

As alluded to earlier, during times of stress, there are numerous compensatory mechanisms that act to maintain cardiac output, and hence, oxygen delivery. Collectively, these mechanisms are known as the neuroendocrine stress response (also commonly called the *fight or flight response*), a series of complex interactions that involve multiple organ systems, all of which act to maintain homeostasis in response to stress. The neuroendocrine stress response is dominated by activation of the central and sympathetic nervous system, which is regulated through a series of highly differentiated, closely integrated, cardiovascular reflex arcs, which include both an afferent component, the central nervous system, and an efferent component [102].

The Afferent Limb of the Neuroendocrine Stress Response

The afferent limb consists of multiple sensory receptors located throughout the cardiovascular system. For example, sensory receptors called arterial baroreceptors are found in the walls of the aorta and carotid arteries. The carotid sinus consists of a rich network of baroreceptors which are innervated by the glossopharyngeal nerve and located at the bifurcation of the common carotid artery into the internal and external carotid artery. In addition, major concentrations of baroreceptors are also found in the wall of the aorta near the transverse arch, called the aortic baroreceptors, which are supplied by the vagus nerve. These baroreceptors *sense* stretch produced by increased transmural pressure – increases in mean arterial blood pressure leads to increased stretch, while decreases in mean arterial blood pressure leads to decreased stretch. In the case of decreased cardiac output (decreased stretch), these receptors decrease their rate of firing, thereby releasing a state of tonic inhibition of sympathetic outflow to the vasculature and heart. The increase in sympathetic tone is responsible for the clinical manifestations of early, compensated shock (tachycardia, vaso- and veno-constriction, in particular) [77, 81]. There are also chemoreceptors located throughout the cardiovascular system that respond to changes in pH, PaO_2, or $PaCO_2$. This vast array of noci- (pain), mechano-, chemo-, and baroreceptors located in the lungs, walls of the atria and ventricles, and central nervous system detect minute changes in intravascular blood volume, pressure, and content and generate signals that are subsequently integrated in the central nervous system, subsequently generating activation of the efferent limb of the neuroendocrine stress response.

The Efferent Limb of the Neuroendocrine Stress Response

The efferent limb consists of the pituitary gland, the brainstem autonomic centers, the adrenal cortex, and the autonomic nervous system (consisting of the sympathetic and parasympathetic nervous systems). As mentioned above, the central nervous system processes all of the information collected by the afferent limb of the neuroendocrine stress response and subsequently triggers several compensatory mechanisms. For example, the anterior pituitary gland releases ACTH which in turn stimulates the adrenal cortex to release cortisol. Cortisol has a variety of effects, one of which is potentiation of the action of endogenous catecholamines, such as epinephrine and norepinephrine on the heart and vasculature. The sympathetic nervous system (which includes the adrenal medulla) epinephrine and norepinephrine, which act in concert to increase cardiac output by increasing heart rate, stroke volume, and blood pressure. Epinephrine primarily increases heart rate and contractility, while norepinephrine primarily increases contractility and systemic vascular tone. To fuel these increased energy needs, glucagon is also released, which increases glucose delivery to the Krebs cycle through activation of glycogenolysis and gluconeogenesis.

Activation of the renin-angiotensin-aldosterone axis further contributes to the neuroendocrine stress response. Decreased perfusion of the rich network of blood vessels in the glomerulus of the kidney results in the release of renin, a proteolytic enzyme that cleaves angiotensinogen (an α_2-globulin produced in the liver), to generate angiotensin I. Angiotensin I is biologically inactive, but is cleaved by the angiotensin converting enzyme in the lungs to form angiotensin II. Angiotensin II increases blood pressure by augmenting contraction of the vascular smooth muscle and by promoting sodium and water retention (resulting in increased intravascular volume), both through direct effects on the renal tubule and through the stimulation and release of aldosterone. Angiotensin II also stimulates norepinephrine synthesis and release from the sympathetic nervous system and epinephrine release from the adrenal medulla, thereby resulting in secondary vasoconstriction and an increase in systemic blood pressure. Angiotensin II also stimulates the release of vasopressin (antidiuretic hormone, ADH) from the posterior pituitary resulting in increased reabsorption of free water in the distal collecting tubule. The increase in intravascular volume exerted by the direct renal activity of angiotensin II, and the secondary release of aldosterone and vasopressin, results in an increase in systemic blood pressure. Vasopressin is released by the posterior pituitary gland in response to either a decrease in the effective circulating volume or an increase in serum osmolality. Vasopressin acts directly on both the kidneys and the blood vessels to enhance

free water reabsorption (via V_2 receptors) and increase systemic vascular resistance via peripheral vasoconstriction (via V_1 receptors), respectively.

Conclusion

There are many facets to cardiovascular physiology, many of which were not covered in this brief review. However, the salient features of cardiovascular physiology pertaining to the management of critically ill children in the PICU have been presented. The interested reader is directed to any of the currently available textbooks on physiology for further information.

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Cardiopulmonary Interactions

18

Ronald A. Bronicki

Abstract

The successful provision of intensive care to the critically ill patient is directly related to optimizing oxygen transport balance. The matching of oxygen delivery to oxygen demand is dependent on the pathophysiologic conditions and, importantly, is often determined by cardiopulmonary interactions that result from both physiologic derangements and the application of clinical therapies. With the advent of newer technologies for monitoring the adequacy of oxygen delivery, the impact of interventions on oxygen transport balance can be more readily and accurately ascertained. As this review points out, the impact of therapies aimed at improving oxygen transport balance is neither predictable nor always entirely beneficial.

Keywords

Cardiopulmonary interactions • Transmural pressure • Mean systemic pressure • Venous return • Heart failure • Congenital heart disease

Introduction

The pulmonary and cardiovascular systems are intimately related. The primary responsibility of this relationship is to deliver oxygen to the tissues commensurate with their needs. Because of this close relationship, dysfunction of either system adversely affects the other, compromising cardiopulmonary function and systemic oxygen delivery. This review focuses on the volume-pressure and pressure-flow relationships of the cardiovascular and pulmonary systems, the effects that changes in intrathoracic pressure and lung volumes have on right and left ventricular loading conditions, the effects of respiration on cardiovascular function in patients with cardiac disease, the effects of heart failure on respiratory function, and the effects of respiratory disease on cardiac function. An understanding of these complex cardiopulmonary interactions is essential to the management of critically ill children in all cases.

Volume-Pressure and Pressure-Flow Relationships

There are numerous elastic structures in the body. The fundamental property of an elastic structure is its inherent ability to offer resistance to a distending or collapsing force and to return to its resting or unstressed volume after the force has been removed. The degree to which a structure undergoes a change in volume depends on the compliance of the structure and the magnitude and direction of the pressure exerted across the wall (i.e., the transmural pressure, Ptm). Compliance is the ratio of change in volume to change in pressure and is inversely related to elastance. The Ptm is equal to the difference between intra- and extracavitary pressures, where a positive Ptm distends the cavity and a negative Ptm causes the structure to reduce in size.

The physical principles that govern the flow of fluids through conducting passages, whether rigid or collapsible, are

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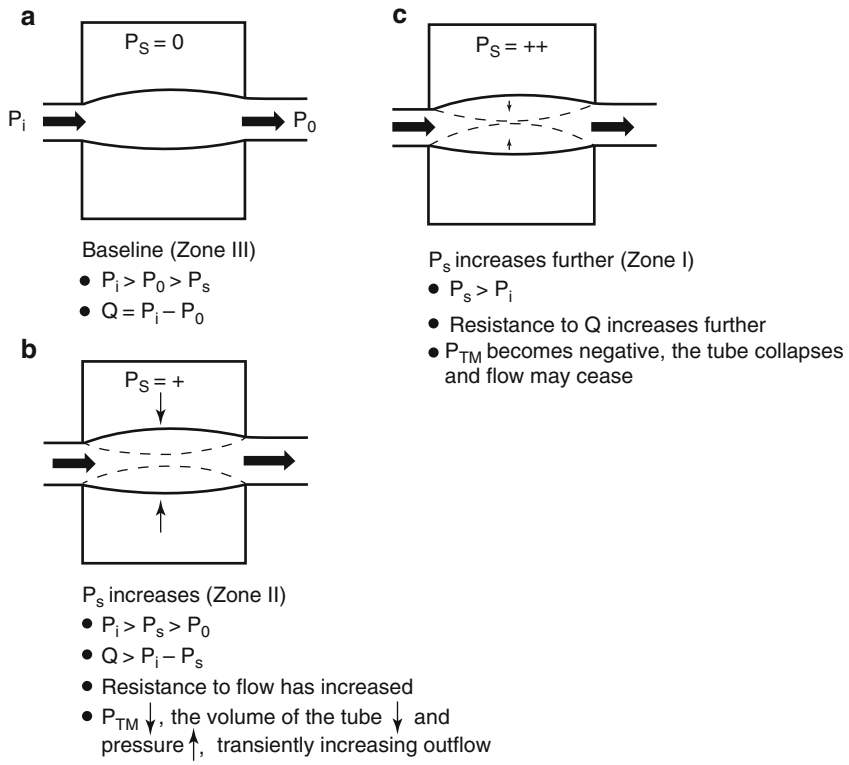


Fig. 18.1 The physical principles that govern the flow of fluids through a collapsible tube. P_i inflow pressure, P_0 outflow pressure, P_S surrounding pressure, P_{TM} transmural pressure, Q flow

derived from the general laws of hydrodynamics. The behavior of flow (Q) through a collapsible tube depends on the inflow pressure (Pi), outflow pressure (Po), the pressure surrounding the tube (Ps), the Ptm and the compliance of the structure (Fig. 18.1). When the tube has a positive Ptm throughout, the tube is widely patent and Q is proportional to the pressure gradient Pi – Po. (i.e., zone III conditions; Fig. 18.1a). With a constant Pi and Po, as the Ps increases, the Ptm decreases. As a result, the volume of the tube decreases, its pressure increases, and volume is translocated from this compartment to the next compartment. Resistance to flow increases and flow is proportional to the pressure gradient Pi – Ps (i.e., zone II conditions; Fig. 18.1b). As Ps increases further, the Ptm becomes negative, the tube collapses and resistance to flow increases even further (i.e., zone I conditions; Fig. 18.1c). The physiologic significance of these relationships is that many areas of the cardiovascular and pulmonary systems behave analogously as intrathoracic, intraabdominal, and intravascular pressures vary.

The Effects of Respiration on Cardiovascular Function

The Effects of Respiration on Right Ventricular Preload

Venous return is proportional to the pressure gradient between the extrathoracic venous system and right atrium (RA), and is inversely related to the resistance to venous return [1]. Resistance to venous return is affected by extremes in blood viscosity and increases slightly with large adrenergic stimulation [2–5]. Otherwise, this pressure gradient is the determinant of venous return and, under most conditions, cardiac output (CO). The pressure within the systemic venous bed is the upstream driving pressure for venous return and is thought to be equal to the mean systemic pressure (Pms) [6]. The Pms is derived by stopping the circulation and allowing blood to redistribute and the pressures throughout the circulation to equilibrate. The Pms is a function of blood volume and capacitance of the systemic circulation. Because the systemic venous circulation is 18 times more compliant than the systemic arterial circulation, the systemic venous circulation has much greater capacitance and therefore a majority of intravascular volume resides with the venous circulation, specifically within the splanchnic, splenic and hepatic venous reservoirs [7, 8].

When Pra rises, a compensatory increase in Pms must occur, otherwise venous return decreases. As Pra increases by 1 mmHg, venous return decreases by 14 % and as Pra increases further and approaches Pms, venous return ceases unless compensatory circulatory reflexes are intact (Fig. 18.2) [9]. Compensatory increases in Pms result from increases in intravascular volume and decreases in venous capacitance. Based on studies in dogs, the relationship between intravascular volume and Pms has been found to be linear [10]. In the absence of circulatory reflexes, an increase in blood volume of 14 % doubles the Pms and an increase of 27 % produces a threefold

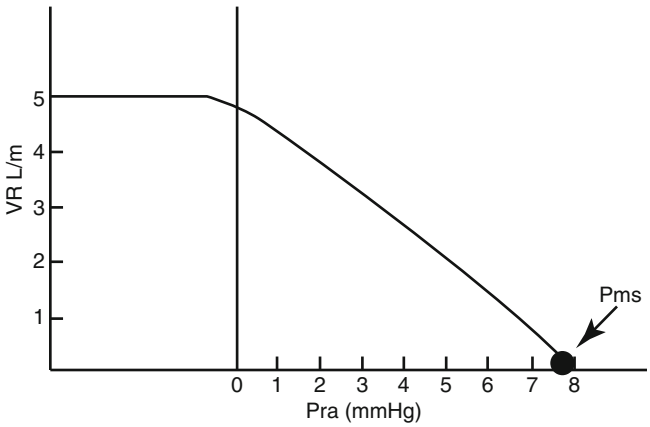


Fig. 18.2 The relationship between right atrial pressure (*Pra*) and venous return (*VR*) under normal conditions. Venous return plateaus as the Pra falls below zero because the vena cava collapse as they enter the thorax (i.e., zone I conditions are created). *Pms* mean systemic pressure

increase in the Pms. The relationship between venomotor tone and the Pms is curvilinear [11]. With removal of all vasomotor tone, the Pms falls from 7 to 5 mmHg; stimulating a Cushing reflex and norepinephrine and epinephrine infusions raise the Pms, plateauing between 15 and 19 mmHg.

Acutely, as Pra increases, α-adrenergic stimulation of venous capacitance vessels reduces their compliance and increases the Pms (β-adrenergic receptor agonist have little effect on veins), mobilizing blood from the peripheral circulation to the thorax [6, 7, 12]. Thus, the function of venous capacitance vessels is essential to acutely maintaining an adequate Pms. This response is complemented over time by the anti-diuretic effects of vasopressin and by stimulation of the renin-angiotensin-aldosterone system [8, 13, 14]. As the Pms decreases, venous return invariably decreases. For example, venodilators such as nitroglycerin and nitroprusside increase venous capacitance and decrease venous return; [15, 16] furosemide also exerts a direct and immediate vasodilatory effect on venous capacitance vessels [17–19]. Similarly, the inflammatory response characteristic of sepsis causes vasomotor paresis, as well as an increase in vascular permeability, both of which lower the Pms.

Changes in intrathoracic pressure (ITP) affect Pra by altering the RA Ptm. During inspiration, the decrease in intrapleural pressure causes the RA Ptm to increase. As a result, the highly compliant RA distends, its pressure decreases, and venous return is augmented. As the diaphragm descends, intra-abdominal pressure increases and the Ptm for the intra-abdominal venous capacitance vessels decreases. This effectively decreases the compliance of these vessels and their pressure increases, thereby increasing the longitudinal pressure gradient for venous return from the inferior vena cava (i.e., zone II conditions) [20, 21]. In other words, during inspiration, venous return from the inferior vena cava is increased due to a decrease in Pra and an elevated inferior vena cava pressure. This is in contrast to venous return from the head and neck vessels, which are exposed to atmospheric pressure.

Venous return increases as Pra decreases and then plateaus. The negative ITP generated during inspiration is transmitted to the RA and to the veins as they enter the thorax. And when the vascular Ptm becomes negative at the thoracic inlet, as may occur with maximal inspiration, the veins collapse limiting venous return (i.e., zone I, II conditions) [22]. Further decreases in Pra have no effect on venous return because flow is now a function of the difference between Pms and atmospheric pressure or abdominal pressure. When the outflow or downstream pressure is elevated, as in heart failure and pericardial tamponade, the Ptm of the veins at the thoracic inlet remains positive even with marked decreases in ITP. In this instance venous return is limited by the outflow pressure (i.e., zone III conditions).

Positive pressure ventilation (PPV) decreases the RA Ptm and Pra increases. As a result, the pressure gradient for venous return decreases. It is important to recognize that the increase in Pra results from an increase in ITP and a reduction in RA volume. It may seem counterintuitive that an increase in Pra causes venous return to decrease because Pra is considered a surrogate for RV volume. However, as ITP changes, it is the change in the RA Ptm that governs venous return. The same holds true for volume expansion. For venous return to increase, Pms must increase to a greater extent than does Pra. In this instance, the increase in venous return causes the Pra and therefore the RA Ptm to increase. Whether it is due to a change in ITP or intravascular volume, it is the effect of these interventions on the pressure gradient Pms-Pra that determines venous return [23].

During PPV, the increase in ITP causes the diaphragm to descend and the resulting increase in intra-abdominal pressure decreases the compliance of abdominal venous capacitance vessels. This contributes to a compensatory increase in Pms. The extent to which venous return is affected by PPV depends on where the ventricle resides on its pressure-volume curve; the adequacy of the circulatory reflexes to maintain Pms; and on the degree to which alveolar pressure is transmitted to the cardiac fossa. While PPV increases lung volume by increasing airway pressure, the degree to which lung volume and ITP increase is a function of respiratory mechanics. As pulmonary compliance is reduced, transmission of airway pressure to the cardiac fossa is diminished [24, 25].

Ultimately, right ventricular filling is a function of ventricular diastolic Ptm, ventricular compliance and venous return [26–28]. A noncompliant ventricle or one surrounded by increased ITP, requires a higher than normal intracavitary pressure to achieve a normal end-diastolic volume (Fig. 18.3). In Fig. 18.3, ventricles "A" and "B" are depicted as having identical compliance and filling pressures. However, because ventricle "B" is surrounded by negative ITP, its Ptm is greater and as a result it distends to a greater extent than ventricle "A."

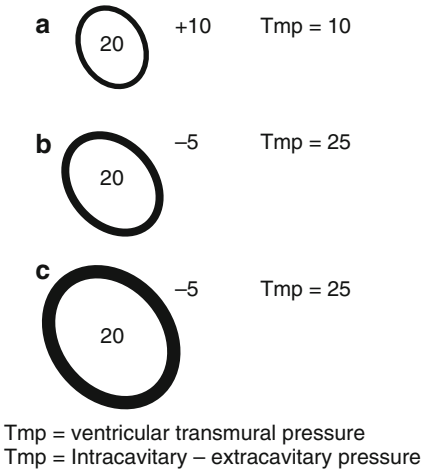


Fig. 18.3 The relationship of ventricular filling pressure (EDP), ventricular compliance, and intrathoracic pressure (ITP) to ventricular filling. The EDP is 15 for each ventricle. (**a**) The ITP is +10 (positive pressure ventilation). (**b**) The ITP is −5 (spontaneous breathing). (**c**) Ventricular compliance is reduced. *Ventricle A vs. B*. Ventricular compliance is the same; however, because ventricle B has a greater Tmp, it fills in a greater extent. *Ventricle B vs. C*. The Tmp is the same; however, because ventricle B is more compliant, it fills to a greater extent

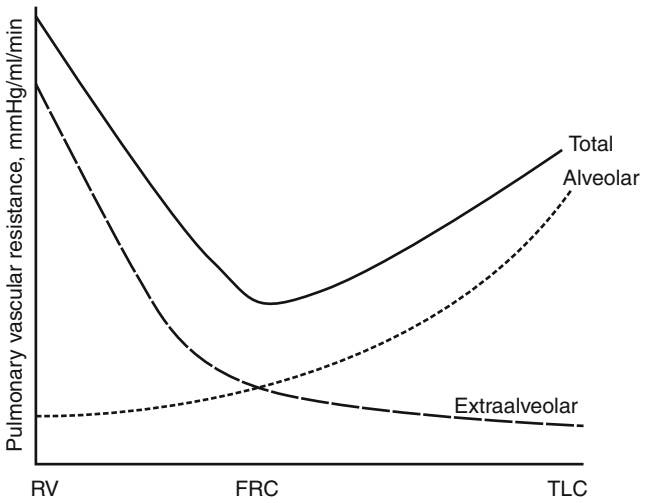


Fig. 18.4 The effects of lung volume on pulmonary vascular resistance. PVR is lowest near the FRC and increases at both high and low lung volumes because of the combined effects on the alveolar and extraaveolar vessels. *RV* residual volume, *FRC* functional residual capacity, *TLC* total lung capacity

The Effects of Respiration on Right Ventricular Afterload

Respiration effects pulmonary vascular resistance (PVR) by altering blood pH, alveolar oxygen tension, and lung volumes. Respiratory and metabolic alkalosis cause pulmonary vasodilation, while acidosis causes pulmonary vasoconstriction. Alveolar hypoxia constricts pulmonary arterioles, diverting blood flow from poorly ventilated to well ventilated alveoli. This improves the matching of ventilation to perfusion, thereby improving oxygenation. This mechanism of hypoxic pulmonary vasoconstriction (HPV) is mediated by the inhibition of nitric oxide production by pulmonary endothelial cells.

Respiration effects PVR by altering lung volumes (Fig. 18.4). Functional residual capacity (FRC) is the lung volume from which normal tidal volume breathing occurs. PVR is lowest near the FRC and increases at both high and low lung volumes. The pulmonary vascular bed consists of alveolar and extra-alveolar vessels. Alveolar vessels lie within the septa, which separate adjacent alveoli. Alveolar pressure is the surrounding pressure for these arterioles, capillaries, and venules. Extra-alveolar vessels are located in the interstitium and are exposed to intrapleural pressure. A second type of extraalveolar vessel is the corner vessel, which is found at the junction of the alveolar septa.

As lung volume decreases below FRC, the radial traction provided by the pulmonary interstitium diminishes, leading to a decrease in the cross sectional area of the extra-alveolar vessel. In addition, at low lung volumes, alveolar collapse leads to HPV and further increases in the resistance of extra-alveolar vessels. Despite a decrease in the resistance of alveolar vessels (Ptm increases as alveolar pressure falls), the net effect is a marked increase in PVR at low lung volumes.

As lung volume rises above FRC, PVR increases. Large tidal volumes or tidal volumes superimposed on an elevated FRC significantly increase PVR. During spontaneous respiration, the fall in interstitial pressure and the radial traction provided by the expanding lung cause the extra-alveolar vessels to distend. Meanwhile, the alveolar Ptm increases compressing interalveolar vessels. The net effect is a marked increase in PVR as lung volumes approach total lung capacity.

With PPV, the interstitial pressure becomes positive and the Ptm for the extra-alveolar vessels decreases. The overall effect of PPV on PVR depends on the degree to which lung volume is recruited and therefore HPV is released and the resistance of extra-alveolar vessels decreases and the extent to which alveoli are overdistended and interalveolar vessels are compressed. This is an important consideration when using PPV, particularly in patients with underlying pulmonary vascular disease and/or right ventricular dysfunction. Jardin and colleagues evaluated the mechanisms responsible for PPV-induced reductions in CO. They demonstrated in patients with acute respiratory failure and normal right ventricular function that CO fell with progressive increases in positive end-expiratory pressure (PEEP). This resulted from progressive increases in PVR and gradual impairment in right ventricular systolic function. The increase in right ventricular impedance led to reduced RV ejection and an increase in right ventricular end-diastolic volume, a finding not consistent with reduced systemic venous return and right ventricular filling. The decrease in systemic output was the result of a decrease in right ventricular output and the encroachment of the interventricular septum on the LV, which further impairs left ventricular filling (i.e., ventricular interdependence)(discussed further below)

[29]. This mechanism seems to be as important if not more important in reducing CO during PPV than a reduction in the gradient for venous return due to increases in Pra [30, 31]. These findings emphasize the importance of titrating PEEP to optimize oxygenation, CO and systemic oxygen delivery.

By applying the laws of hydrodynamics for a collapsible tube to the pulmonary circulation one can appreciate the effects that changes in lung volume and ITP have on the regional distribution of pulmonary blood flow and gas exchange. The Pi is pulmonary arterial pressure (Ppa), the Ps is alveolar pressure (Palv), and the Po is pulmonary venous pressure (Ppv). In the pulmonary circulations, there is a vertical hydrostatic pressure gradient from the most dependent to the most superior portions of the lung. Because the weight of air is negligible, there is no measurable vertical gradient for Palv. In the more gravity-dependent regions of the lung, Ppa and Ppv are greater than Palv, and the Ptm for the alveolar vessel is positive throughout. In this instance, flow is proportional to the pressure gradient between Ppa and Ppv (i.e., zone III conditions; Fig. 18.1a). In regions of the lung where Palv exceeds Pv and Ppa >Palv, the alveolar vessel is compressed as its Ptm decreases. In this region, resistance to blood flow increases, and blood flow is governed by the difference in pressure between Ppa and Palv (i.e., zone II conditions; Fig. 18.1b). And when Palv exceeds Ppa, the vascular Ptm is negative and the alveolar vessel collapses and blood flow ceases (i.e., zone I conditions; Fig. 18.1c). This initially occurs in the less gravity- dependent portions of the lung, and leads to wasted ventilation or to the creation of dead space as alveoli are ventilated but not perfused. This creates an arterial to end-tidal CO_2 gradient. A worsening of oxygenation may also occur under zone I conditions because pulmonary blood flow is shunted to poorly ventilated alveoli from overdistended regions of the lung [32, 33].

In the absence of cardiopulmonary disease, zone I conditions do not exist; however, they may be created in a variety of clinical scenarios. In addition to increases in Palv, zone I conditions may be created when CO and Ppa are low. Conversely, an increase in Palv may not create alveolar dead-space if, for example, pulmonary venous hypertension is present as in congestive heart failure. It is important to realize that the distribution of zones is dependent on physiological conditions and is not fixed.

The Effects of Respiration on Left Ventricular Preload

Respiration effects left ventricular preload by altering right ventricular preload, afterload and left ventricular diastolic Ptm. As a thin-walled structure, the RV has less contractile reserve and is therefore more sensitive to increases in afterload than the LV. Right ventricular failure adversely effects left ventricular filling by three mechanisms. First, pulmonary venous return is diminished. Second, right ventricular diastolic hypertension decreases the normal transeptal pressure gradient. As a result, the ventricular septum occupies a more neutral position between the two ventricles during diastole (Fig. 18.5). As the transeptal pressure gradient becomes reversed, the septum actually bows into the LV. The LV is restrained not only by the deviated septum and RV pressure but also the LV free wall is constrained by the pericardium [34]. This effectively decreases left ventricular compliance. Even though LV filling pressures are elevated, intrapericardial pressures have risen to a greater extent, and the net effect is a reduced LV diastolic Ptm. As a result, LV cavitary volume is reduced and filling is impaired [35, 36]. The mechanism by which the filling of one ventricle affects the filling of the other is known as diastolic ventricular interdependence and also occurs in the normal circulation. During spontaneous respiration, the decrease in ITP that occurs with inspiration enhances venous return and right ventricular filling, while diminishing left ventricular filling. This mechanism is partly responsible for pulsus paradoxus, the decrease in arterial blood pressure that occurs during inspiration. Finally, as left ventricular filling decreases, the pressure generating capabilities of the LV are diminished. This leads to a decrease in left ventricular assistance to right ventricular function, further increasing right ventricular volumes and impairing left ventricular filling [37]. This phenomenon is referred to as systolic ventricular interdependence. Ultimately, the extent to which the LV fills is a function of pulmonary venous return, ventricular diastolic Ptmp and its compliance (Fig. 18.3) [8, 15, 16].

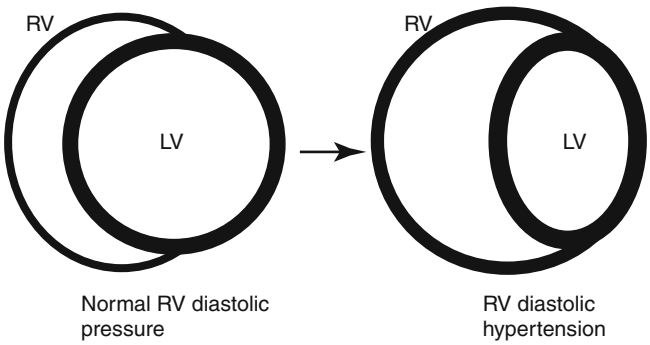


Fig. 18.5 Illustration of the geometry of the right ventricle (*RV*) and left ventricle (*LV*) and position of the interventricular septum during diastole under normal conditions (*left*) and when RV diastolic pressures are elevated (*right*). As the septum shifts to the left, the volume of the LV is reduced and LV filling is impaired

The Effects of Respiration on Left Ventricular Afterload

Respiration has a profound effect on left ventricular afterload. According to La Place's law, the systolic Ptm is an important determinant of left ventricular afterload. The Ptm

is equal to the difference between peak left ventricular cavitary or aortic systolic pressure and ITP. Thus, as ITP falls or aortic systolic pressure rises, left ventricular afterload increases (Fig. 18.6). Positive ITP, which occurs with grunting, thoracic compressions, and with the application of PPV, produces the opposite effects [38].

As ITP varies, so too does the Ptmp for the intrathoracic vascular structures. As discussed, this alters the pressure gradient for systemic venous return. On the arterial side, changes in the Ptm for the intrathoracic arterial system alter the driving pressure responsible for propelling blood from the thorax. Since both the RV and the pulmonary circulation reside within the intrathoracic compartment, changes in ITP do not alter the pressure gradients between the RV and the pulmonary vasculature.

With spontaneous respiration, a fall in ITP causes the Ptm for the intrathoracic arterial vessels to increase and as a result their volumes increase and their pressures decrease. This represents the systolic component of pulsus paradoxus [39]. With PPV, the decrease in Ptm for the intrathoracic arterial vessels decreases their effective compliance. As a result, their volumes decrease and their pressures increase relative to extrathoracic arterial vessels. As a result, blood is driven into the extrathoracic compartment [40]. Even though aortic systolic pressure increases, ITP rises to a greater extent and the net effect is a reduction in the calculated LV systolic Ptm. This phenomenon is further appreciated by altering the timing, magnitude and duration of the rise in ITP during the cardiac cycle. A selective increase in ITP during ventricular systole augments left ventricular ejection to a greater extent than that seen when the increase in ITP occurs at random in the cardiac cycle [41, 42]. In this instance, venous return and ventricular filling are unaffected as the increase in ITP is limited to systole. If the increase in ITP is confined to diastole, the LV ejects into a relatively depleted thoracic arterial system. This is analogous to the benefits ascribed to the technique of counterpulsation employed by the intra-aortic balloon pump [43]. Lastly, both the magnitude of the rise in ITP and its duration affect peak aortic flow [44].

Understanding the physiologic principles that govern the effects of respiration on cardiovascular function is essential to optimizing the care of critically ill patients. Consideration must be given to whether right or left ventricular dysfunction is present; whether the primary problem is ventricular filling or emptying; to what extent diastolic or systolic ventricular interdependence is a factor; and to what degree right and left ventricular afterload are affected. Ultimately, the various therapies that may be employed must optimize systemic oxygen transport.

The Effects of Respiration on Cardiovascular Function in Patients with Cardiac Disease

Left Ventricular Systolic Heart Failure

Systolic heart failure is characterized by small stroke volumes and low CO despite elevated ventricular volumes. The failing ventricle resides on the flat portion of its pressure-volume curve. As a result, the effects of changes in ITP on left ventricular afterload predominate over the effects on venous return. So long as an adequate albeit elevated ventricular filling pressure is maintained, PPV improves ventricular emptying and CO increases [45]. Another strategy that may be used is non-invasive continuous positive airway pressure (NCPAP). By increasing ITP, the administration of NCPAP increases stroke volume and CO [46–48]. In addition to increasing CO, PPV reduces myocardial oxygen consumption (VO_2) by decreasing LV end-diastolic volume and LV systolic Ptm, two major determinants of left ventricular wall stress. Furthermore, mechanical ventilation unloads the respiratory pump allowing for a redistribution of CO from the

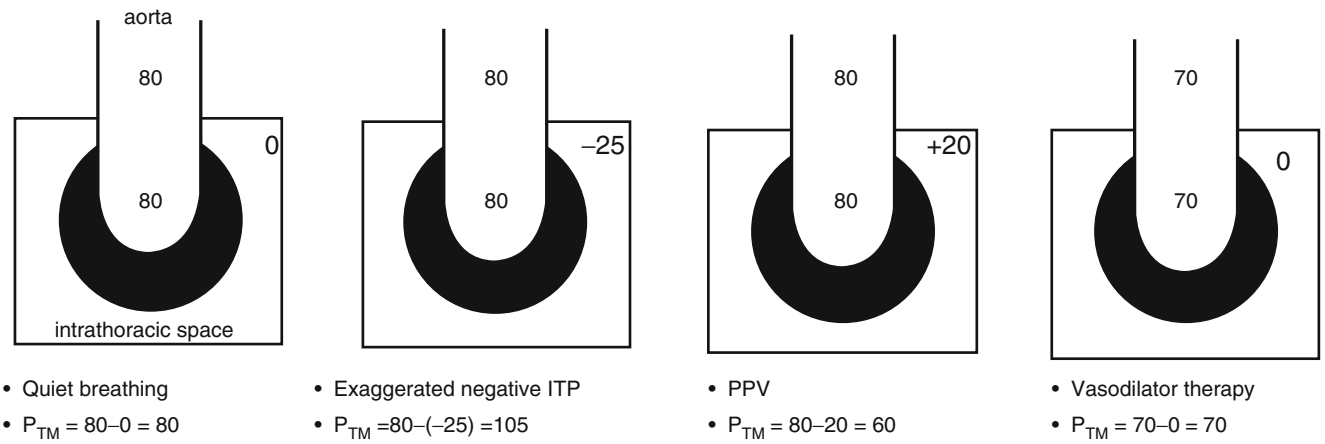


Fig. 18.6 Illustration of the left ventricle, thoracic cavity, and aorta and the effects of changes in aortic and intrathoracic pressure (*ITP*) on left ventricular afterload. P_{TM} transmural pressure, *PPV* positive pressure ventilation

respiratory apparatus to other vital organs, decreasing respiratory muscle and cardiac VO_2 (see below). The net effect of these changes is an improvement in respiratory muscle, cardiac and global oxygen transport balance (i.e., the relationship of VO_2 or oxygen demand to oxygen delivery, DO_2).

The beneficial effects of PPV on myocardial oxygen transport balance in patients with left ventricular systolic dysfunction have been demonstrated in several studies [49–51]. Rasanen and colleagues found that progressing from full ventilatory support to spontaneous breathing adversely affected myocardial oxygen transport balance and function in 5 of 12 patients with acute myocardial infarction complicated by respiratory failure [37]. In these 5 patients, increasing electrocardiographic ischemia and a significant rise in left ventricular filling pressure occurred upon removal of PPV. Scharf and colleagues evaluated the effects of the Mueller maneuver (decrease in airway pressure against a closed glottis) in patients with left ventricular systolic dysfunction [52]. Using radionuclide ventriculography they demonstrated the development of akinesis in at least one region of the LV in 9 of 14 patients with left ventricular dysfunction and in none of the 12 control patients. In addition to ensuring adequate gas exchange, PPV plays a vital role in the management of patients with low CO due to LV systolic heart failure.

Diastolic Heart Failure

Diastolic heart failure is characterized by small stroke volumes and low CO, which results from inadequate ventricular filling. Systolic function is normal. The function of venous capacitance vessels is of great importance, as has been demonstrated in patients with hypertrophic cardiomyopathies [53, 54]. For similar reasons, the effects of PPV on venous return and ventricular filling predominate over the effects of PPV on ventricular afterload. This is exemplified in the post-operative management of patients following repair of tetralogy of Fallot. Biventricular systolic function is normal, however there is invariably some degree of right ventricular diastolic disease. In approximately one-third of these patients, right ventricular diastolic heart failure develops. Shekerdemian and colleagues demonstrated a significant increase in right ventricular output when patients were converted from PPV to negative pressure ventilation (NPV) [55]. Pulmonary perfusion increased from 2.5 to 3.5 L/min/m^2 ($p<0.0001$). This favorable response was greatest in those patients with the most severe diastolic disease. Another potential mechanism for impaired CO during PPV is an increase in right ventricular afterload. As discussed, this occurs as lung volumes rise above FRC, regardless of the means by which means ventilation occurs (i.e., PPV versus NPV). In either case, the adverse effect of increases in PVR would be exaggerated in the presence of pulmonary valve incompetency, a finding present in most of these patients post-operatively. To this point, they found that the duration of pulmonary regurgitation increased during inspiration and was shortened during expiration [56].

Although converting from PPV to NPV improves CO in these patients, it is unclear if global and regional oxygen transport balance improves when CO is limited and the respiratory pump is loaded (see below). Bronicki et al. retrospectively evaluated the hemodynamic effects of converting from PPV to spontaneous negative pressure breathing following repair of tetralogy of Fallot [57]. With extubation, systolic blood pressure and cerebral oxygenation (measured by near infrared spectroscopy; INVOS oximeter, Covidien, Boulder, Colorado) increased significantly (87.2–95.9 mmHg, $p=0.001$ and 68.5–74.2 %, $p<0.0001$, respectively) whereas heart rate remained unchanged. Thus, despite loading the respiratory apparatus and an obligatory increase in perfusion of the respiratory pump, it appears that CO and more importantly cerebral blood flow increased significantly.

Cavopulmonary Anastomosis

Following the Fontan procedure, the transpulmonary pressure gradient is the difference between the Pms and common atrial pressure. There is no subpulmonic pumping chamber to overcome the resistance of the pulmonary circulation. As a result, any increase in pulmonary arterial pressure, due to pulmonary vascular disease or ventricular dysfunction, is poorly tolerated and significantly impairs pulmonary blood flow and ultimately ventricular filling. Although systolic function is generally normal, there is some degree of ventricular diastolic dysfunction, which further compromises ventricular filling. For these reasons, the function of venous capacitance vessels is of great importance and the effects of changes in ITP on venous return and ventricular filling predominate over the effects on afterload of the systemic ventricle [58, 59]. Shekerdemian and colleagues demonstrated a marked increase in pulmonary blood flow when converting patients from PPV to NPV (2.3–3.3 L/min/m^2, $p=0.01$) immediately following the Fontan procedure [60]. They also found similar results in patients remote (months to years) following the Fontan procedure (2.6–3.7 L/min/m^2, $p=0.01$). The increase in output was due to an increase in venous return, pulmonary blood flow and ventricular filling. Redington and colleagues demonstrated using pulsed wave Doppler flow analysis, a marked increase in pulmonary blood flow with inspiration and further increases with the Mueller maneuver [61]. Conversely, the Valsalva maneuver (increase airway pressure against a closed glottis) generated retrograde flow (away from the lungs) and cavitary size was significantly reduced. These maneuvers demonstrate the effects of changes in ITP without an attendant change in lung volume and therefore PVR. If lung volumes were allowed to increase significantly,

even modest increases in PVR would significantly impair pulmonary blood flow, a finding demonstrated by Williams and colleagues in their study of children following the Fontan procedure [62]. They found that progressive increases in PEEP (from 0 to 12 cm H_2O), produced significant increases in PVR and decreases in CI (from 2.7 to 2.0 L/min/m^2, p=0.02).

The Effects of Respiration on Cardiopulmonary Resuscitation

The affect of respiration on cardiovascular function during cardiopulmonary resuscitation (CPR) not only provides another example of the clinical relevance of cardiopulmonary interactions but may also lead to changes in the way in which CPR is performed. Effective CPR depends on adequate venous return to the chest after each compression cycle and the advent of mechanical devices that enhance venous return has been an area of investigation for the last several years [63]. One such device is the inspiratory impedance threshold valve (ITV). During the decompression phase of CPR, a negative ITP is created as the chest wall recoils back to its resting position. This creates a pressure gradient for systemic venous return. The ITV prevents the inflow of gas during the decompression phase, generating a greater negative ITP in a manner akin to the Mueller maneuver (spontaneous respiratory effort with a closed glottis). Several studies in animals have demonstrated a significant increase in stroke volume and CO, including a significant increase in myocardial and cerebral perfusion, with the use of the device [50, 64, 65].

The Effects of Heart Failure on Respiratory Function

Respiratory pump failure occurs when neuromuscular competency of the ventilatory pump is impaired (e.g., apnea, disuse atrophy), when the load imposed on the respiratory system is excessive (e.g., severe asthma), or when diaphragmatic oxygen transport balance is impaired (inadequate perfusion of the respiratory pump). The benefits of mechanical ventilation in supporting respiratory function in the setting of impaired neuromuscular function or severe respiratory disease are well documented. Mechanical ventilation also plays a vital role in the management of the low CO state by improving not only respiratory muscle but also myocardial and global oxygen transport balance [66, 67].

Under normal conditions, the diaphragm consumes less than 3 % of global VO_2 and receives less than 5 % of CO. However, with an increase respiratory load, diaphragmatic VO_2 may increase to values over 50 % of the total VO_2. In order to meet these increased demands, diaphragmatic blood flow must increase. When diaphragmatic oxygen transport balance is inadequate, either because of excessive oxygen requirements or limited DO_2, respiratory pump failure ensues [68]. Aubier and colleagues demonstrated in a dog model of cardiogenic shock that the ability of the diaphragm to generate force (ie., the generation of transdiaphragmatic pressure) was not much greater than that required for ordinary quiet breathing [69]. In a dog model of cardiogenic shock in which CO was decreased by 70 %, respiratory muscle blood flow increased to 21 % of CO during spontaneous respiration [47]. The minute ventilation nearly tripled in the spontaneously breathing dogs and was elicited by acidemia and hypoxia [70]. In the group receiving mechanical ventilation, respiratory muscle blood flow decreased to 3 % of CO and blood flow to the liver, brain and kidneys increased significantly.

The importance of maintaining respiratory muscle oxygen transport balance has also been demonstrated in patients receiving mechanical ventilation for acute respiratory failure accompanied by underlying ventricular dysfunction. Several studies in adults have found that up to one-third of patients receiving mechanical ventilation for respiratory failure are unable to wean from mechanical ventilation due to a worsening of left ventricular function and respiratory muscle oxygen transport balance [71].

These studies demonstrate not only the importance of diaphragmatic blood flow in preserving respiratory pump function but also the phenomenon that diaphragmatic blood flow is protected to an equal or even greater extent than is cerebral and myocardial blood flow when CO is limited. With mechanical ventilation, substantial quantities of oxygen are released for other organs meanwhile respiratory muscle and cardiac VO_2 are decreased significantly.

The Effects of Respiratory Disease on Cardiovascular Function

The importance of discussing disorders of the respiratory system in the context of cardiopulmonary interaction is that they may be a cause of or contribute to cardiovascular disease. This is exemplified in the syndrome of obstructive sleep disordered breathing (OSDB). OSDB is a relatively common respiratory disorder occurring in approximately 3 % of all children, and it is associated with other conditions commonly found in the intensive care setting, such as Down syndrome, neuromuscular disease, craniofacial abnormalities, and heart failure. OSDB, like other disease of the respiratory system, primarily affects cardiovascular function by altering ITP and gas exchange.

OSDB is characterized by repetitive episodes of inspiratory flow limitation or cessation of inspiratory flow and results primarily from impaired upper airway function during sleep. This leads to the generation of exaggerated negative ITP and impaired gas exchange. Hypoxemia and hypercapnia stimulate baroreceptors and chemoreceptors, leading to activation of the sympathetic nervous system and renin-angiotensin-aldosterone system. As a result,

biventricular afterload increases and stroke volume and CO fall. Exaggerated negative pressure breathing also leads to an increase in venous return, leftward deviation of the ventricular septum, reduced left ventricular filling and CO falls further. The impact of exaggerated negative pressure breathing on cardiovascular function is even greater in the patient with underlying LV systolic dysfunction. These factors adversely affect myocardial oxygen transport balance and may precipitate myocardial ischemia. Kuniyoshi and colleagues prospectively evaluated the relationship between the day-night variation of presentation for acute myocardial infarction (AMI) (n = 92) in patients for which the time of onset of chest pain was clearly identified and the incidence of OSDB [72]. The odds of having OSDB in those patients whose AMI occurred between 12 and 6 am was sixfold higher than in the remaining 18 h of the day and of all the patients having an AMI between 12 and 6 am, 91 % had OSDB.

Recurrent hypoxia leads to ischemia-reperfusion injury and the generation of an inflammatory response. Inflammatory mediators such as oxygen free radicals further injure the myocardium and impair endothelial function, contributing to increases in ventricular afterload. Over time, these cumulative effects lead to ventricular remodeling and the development of right and/or left ventricular diastolic and systolic heart disease [73–78]. Noninvasive continuous positive airway pressure (NCPAP) markedly reduces the incidence and severity of OSDB and in doing so improves gas exchange and eliminates wide swings in ITP. Over time, the use of NCPAP improves cardiovascular function. Several studies have demonstrated significant improvements in right and left ventricular diastolic and systolic function and reductions in biventricular afterload [56–58].

Conclusion

The successful provision of intensive care to the critically ill patient is directly related to optimizing oxygen transport balance. The matching of oxygen delivery to oxygen demand is dependent on the pathophysiologic conditions and, importantly, is often determined by cardiopulmonary interactions that result from both physiologic derangements and the application of clinical therapies. With the advent of newer technologies for monitoring the adequacy of oxygen delivery, the impact of interventions on oxygen transport balance can be more readily and accurately ascertained. As this review points out, the impact of therapies aimed at improving oxygen transport balance is neither predictable nor always entirely beneficial.

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The Classification and Nomenclature of Congenital Heart Disease

19

Ali Dodge-Khatami

Abstract

Congenital Heart Disease (CHD) encompasses a very large number of defects. For each defect, there may be broad anatomic/morphological variations across a spectrum, giving the possibility of describing the same malformation in many ways. From a functional standpoint, similar morphological defects may present with different physiologies depending on severity, location, or interaction with other concomitant malformations, so that any given defect may functionally behave in multiple different ways. Nomenclature and classification strive to find a common language to describe the defects in a comprehensive fashion, spoken and heard by all specialists caring for patients with congenital heart disease, so that any given lesion, simple or in combination with others, may be properly visualized, conceptualized, and thoroughly understood in the same clear way, in order to provide the best possible care in an efficient and streamlined manner. The International Congenital Heart Surgery Nomenclature and Database Project has succeeded in incorporating the extant Van Praaghian and Andersonian segmental and sequential approaches in a comprehensive fashion, allowing all caregivers for patients with CHD to communicate using the same language.

Keywords

Nomenclature • Classification

Introduction

Few disease entities require the intensive, multi-disciplinary interaction and team approach for a successful outcome such as Congenital Heart Disease (CHD). The patient population is heterogenous, the spectrum of cardiac lesions and underlying physiology very broad, and the number of highly specialized individuals from differing backgrounds managing the patients probably higher than in any other condition in the Pediatric Intensive Care Unit (PICU). Respectively, the path taken by any given patient may involve: (1) Prenatal diagnosis by Obstetricians and/or Pediatric Cardiologists; (2) Post-natal stabilization by Neonatologists and Critical Care Physicians; (3) Pre-interventional or pre-operative preparation and treatment involving Cardiologists and Surgeons; (4) Operative repair, requiring the tight interaction between Surgeon, Anesthesiologist and Perfusionist; and (5) Post-operative treatment by the Surgeon, Intensive Care Specialists, Nursing, and Respiratory Therapy (to name but a few). The constructive communication and ease of flow of pertinent information surrounding any given congenital heart defect between all members of a care team are often taken for granted. However, in order for this complex interaction to succeed, in order for caregivers of all specialities to apply this self-evident confidence in providing the optimal management at all phases pertaining to a patient, we all need to understand and speak *the same language*. This requires both a very specific but yet highly comprehensive definition of the various congenital cardiac malformations, and their respective pathophysiology, which in turn can be understood and treated by all team

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members alike. While *Nomenclature* is defined as the system of names used in a branch of learning or activity, *Classification* is defined as an arrangement, according to some systematic division, into classes or groups based on some factor common to each [1]. Therefore, efficient nomenclature strives to develop a common language, encompassing the systematic and reproducible classification of CHD which is universally understood by all, and thereby triggering the same therapeutic reflexes for a successful patient outcome.

Various anatomic nomenclature systems have attempted to comprehensively define the entire spectrum of CHD. The two most commonly used have been or remain that of Richard Van Praagh [2] and that of Robert H. Anderson [3], giants in the field of cardiac developmental and morphological description. Both of these individuals have undeniably helped to advance the understanding of congenital heart defects.

Van Praagh's Segmental Approach

The system advocated by Van Praagh describes the position of the heart in a sequence of three letters designating segments starting from the venous inflow of the heart, to the ventricular loop, and finally to the position of the great arteries {atria, ventricles, great arteries}. This approach describes segments as they are orientated in space through understanding of the development of the embryonic heart. Respectively, the viscero-atrial situs is defined (S = situs solitus, I = situs inversus, A = ambiguous), followed by the ventricular loop (D = D-loop, L = L-loop), and finally the relation of the great arteries to one another (S = normally related great arteries, I = inverted normally related great arteries, D = D-transposition, and L = L-transposition). Looping pertains to the way the ventricular mass is oriented after looping of the embryonic cardiac tube during development. Morphologically, the right ventricle has coarse trabeculations, while the left is covered by fine trabeculations. Normally, the morphologic right ventricle is oriented to the right and anterior to the morphologic left ventricle (D-looping). With L-looping to the left, the morphologic right ventricle lies posterior and to the left of the morphologic left ventricle. A normal heart is designated {S,D,S}.

Anderson's Sequential Segmental Approach

The sequential segmental approach as described by Anderson also starts with the viscero-atrial situs, then defines the atrio-ventricular connection, and finally ends with the ventriculo-arterial connection. The sequential segmental approach is more based on the sequences in which blood flows through the heart from inflow to outflow. Successively, the terminology includes situs solitus, situs inversus, left isomerism, and right isomerism pertaining to the atrial position, followed by concordant, discordant, ambiguous, double inlet, absent right or left connection with regards to the atrio-ventricular connection, and finally concordant, discordant (transposition), double outlet or single outlet – common arterial trunk for the ventriculo-arterial connection. Further specifications pertain to the mode of atrio-ventricular connection: two perforate valves, single perforate valve, one perforate and one imperforated, and common valve. Also, although not advocated by Anderson himself, sequential segmental analysis users include the side of the aortic arch, either left or right. There is no formal alphabetical shorthand for the "Andersonian" approach, as the system involves a comprehensive description of cardiac findings; however, the normal heart is described as SCCL or situs solitus, concordant atrio-ventricular connection, concordant ventriculo-arterial connection and left aortic arch.

Isomerism or heterotaxy is often interchangeably used to designate complex defects whereby there is a lack of visceral sidedness and/or discordance between cardiac and visceral organ positions [4]. The sidedness of the atria, based on the morphology, will determine the situs of an isomerism. The morphologic right atrium has an appendage which is broad and blunt, with an interatrial septum containing the limbus of the fossa ovalis. The left atrium has an appendage like a finger: long, pointed, and narrow, with an interatrial septum containing the flap valve of the fossa ovalis. When two atria are present, they and their respective broncho-pulmonary structures are either of left-sided or right-sided morphology, hence left or right atrial isomerism. With a single atrium, or when the situs of the atria cannot be determined, the term situs ambiguous may be used. As mentioned, atrial situs is highly consistent, but not absolute, with broncho-pulmonary situs. Indeed, the morphologic right lung has eparterial bronchi leading to three lobes, while the morphologic left lung has hyparterial bronchi and two lobes. Therefore, patients with right isomerism will commonly have both bronchi and trilobed lungs with right-sided morphology (bilateral "right-sidedness"), while those with left isomerism bilateral left-sidedness of hyparterial bronchi and bilobed lungs. Commonly but less consistently with atrial situs is the splenic anatomy. Patients with left isomerism may present with polysplenia and those with right isomerism with asplenia (Ivemark's syndrome). Finally, patients with right isomerism are often in sinus rhythm and have two sinus nodes, while those with left isomerism commonly have a hypoplastic or absent sinoatrial node [5].

International Congenital Heart Surgery Nomenclature and Database

The need for a very specific yet highly comprehensive common nomenclature for CHD was recognized in the early to mid-nineties, when almost in parallel, the European Congenital Heart Surgeons Foundation (ECHSF) and the Society of Thoracic Surgeons (STS) National Congenital Heart Surgery Database Committee commissioned multi-institutional data retrieval from patients with CHD. Besides the huge amount

of valuable data gathered, both Databases pointed to a common flaw, namely that unless a unified, specific yet inclusive, nomenclature was found, incomplete or false data would be inevitable, and interpretation of the data correspondingly inaccurate and limited. Conversely, confusion or redundancy will result from an excessively inclusive nomenclature system which allows for many names corresponding to segmental anatomies, although functionally similar, who will be corrected by the same operation. Examples include the synonyms transposition of the great arteries (TGA), d-TGA, complete transposition, or uncorrected transposition, also designated as hearts with segmental anatomy {S,D,D}, {S,D,A}, {S,D,L}, {I,L,L}, {I,L,D}, {A,L,L} and {A,D,D}, all of which may be managed by performing an arterial switch operation. The same pertains to congenitally corrected TGA, l-TGA, double discordance, or physiologically corrected transposition, which apply to segmental anatomy {S,L,L}, {S,L,D} and {I,D,D}. Stemming from joint members of both North American and European Congenital Cardiothoracic Surgeon databases, the International Congenital Heart Surgery Nomenclature and Database Project was launched [6]. After tremendous groundwork established through multiple Conferences, Business and Subcommittee meetings amongst surgeons, cardiologists and morphologists thereby incorporating the Andersonian and Van Praaghian systems, a comprehensive Nomenclature System was developed and adopted, and more importantly, codified into a reproducible, inclusive and universal software system allowing congenital heart surgeons around the globe to register and share data using the same language. Independently and simultaneously, the Association for European Pediatric Cardiology (AEPC) developed a diagnostic list for congenital heart defects, based on the Andersonian nomenclature [7]. The next step involved the acceptance and shared utilization of both nomenclatures by the various surgical and cardiology societies, by merging the two coding systems in a complementary way, and not in a competitive fashion. Successively, the third through the *sixth World Congresses of Pediatric Cardiology and Cardiac Surgery* in Buenos Aires (2005), Cairns (2009) and Cape Town (2013), have consolidated the common efforts of the largest concerned Societies and Associations to reunite the extant nomenclature systems into one universal language [8]. Through a similar inclusive listing of diagnoses using the same nomenclature, has communication amongst all level of caregivers been secured, allowing for meaningful input, analysis, and sharing of data pertaining to patients with congenital heart disease.

Functional Classification

Independently of the international nomenclature and database project which accurately describes the lesions according to anatomy/morphology, congenital heart defects may also be understood and classified functionally, according to whether a lesion is acyanotic or cyanotic, which itself may also be separated in lesions with decreased or increased pulmonary blood flow, or in lesions with single ventricular physiology (indeed, the chapters on management of congenital heart disease in this textbook are arranged in this manner). This classification helps with regards to therapeutic implications, as it helps to distinguish defects which will lead to biventricular repair or "correction", rather than univentricular repair and "palliation". However, the distinction between acyanotic or cyanotic mostly describes the physiology of a patient at a certain time point, and does not help with regards to anatomical details of a lesion. A useful summary is provided in Table 19.1.

Table 19.1 Functional classification of congenital heart lesions and incidence

Acyanotic congenital heart disease
Left-to-right shunts
Atrial septal defects (10 %)
Ventricular septal defects (20 %)
Atrioventricular septal defects (2–5 %)
Aortopulmonary window
Patent ductus arteriosus (10 %)
Left-sided obstructive lesions
Coarctation of the aorta (10 %)
Congenital aortic stenosis (10 %)
Interrupted aortic arch (1 %)
Mitral stenosis
Cyanotic congenital heart disease
Lesions associated with decreased pulmonary blood flow (right-to-left shunts)
Tetralogy of fallot (10 %)
Pulmonary stenosis (10 %)
Pulmonary atresia (5 %)
With intact ventricular septum (pa/ivs)
With ventricular septal defect (pa/vsd)
Tricuspid atresia (3 %)
Ebstein's anomaly (0.5 %)
Lesions associated with increased pulmonary blood flow (complete mixing lesions)
Transposition of the great vessels (5–8 %)
With intact ventricular septum (tga/ivs, simple tga)
With ventricular septa defect (tga/vsd)
Double outlet right ventricle (dorv) with subpulmonary vsd
Total anomalous pulmonary venous connection (2 %)
Truncus arteriosus (3 %)
Single ventricle physiology
Hypoplastic left heart syndrome (2 %)
Double inlet left ventricle (dilv)

The International Congenital Heart Surgery Nomenclature and Database project allows for a hierarchical system, with up to five levels of anatomical detail, and additional modifiers [6]. An example of Level 4 is provided in Table 19.2 [1]. Furthermore, the system incorporates a short list of procedures relating to each defect, so that not only the anatomical description is comprehensive, but also the way in which a lesion will be surgically managed. Details of each defect and

Table 19.2 Segmental system of classification and nomenclature of lesions of congenital heart disease: level 4

I. Great veins	Secundum
Systemic veins	Sinus venosus
Systemic venosus anomaly, SVC	Left Atrium
Abnormal RSVC	**III. Atrioventricular junction**
Absent RSVC	Right AV valve
Bilateral SVC	Tricuspid stenosis
CS ostial atresia or stenosis (CS draining cephalad through LSVC)	Congenital
Levoatrial-cardinal vein	Valvar hypoplasia
Other (specify)	Abnormal subvalvar apparatus
Retroaortic innominate vein	Double-orifice valve
SVC occlusion	Parachute deformity
SVC stenosis	Other
Systemic venous anomaly, IVC	Acquired
Abnormal RIVC	Status post cardiac surgery
Biatrial drainage of IVC	Tricuspid regurgitation
Cor triatriatum dexter	Congenital
IVC occlusion	Primary annular dilatation
IVC stenosis	Prolapse
LIVC	Leaflet underdevelopment
Other (specify)	Absent papillary muscle or chordae
Separate entry of hepatic veins (RIVC to right-sided atrium)	Other
Pulmonary veins	Acquired
Total anomalous PV connection	Status post cardiac surgery
Type 1 (supracardiac)	Ebstein's anomaly of the tricuspid valve
Type 2 (cardiac)	Ebstein's anomaly, type I
Type 3 (infracardiac)	Ebstein's anomaly, type II
Type 4 (mixed)	Ebstein's anomaly, type III
Partial anomalous PV connection	Ebstein's anomaly, type IV
Nonscimitar	Ebstein's anomaly, "left-sided" Ebstein's anomaly
Scimitar	Ebstein's anomaly, atypical Ebstein-like anomalies associated with hypoplastic right heart syndrome
Cor triatriatum	Ebstein's anomaly, other
Accessory atrial chamber receives all PV and communicates with LA	Common AV valve
Accessory atrial chamber receives all PV and does not communicate with LA	AV canal defect (AVSD)
Accessory atrial chamber receives part of the PV (subtotal cor triatriatum)	AVC (AVSD), Partial (incomplete) (PAVSD) (ASD, Primum)
Pulmonary venous stenosis	AVC (AVD), Intermediate (transitional)
Congenital	AVC (AVSD), Complete (CAVSD)
Congenital, Diffusely hypoplastic	Left atrioventricular valve
Congenital, Long segment focal (tubular) stenosis	Mitral stenosis
Congenital, Discretes stenosis	Congenital
Acquired	Subvalvar
Acquired, Postoperative	Valvar
Acquired, Not postoperative	Supravalvar
II. Atria	Mixed
Right atrium	Other
Atrial septum	Acquired
Atrial septal defect	Status post cardiac surgery
Common atrium (single atrium)	Mitral regurgitation
Coronary sinus	Congenital
PFO	Subvalvar
Primum	Valvar

Table 19.2 (continued)

IV. Ventricles
Right ventricle
Tetralogy of Fallot
TOF, Pulmonary stenosis
TOF, Pulmonary atresia
TOF, Common atrioventricular canal (TOF/CAVSD)
TOF, Absent pulmonary valve
Double-chamber right ventricle
DCRV, no VSD
DCRV, VSD
VSD to lower RV chamber
VSD to upper RV chamber
VSD to lower and upper RV chambers
Ventricular septum
VSD
VSD, Multiple
VSD, Type 1 (Subarterial) (Supracristal) (Conal septal Defect) (Infundibular)
VSD, Type 2 (Perimembranous) (Paramembranous) (Conoventricular)
VSD, Type 3 (Inlet) (AV canal type)
VSD, Type 4 (Muskular)
VSD, Type: Gerbode type (LV-RA communication)
Left ventricle
Single ventricle
Single ventricle, Double-inlet left ventricle
DILV (S,L,L), Outlet chamber (bulboventricular foramen)
DILV (S,D,D), Outlet chamber (bulboventricular foramen)
DILV (S,D,N) (Holmes heart)
DILV, DOLV
DILV, DORV
Single ventricle, Double-inlet right ventricle
DIRV, DORV
DIRV, Outlet chamber (bulboventricular foramen)
DIRV, Other
Single ventricle, Mitral atresia
Mitral atresia DORV
Mitral atresia, (S,D,N)
Mitral atresia, (S,L,L) (corrected transposition)
Single ventricle, Tricuspid atresia
Type 1a (No TGA, pulmonary atresia)
Type 1b (No TGA, pulmonary hypoplasia, small VSD)
Type 1c (No TGA, no pulmonary hypoplasia, large VSD)
Type 2a (D-TGA, pulmonary atresia)
Type 2b (D-TGA, pulmonary or subpulmonary stenosis)
Type 2c (D-TGA, large pulmonary artery)
Type 3a (L-TGA, pulmonary or subpulmonary stenosis)
Type 3b (L-TGA, subaortic stenosis)
Single ventricle, Unbalanced AV canal defect
Single ventricle, Unbalanced AV canal, Right dominant
Single ventricle, Unbalanced AV canal, Left dominant
Mixed
Other
Acquired
Status post cardiac surgery
Heterotaxia syndrome, Other
Single ventricle, Other
Single ventricle, Other Mostly LV
Single ventricle, Other Mostly RV
Single ventricle, Other, Indeterminate
Hypoplastic left heart syndrome
HLHS, aortic atresia + mitral atresia
HLHS, aortic atresia + mitral stenosis
HLHS, aortic atresia + VSD (well developed mitral valve and LV)
HLHS, aortic stenosis + mitral atresia
HLHS, aortic stenosis + mitral stenosis
HLHS, aortic stenosis + mitral valve hypoplasia
HLHS, hypoplastic AV + MV + LV (HLHC)
V. Ventriculoarterial junction
Right ventriculoarterial valve
Pulmonary stenosis
Pulmonary stenosis, Subvalvar
Pulmonary stenosis, Valvar
Pulmonary stenosis, Supravalvar
Pulmonary insufficiency
Pulmonary atresia with intact ventricular septum
No coronary fistulas/sinusoids
Coronary fistulas/sinusoids: non-RV-dependent coronary circulation
Coronary fistulas/sinusoids: RV-dependent coronary circulation
Pulmonary atresia with VSD
Type A (native Pas present, no MAPCA)
Type B (native Pas present, MAPCA present)
Type C (no native Pas, MAPCA present)
Common ventriculoarterial valve
Truncus arteriosus
With confluent or near confluent PAs (large aorta type) (Van Praagh A1, A2; Colett and Edwards I, II, III)
With absence of one PA (large aorta type with absence of one PA) (Van Praagh A3)
With interrupted aortic arch or coarctation (large PA type) (Van Praagh A4)
Left ventriculoarterial valve
Aortic stenosis
Aortic stenosis, Subvalvar
Aortic stenosis, Valvar
Aortic stenosis, Supravalvar
Aortic insufficiency
Congenital
Acquired
Aortic atresia
Sinus of Valsalva aneurysm
Sinus of Valsalva aneurysm, Left sinus
Sinus of Valsalva aneurysm, Right sinus

(continued)

Table 19.2 (continued)

Single ventricle, Heterotaxia syndrome	Sinus of Valsalva aneurysm, Non-coronary sinus
Heterotaxia syndrome, DORV, CAVC (CAVSD), Asplenia	Aortic-LV tunnel
Heterotaxia syndrome, DORV, CAVC (CAVSD), Polysplenia	Type I: simple tunnel
Heterotaxia syndrome, Single LV	With tracheal stenosis and tracheomalacia
Type III: intracardiac aneurysm	Without tracheal stenosis or tracheomalacia
Type IV: aortic wall aneurysm and intracardiac aneurysm	Aorta
Both ventriculoarterial valves	Aortic coarctation
Transposition of the great arteries	COA, Isolated
TGA: IVS	COA, With VSD
TGA: IVS, LVOTO	COA, With complex intracardiac anomaly
TGA: VSD	Interrupted aortic arch
TGA: VSD, LVOTO	Type A: interruption distal to the left subclavian artery
Double-outlet right ventricle	Type B: interruption between the left carotid and left subclavian arteries
DORV, VSD type	Type C: interruption between the innominate and left carotid arteries
Subaortic VSD + NO PS	Both great arteries
Doubly committed VSD + NO P	Patent ductus arteriosus
DORV, TOF type	PDA, Normal origin and insertion
Subaortic VSD + PS	PDA, Abnormal origin and insertion
Doubly committed VSD + PS	Aortopulmonary window
DORV TGA type	Type 1 proximal defect
Subpulmonary VSD + NO PS (Taussig-Bing)	Type 2 distal defect
Subpulmonary VSD + PS	Type 3 total defect
DORV, Remote VSD (uncommitted VSD)	Intermediate type
Common atrioventricular canal (CAVSD) + PS	Vascular ring
Common atrioventricular canal (CAVSD) + NO PS	Double aortic arch
NO CAVSD + PS	Right aortic arch-left ligamentum or left PDA
No CAVSD + No PS	Innominate artery compression
DORV, IVS	Vascular ring, other
Double-outlet left ventricle	PA origin from ascending aorta (hemitruncus)
DOLV, Subaortic VSD	Left PA
DOLV, Subpulmonary VSD	Right PA
DOLV, Doubly committed VSD	Coronary arteries
DOLV, Noncommitted VSD	Anomalous origin of coronary artery from PA
DOLV, IVS	Anomalous left coronary from the PA (ALCAPA)
DOLV, Ebstein's anomaly	Anomalous right coronary from the pulmonary artery (ARCAPA)
VI. Great arteries	Anomalous circumflex from the pulmonary artery (ACxPA)
Pulmonary artery	Anomalous left and right coronaries from the pulmonary artery (both ALCAPA and ARCAPA)
PA stenosis	
PA stenosis (hypoplasia), main (trunk)	
PA stenosis (hypoplasia), branch	
PA sling	
With tracheal stenosis	
With tracheomalacia	

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ASD atrial septal defect, *AV* atrioventricular, *CAVSD* complete atrioventricular septal defect, *COA* coarctation of the aorta, *CS* coronary sinus, *DCRV* double –chamber right ventricle, *DILV* double-inlet left ventricle, *DIRV* double-inlet right ventricle, *DOLV* double-outlet left ventricle, *DORV* double-outlet right ventricle, *HLHC* hypoplastic left heart complex, *HLHC* hypoplastic left heart complex, *HLHS* hypoplastic left heart syndrome, *IVC* inferior vena cava, *IVS* Intact Ventricular septum, *LA* left atrium, *LIVC* left inferior vena cava, *LSVC* left superior vena cava, *LV* left ventricle, *LVOTO* left ventricular outflow tract obstruction, *MAPCA* major aortopulmonary collateral arteries, *MV* mitral valve, *PA* pulmonary artery, *PAVSD* partial atrioventricular septal defect, *PDA* patent ductus arteriosus, *PFO* patent foramen ovale, *PS* pulmonary stenosis, *PV* pulmonary vein, *RA* right atrium, *RIVC* right inferior vena cava, *RSVC* right superior vena cava, *RSVC* right superior vena cava, *RV* right ventricle, (S,D,D), (S,D,N), (S,L,L), Van Praagh descriptors of atrial situs solitus, D-loop (solitus or non-inverted) or L-loop (inverted) ventricles, and D-transposed, normal, or L-transposed great arteries, *SVC* superior vena cava, *TGA* transposition of the great arteries, *TOF* tetralogy of Fallot, *VSD* ventricular septal defect

their respective procedures short list were described in a full supplementary issue of the Annals of Thoracic Surgery, rendering in detail the minutes of the International Nomenclature and Database Conferences for Pediatric Surgery through 1998–1999 [9].

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Shunt Lesions

20

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Abstract

Defects in the atrial or ventricular septum or abnormal communications between the great arteries can lead to left to right shunts. This chapter describes the key anatomic features, pathophysiology, clinical features and management options for defects of the atrial and ventricular septum, patent ductus arteriosus, and aortopulmonary window.

Keywords

Shunt • Congenital heart disease • Septal defects

Introduction

The four congenital heart defects discussed in this chapter are grouped together because of their shared physiology. In all four, the defects provide avenues for augmentation of pulmonary blood flow via a left-to-right shunt. Defects of the ventricular septum or abnormal connections between the great vessels impose both flow and pressure related stressors on the pulmonary vascular bed, while isolated defects of the atrial septum impose a flow related hemodynamic burden. Untreated, pulmonary vascular disease develops and lifespan is curtailed in all four defects if the communications are large and unrestrictive. The natural history of these defects has been altered substantially with the availability of surgical repair and more recently, closure by percutaneous techniques. Procedural mortality is very low and a normal life span is expected in the current era.

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Atrial Septal Defect (ASD)

Any opening in the atrial septum constitutes an atrial septal defect (ASD). A patent, competent foramen ovale is excluded from this definition. ASD's can be isolated or found in conjunction with other congenital heart malformations. Only isolated ASD's are the subject of further discussion here. ASD's can be classified into different types based on their location (Fig. 20.1):

Secundum ASD: The interatrial communication is in the region of the fossa ovalis.

Primum ASD: The defect is anterior to the fossa ovalis. A common atrioventricular valve and an inlet ventricular septal defect are associated features.

Sinus venosus ASD: The defect is posterior and superior to the fossa ovalis at the junction of the superior vena cava with the right atrium. Anomalous drainage of the right pulmonary veins is almost always associated.

Coronary sinus ASD: The defect in the atrial septum is in the region of the coronary sinus ostium.

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Embryology

The process of septation of the common atrium begins around week 4–5 of gestation (Fig. 20.2) [1]. The septum primum grows from the roof of the common atrium towards the developing endocardial cushions. The merger of the septum primum and the endocardial cushions obliterates the ostium primum. Prior to this event, multiple defects appear in the mid region of the septum primum and coalesce to form a single large interatrial communication (ostium secundum). The septum secundum develops to the right of the septum primum. The concave leading edge of the septum secundum partially covers the ostium secundum. The septum secundum forms the limbus, the septum primum, the valve of the fossa ovalis and the oblique channel between the two, forms the foramen ovale. Postnatal closure of the foramen ovale occurs when the left atrial pressure exceeds that of the right atrium and the valve of the fossa ovalis apposes against the limbus. Anatomic closure of the foramen ovale occurs in most individuals. In 25–30 % of people, a persistent patent foramen ovale represents a potential route for paradoxical embolization [2].

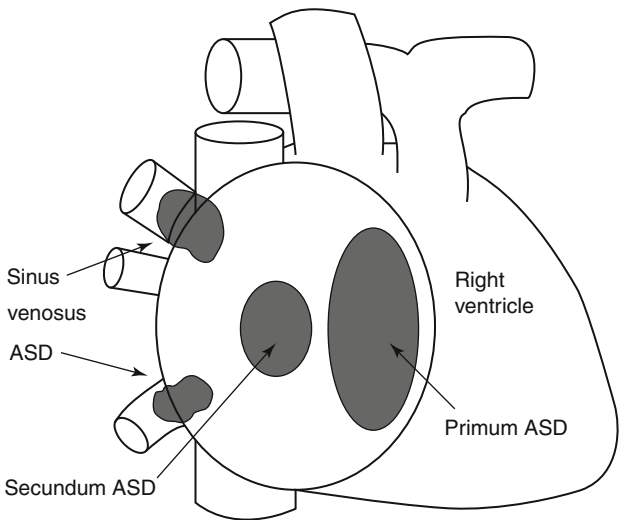


Fig. 20.1 Atrial septal defect types: View of the atrial septum with the right atrial wall removed to show the positions of the different types of ASD's. *ASD* atrial septal defect

Secundum ASD's arise when the ostium secundum is unguarded by the septum secundum either because of excessive resorption or deficiency of septum primum or due to poor development of the septum secundum. Primum atrial septal defect occurs anterior to the fossa ovalis and is due to maldevelopment of the endocardial cushions at the atrioventricular junction. The exact embryological basis for the sinus venosus defects is unclear and considerable controversy persists [3–7]. Coronary sinus defect results from either developmental failure or resorption of the common wall separating the coronary sinus ostium and the left atrium. The anatomy, physiology, clinical features and management of the different forms of ASD's (except primum ASD's) are described in the following pages. Primum ASD's are beyond the scope of this chapter as they also involve malformations of the atrioventricular valve.

Secundum ASD's

Secundum ASD's are located in the region of the fossa ovalis. ASD's as a group occur in 1:1,500 live births [8]. Secundum ASD, the most common form of ASD, demonstrates a female predilection [8]. Tremendous strides have been made in recent years towards uncovering the molecular basis of congenital heart disease [9–15]. Mutations in genes encoding transcription factors critical in cardiac morphogenesis, i.e. *NKX2.5* and *GATA4* can result in familial forms of secundum ASD [10–12]. Mutations in genes encoding another transcription factor TBX5, causes the Holt-Oram syndrome characterized by ASD and deformities of the upper extremities [13–15].

Pathophysiology

The extent of left to right shunting across the ASD depends upon the size of the defect, the relative compliances of the ventricles, and the relative resistances across the pulmonary and systemic vascular bed [16]. The primary determinant of the directionality of the shunt across the ASD is the relative compliances in the two ventricles. In the postnatal period, when the right ventricle is still thick and poorly compliant, there is no, or at most, minimal bidirectional atrial level

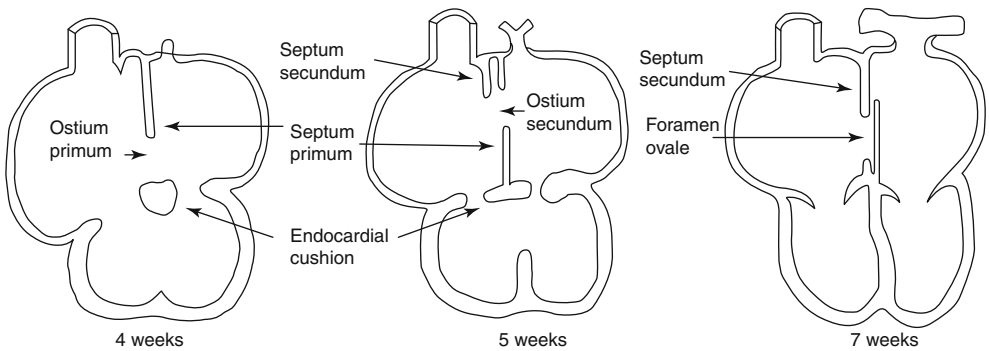


Fig. 20.2 Development of the atrial septum is depicted at 4, 5 and 7 weeks of gestation

shunt. The postnatal fall in pulmonary vascular resistance favors a relative reduction in the right ventricular myocardial mass resulting in progressive improvement in compliance over several months. Consequently, there is an increase in left to right atrial level shunting with age and a progressive increase in pulmonary blood flow. The increased volume load on the right ventricle does not impose significant circulatory burden for several decades. Right heart failure is unusual before adulthood and is extremely rare in childhood. Despite the increase in pulmonary blood flow, the pulmonary artery pressure and pulmonary vascular resistance is usually normal during childhood. Pulmonary vascular disease though rare, can occur in adulthood. The atrial level shunt is decreased, abolished, or reversed with progression of pulmonary vascular disease.

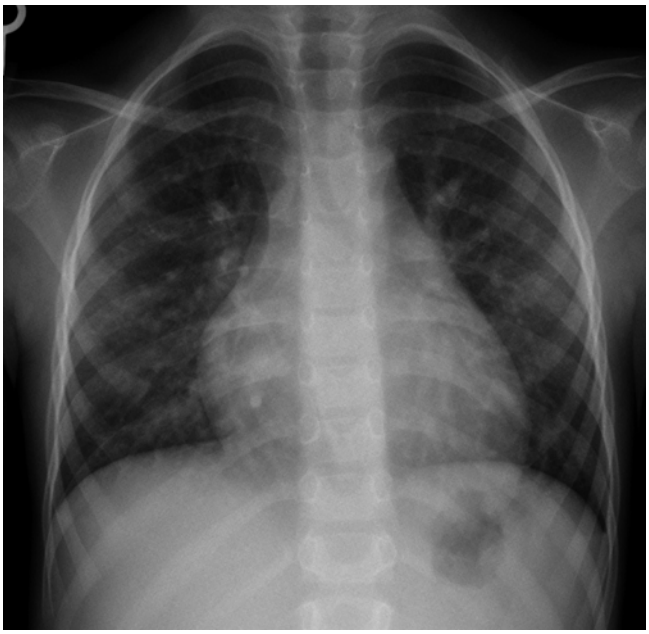


Fig. 20.3 Chest radiograph of a patient with an ASD: Cardiomegaly and prominent pulmonary vascular markings are present

Clinical Features

Most children with ASD's do not manifest overt symptoms of their cardiac lesion and may escape diagnosis. Symptoms are more likely to emerge in adulthood and most patients are symptomatic by the end of the fourth decade of life [17]. The most common presenting symptom is easy fatigability and exertional dyspnea. Palpitations secondary to atrial flutter and fibrillation may emerge after the fourth decade of life and is due to long-standing right atrial dilatation. Older adults may present in decompensated right heart failure often with concomitant moderate pulmonary hypertension. Transient ischemic attack or stroke due to paradoxical embolization may rarely be the heralding symptom of an atrial communication. In the presence of a large left to right shunt, a prominent, hyperdynamic impulse due to right ventricular volume overload may be appreciated at the lower left sternal border. There is wide splitting of the second heart sound which may sometimes be fixed. A systolic, ejection murmur reflecting increased flow across the pulmonary valve is best heard in the left upper sternal border. With large shunts, an early diastolic rumble may be heard in the lower left sternal border and reflects high flow across the tricuspid valve.

On chest radiograph, the heart size may be variably enlarged depending upon the size of the atrial shunt. In large left to right shunts, cardiomegaly and prominent pulmonary vascular markings are present (Fig. 20.3). Right ventricular volume overload is indicated by rsR' or RSR' pattern in right precordial leads on a standard 12-lead electrocardiogram (ECG) (Fig. 20.4). Right atrial and right ventricular enlarge-

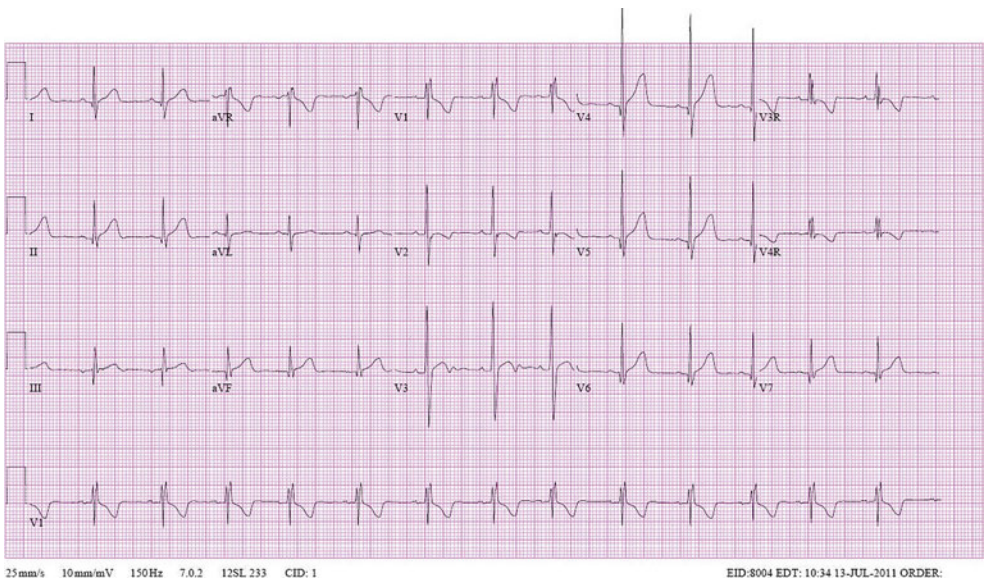


Fig. 20.4 Electrocardiogram of a patient with an ASD: Right ventricular conduction delay is indicated by an RSR' in V1

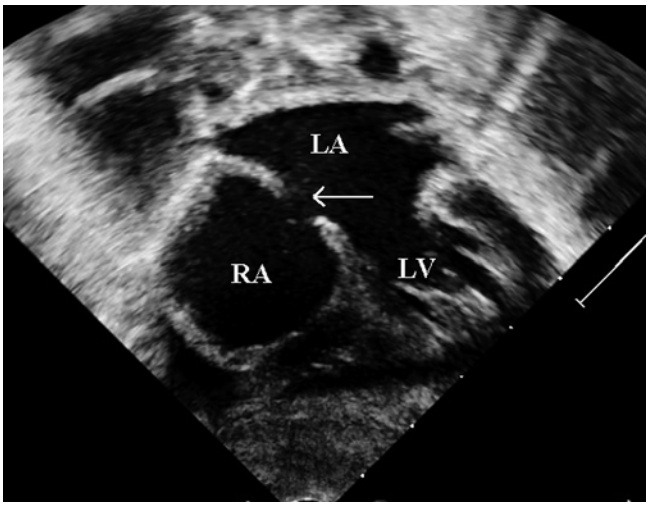


Fig. 20.5 Echocardiogram with a subxyphoid long axis view of the atrial septum. The arrow indicates a secundum ASD. *RA* right atrium, *LA* left atrium, *LV* left ventricle

ment is invariably present. The type of ASD in the pediatric patient can usually be determined by two- dimensional transthoracic echocardiogram and color flow mapping (Fig. 20.5).

Natural History

Clinical symptoms and natural history are largely dependent upon the magnitude of the left to right shunt. Patients with ASD's are generally free of symptoms for the first two decades of life [17–20]. Symptoms in young adulthood are minor and no restrictions in normal activities are expected. Functional limitations emerge later in life and are due to atrial arrhythmias or progressive right ventricular failure [18–20]. Most patients with untreated, unrestrictive large secundum ASD die by the end of the fourth decade of life [17–19]. Death is usually due to serious respiratory infections, progressive right ventricular failure, stroke or pulmonary hypertension. Secundum ASD's can become smaller and close spontaneously [21–25]. The rate of closure is higher with smaller defects and an earlier age at diagnosis [21–25].

Surgical Management

ASD's should be closed if there is evidence of significant left to right shunt (i.e. right ventricular volume overload) beyond 2 years of age [26, 27]. Elective repair of hemodynamically significant ASD's can be delayed until children are at least 3–5 years old due to the high rate of spontaneous closure of the defects in the first years of life [21–27]. Major ASD's are unlikely to close after this time and there appears to be no added benefit to deferring treatment. In symptomatic patients with large ASD's, closure may be performed earlier than the recommended age for elective therapy. ASD's may be closed surgically or by transcatheter techniques. Many institutions offer device closure of secundum ASD by interventional techniques as first-line therapy. Device closure is restricted to the secundum variety of ASD with favorable anatomic features [26]. The surgical approach is indicated for other variants of ASD's, unusual location of ASD, when device closure is not feasible or when secundum ASD's are associated with other cardiac malformations that require repair.

Gibbon first performed surgical closure of ASD under extracorporeal support in the 1950's [28]. Since then, surgical and cardiopulmonary bypass techniques have evolved. The atrial septal defect is closed primarily or with a biologic or synthetic patch. More recent techniques have focused on limited access surgery via a ministernotomy, lateral thoracotomy or axillary approaches for cosmetic reasons and to hasten postoperative recovery [29–31]. Surgical closure of ASD in children has minimal mortality in the current era [30]. Murphy described the long-term follow up results on 123 patients who underwent surgical closure of an ASD at the Mayo Clinic in the late 1950's [32]. The overall 30- year actuarial survival was 74 % compared to 85 % in age and sex matched controls. Actuarial survival in patients varied significantly from controls depending upon the age and systolic pressure in the pulmonary artery at the time of surgery. Survival curve of patients less than 24 years of age at surgery were excellent and no different from comparable controls. The survival rates were appreciably unfavorable beyond this age with the lowest survival in patients undergoing surgery after 41 years (40 % vs 59 % in controls).

Postoperative Management

Routine care is expected. Many patients are eligible for fast-tracking and can be extubated in the operating room or within the first few hours after surgery [30, 31]. Significant morbidity occurs infrequently. The most common complications are arrhythmias and post-pericardiotomy syndrome [30]. Median hospital length of stay is 3–4 days [30, 31].

Transcatheter Device Closure

Transcatheter techniques to close secundum ASD's have been employed since the 1970's [33]. Several innovative device and delivery systems have evolved in the subsequent decades [34]. In the USA, the approved devices for secundum ASD closure include the Amplatzer Septal Occluder and the HELEX Septal Occluder. The Amplatzer Septal Occluder enjoys wide spread use and is the only one available for closure of larger ASD's (Fig. 20.6) [34]. Indications for transcatheter device closure are similar to surgical indications. However, favorable anatomic features: adequate rim and distance from important surrounding structures is necessary for feasibility of device closure [26, 35]. Outcomes from transcatheter device closure are comparable to surgical outcomes [36–40]. Transcatheter intervention offers the obvious advantage of avoidance of cardiopulmonary bypass

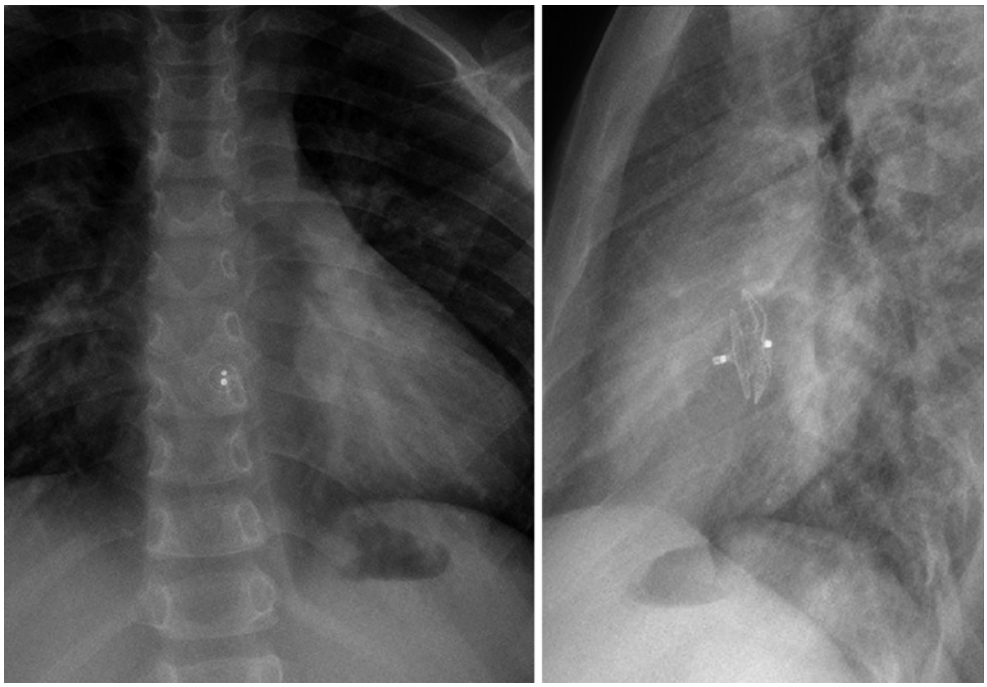


Fig. 20.6 Chest radiograph (posterior- anterior and lateral projections) shows an Amplatzer Septal Occluder device

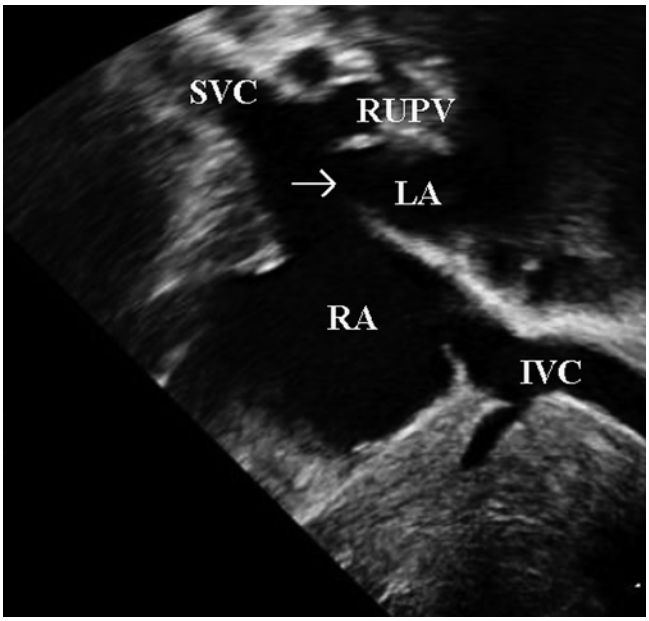


Fig. 20.7 Echocardiogram with a subxyphoid short axis view of the atrial septum. The *arrow* indicates a sinus venosus ASD in the posterior and superior position of the atrial septum. *SVC* superior vena cava, *RUPV* right upper pulmonary vein, *RA* right atrium, *LA* left atrium, *IVC* inferior vena cava

and surgical incision. Other advantages include lower complication rates, shorter anesthetic times and shorter hospitalization [37–40]. Major peri-procedural complications including device malposition or embolization, cardiac erosion or perforation, arrhythmias or stroke occur infrequently [37–39, 41, 42]. Serious long-term complications are rare; the most important one being cardiac erosion by the device [41]. The overall incidence for this complication is less than 0.1 % for the Amplatzer Septal Occluder [42]. Long- term results after device implantation show complete closure of the defect in almost all patients [43, 44]. Late deaths or major complications are rare [43, 44].

Sinus Venosus ASD's

Sinus venosus defects are located posterior and superior to the fossa ovalis. These defects comprise 5–10 % of all forms of ASD's. Anomalous drainage of the right pulmonary veins into the superior vena cava is almost always present; typically the right upper pulmonary vein is involved (Fig. 20.7). Spontaneous closure does not occur and surgical correction must be performed. Surgery involves closure of the defect with a biologic or synthetic patch and rerouting the pulmonary veins into the left atrium. The Warden procedure is favored when the pulmonary veins drain higher into the superior vena cava [45]. Surgical mortality is less than 1 % [45]. The surgical repair of sinus venosus defects is more complex and carries a greater risk of complications. These include sinus node dysfunction, superior vena caval or pulmonary venous obstruction. Long-term results are excellent. In one long-term follow-up at a single center, survival was no different from age and sex matched controls [46]. No reoperation was required during an average follow up period of 12 years although 20 % of patients either had sinus node dysfunction, pacemaker or atrial fibrillation.

Coronary Sinus ASD's

Coronary sinus atrial septal defect occurs rarely. The defect is located anterior to the fossa ovalis in the region of the coronary ostium. Drainage of a persistent left superior vena cava into the coronary sinus is a common association. Surgical closure is recommended for hemodynamically significant defects.

Ventricular Septal Defects (VSD's)

Any opening in the ventricular septum constitutes a ventricular septal defect (VSD). VSD's may be isolated or an integral part of a major congenital heart disease, i.e. as in Truncus Arteriosus or Tetralogy of Fallot. Only isolated VSD's will be discussed further here. Isolated VSD is the most common congenital heart lesion [47, 48]. A regional population study provides a prevalence estimate of 42 cases of VSD's per 10,000 live births [48]. Like most congenital heart defects, a multifactorial causation has been proposed [49]. VSD's are commonly seen in chromosomal aberrations (trisomy 13, 18, 21), fetal alcohol syndrome, teratogen exposure and maternal conditions like untreated phenylketonuria and diabetes mellitus [50–52]. Tremendous advances in molecular genetics have uncovered the genetic basis of cardiac morphogenesis [53–55]. Mutations in genes encoding transcription factors (*GATA4*,NKX2.5,*TBX5*) critical in cardiac development can result in defective septation of the atrium or ventricles [11–15, 56–58].

Embryology

The primitive ventricular septum has muscular and mesenchymal components. The endocardial cushions at the atrioventricular junction and developing conotruncus contribute to the mesenchymal regions of the embryonic interventricular septum. The origins of the muscular element of the interventricular septum are disputed [59, 60]. Derivatives of the primary interventricular septum and endocardial cushions ultimately merge in the region of the future membranous septum. Failure of development or fusion of these diverse embryonic derivatives leads to defects in the ventricular septum.

Anatomy

The ventricular septum can be divided into four regions (Soto) [61]:

Inlet septum separates the two atrioventricular valves and merges anteriorly with the trabecular septum.

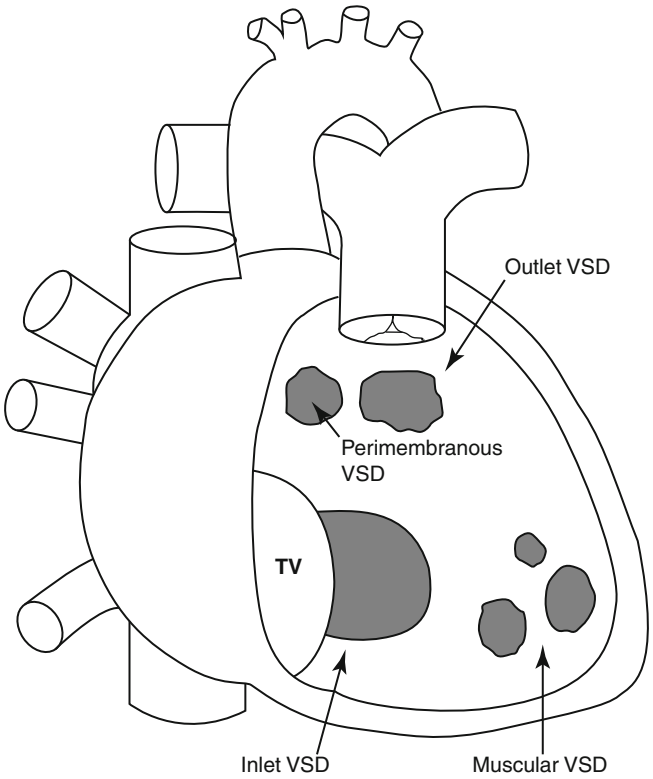


Fig. 20.8 Ventricular septal defect (*VSD*) types: Anatomic locations of VSD's as viewed with the right ventricular wall removed. *TV* tricuspid valve

Trabecular septum extends anteriorly from the inlet septum towards the apices of the two ventricles and superiorly where it integrates with the smooth walled outlet septum.

Outlet septum extends from the crista supraventricularis to the pulmonary valve and separates the pulmonary and aortic outflow tracts.

Membranous septum is a small area where the three other septal regions intersect .

Hence, VSD's are generally classified as (Fig. 20.8):

Inlet ventricular septal defects: 5–8 % of defects are of this type [62]. Defects in the inlet region are seen below the septal attachment of the tricuspid valve. These defects tend to be large and spontaneous closure is unusual.

Muscular ventricular septal defects: Defects in the trabecular septum occur in 5–20 % of cases and can vary in size, location and number. Multiple muscular defects can assume a "Swiss cheese" appearance. Spontaneous closure of small muscular defects is expected.

Outlet septal defects: Defects of the outlet septum occur below the aortic and pulmonary valve cusps. These defects are generally large and do not close spontaneously. Prolapse of the right coronary cusp can lead to aortic regurgitation. These defects are more common in people of far Eastern descent [63].

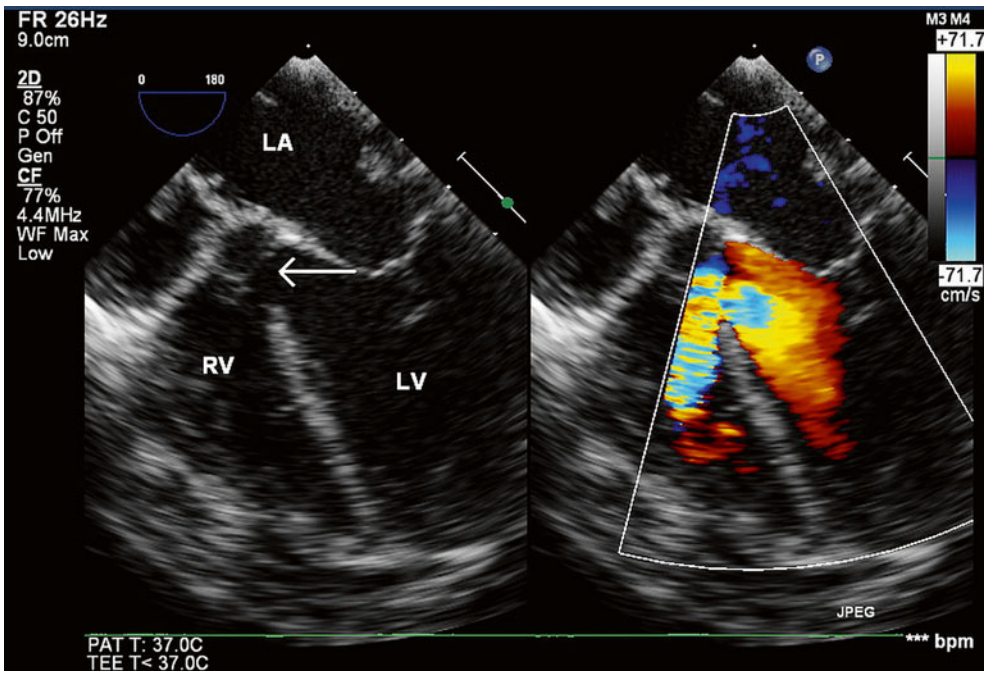


Fig. 20.9 Echocardiogram (apical view) demonstrates a perimembranous VSD. Color flow mapping indicated left to right shunting across the VSD. *LA* left atrium, *LV* left ventricle, *RV* right ventricle

Membranous or perimembranous defects: This type is the most common, occurring in 80 % of cases [62]. The membranous septum is closely related to the tricuspid valve and may be completely or partially occluded by accessory or redundant valve tissue. Occasionally, there is prolapse of the right or non-coronary cusp into the defect causing aortic valve insufficiency and partial closure of the ventricular septal defect. A significant proportion of membranous VSD's close spontaneously.

Pathophysiology

The amount and direction of flow across a VSD is influenced by the size of the defect and the relative resistances across the outflow tracts. The pulmonary vascular resistance usually declines after birth and approaches adult levels within 7–10 days [16]. In the presence of a non-restrictive VSD, the magnitude of the left to right shunt increases as the pulmonary vascular resistance decreases. Congestive cardiac failure can develop in moderate and large sized defects. Manifestations of failure usually emerge between 4 and 8 weeks of life when the volume overloaded left ventricle is unable to overcome the hemodynamic burden imposed by physiologic anemia [64].

Clinical Features

The clinical manifestations of VSD vary depending upon the size of the defect and the degree of left to right shunt [16]. Most children with a small VSD are asymptomatic. They feed, grow and thrive well and follow an uncomplicated, benign course. Diagnosis is usually made when a murmur is heard during a routine physical examination. The murmur is loud and holosystolic and is best heard at the lower left sternal border. Symptoms of congestive cardiac failure usually develop in the first or second month of life in children with moderate or large sized VSD. These infants do no thrive and are prone to recurrent respiratory tract infections. The precordium is hyperdynamic. A systolic murmur is appreciated in the lower left sternal border. A mid- diastolic rumble may be heard at the cardiac apex and represents increased flow across the mitral valve.

The chest radiograph is normal in children with small VSD's. In moderate and large sized VSD's, there is cardiomegaly and left atrial and ventricular enlargement. Prominent pulmonary vascular markings extend from the hilum into the peripheral lung fields. The right ventricle and the central pulmonary arteries remain prominent but peripheral pulmonary vascular markings are attenuated in patients with significant pulmonary vascular disease.

The ECG is usually normal in patients with small VSD's. Mild to moderate left ventricular hypertrophy is seen in moderate sized VSD's. Biventricular hypertrophy in large, unrestrictive VSD's is reflective of the volume and pressure load on the ventricles. Right ventricular hypertrophy worsens with the development of significant pulmonary vascular disease.

The size, location of the VSD and additional cardiovascular malformations can be determined by two- dimensional Echocardiography and color flow mapping (Fig. 20.9). Right ventricular pressure can be estimated by flow jet velocity

measurements across the defect by Doppler echocardiography. Doppler and color flow mapping can be used to establish directionality of flow across the VSD.

Diagnostic cardiac catheterization is rarely employed in patients with isolated and uncomplicated VSD's. It should be reserved for measurement of pulmonary vascular resistance in patients in whom advanced pulmonary vascular disease is suspected or where device closure of the defect is contemplated.

Natural History

Postnatal spontaneous closure of VSD occurs frequently [65, 66]. The likelihood of spontaneous closure or reduction in size is greater in childhood, with smaller defects and if the defects are of the muscular type [17, 65–73]. Patients with small VSD's are generally asymptomatic. Most patients with moderate to large VSD's develop symptoms of congestive cardiac failure by 4–8 weeks of age. Untreated, infants with large VSD's may not survive early infancy [74]. Failure symptoms can improve in some patients in the latter part of the first year and represents a decline in the amount of left to right shunt. The decrease in shunt flow may be due to a decrease in defect size, development of obstruction across the right ventricular outflow tract or due to development of pulmonary vascular disease. The risk for pulmonary vascular disease and Eisenmenger syndrome is high in large, unrepaired VSD's but its development is unusual before 1 year of age [74–76]. Survival with Eisenmenger syndrome is rare after 50 years of age [77, 78].

Management

Management decisions differ based on the size and location of the defect, the likely natural history, the hemodynamic burden imposed by the defect, and the risk of developing pulmonary vascular disease. If the VSD is located in a region where spontaneous closure is not expected, i.e. outlet type of VSD, early surgical repair is recommended. Expectant management would be prudent in defects expected to close spontaneously. Infants or children with small VSD's are unlikely to progress into cardiac failure or develop pulmonary vascular disease. Hence, closure of the defect either surgically or by transcatheter route is not advocated.

Cardiac failure in children with moderate sized VSD's can be managed medically with diuretics and digoxin. Medical management of failure is usually successful and allows time for spontaneous closure or decrease in size of the defect. Pulmonary vascular disease is unusual and hence a conservative approach may be followed. Surgical or transcatheter device closure (for muscular VSD only) should be employed if defect size is unchanged or if medical management fails. Moderate sized defects that demonstrate a reduction in dimensions may be observed for many years without intervention [79]. Most infants with large VSD's develop cardiac failure in the first few months of life. Untreated, they are at high risk for pulmonary vascular disease and hence surgical closure of the defect is best not deferred beyond 6–12 months of age [80].

Surgery

Pulmonary artery banding was the first surgical procedure performed for VSD [81]. Since then, the role of pulmonary artery banding has evolved. It is now reserved as an interim palliative procedure for patients with complex malformations, patients with multiple VSD's in whom primary repair is difficult or in small, premature patients. Dr. Lillehei in 1955 provided the first description of VSD closure under direct vision [82]. Since then, tremendous advances in surgical techniques and cardiopulmonary bypass have followed. Surgical closure of VSD is preferred in children in whom transcatheter closure is not feasible due to young age or unfavorable location or where repair of associated lesions is necessary. VSD repair is performed under cardiopulmonary bypass through a median sternotomy. Defects are closed primarily or with a synthetic patch. Surgical approach to VSD closure can vary depending upon the location of the defect. Inlet and perimembranous VSD's are closed through a transatrial route while outlet VSD's can be approached through the semilunar valves. Surgical mortality after isolated VSD closure is less than 1 %; significant morbidity is unusual [83, 84].

Right bundle branch block is common after VSD closure [85, 86]. In the current era, permanent complete heart block is extremely unusual after surgical closure [83, 84]. Transient complete heart block is more common and recovery of atrioventricular function is expected within 10 days of surgery [87]. However, these patients remain at risk for late onset permanent complete heart block [88, 89].

Postoperative Management

In most patients, an uneventful postoperative course is expected after isolated VSD closure. Recovery is rapid; ventilatory and hemodynamic support can be weaned within 24 h. Rhythm disturbances including complete heart block can occur. Placement of temporary pacing wires is useful for diagnostic and therapeutic purposes. Intensive care unit stay is expected to be brief.

Transcatheter Device Closure of VSD

Lock and associates first reported percutaneous muscular VSD closure in 1987 [90]. Substantial success has been achieved with device closure in the decades that have followed [91, 92]. The Amplatzer muscular VSD occluder is

especially designed for congenital muscular VSD's and may be used when the VSD's are at a favorable location (safe distance from the systemic and atrioventricular valves and the atrioventricular node). Device closure of membranous VSD's is fraught with a significant risk of complete heart block and is not recommended [93].

Hybrid Procedures

Hybrid techniques have been employed for closure of muscular VSD's in children who are too small for transvenous device systems or in whom avoidance of cardiopulmonary bypass is desired. Following sternotomy, perventricular deployment of device to close muscular VSD's has been successfully accomplished under transesophageal echocardiographic or fluoroscopic guidance [94, 95].

Patent Ductus Arteriosus (PDA)

The ductus arteriosus is a vascular structure that connects the main pulmonary artery to the proximal descending aorta. Spontaneous postnatal closure of the ductus arteriosus is expected within the first few days after birth [96]. Persistent patency of the ductus arteriosus beyond the neonatal period is abnormal. Patent ductus arteriosus (PDA) can occur in isolation or may be associated with other cardiovascular malformations. In some forms of critical congenital heart disease a PDA is crucial for survival. Only isolated PDA in term infants will be discussed further here.

Embryology

The paired sixth aortic arches form the proximal right and left pulmonary arteries. The distal part of the left sixth aortic arch forms the ductus arteriosus and connects the left pulmonary artery to the left dorsal aorta.

Anatomy and Physiology

The ductus arteriosus connects the main pulmonary artery at its junction with the left pulmonary artery to the proximal descending aorta just distal to the origin of the left subclavian artery. PDA may be small, moderate and large and can assume various configurations [97].

The ductus arteriosus plays an important role in mammalian fetuses. It carries the bulk of right ventricular output into the descending aorta and into the umbilico-placental circulation for oxygenation [16]. Several vasodilatory factors are presumed to maintain ductal patency in fetal life. These include low Po2, high levels of local or circulating PGE_2 and PGI_2, adenosine, and nitric oxide [98–104]. Of these, the most critical are a low oxygen tension and prostaglandins. The microscopic structure of the ductus arterious differs from that of the aorta and the pulmonary artery. The tunica media contains muscle fibers that traverse in a longitudinal, circumferential or spiral manner. The internal elastic lamina is well formed and fragments in later gestation. The intima, which is thin during most of gestation, thickens prior to birth.

Postnatal increase in oxygen tension and decline in locally produced and circulating prostaglandins removes the vasodilatory effects on the ductus arteriosus and causes contraction of the ductal musculature resulting in constriction. The intima and media form mounds promoting luminal obliteration [105–108]. Functional closure is established in most full term infants by 48 h and anatomic closure by the end of the first week of life [96]. Respiratory disease, birth asphyxia, and birth at high altitudes may result in delayed closure of the ductus arteriosus [109]. Persistent patency of the ductus arteriosus in term infants beyond the neonatal period has been attributed to microstructural abnormalities in the ductus arteriosus [108].

Epidemiology

PDA is a common congenital malformation comprising almost 5–10 % of all heart defects [110]. Incidence of 1:2,000 is reported in full term infants and a female predilection is appreciated in most studies [110]. Isolated PDA occurs sporadically though familial forms with both dominant and recessive patterns of inheritance have been described [111–113]. PDA can occur in chromosomal aberrations (Trisomy 21), deletion syndromes like Rubinstein–Taybi, CHARGE syndrome, first trimester exposure to Rubella, and birth at high altitudes [109, 114].

Pathophysiology

The hemodynamic consequences of a PDA depend upon the magnitude of the left to right shunt and the ability of the left ventricle to handle the additional volume load. The size of the ductus arteriosus and the relative difference in the resistances between the systemic and pulmonary circuits are the major factors that govern the degree of left to right shunting. Hemodynamic burden is minimal in patients with a small PDA. In patients with a large PDA, pulmonary blood flow increases considerably with postnatal decline in pulmonary vascular resistance. In these patients, left ventricular failure can ensue once compensatory mechanisms to augment left ventricular output are overwhelmed. Chronic high flow and pressure can induce pulmonary vascular disease similar to patients with unrestrictive VSD [115]. The left to right shunt can decrease and eventually reverse in advanced pulmonary vascular disease.

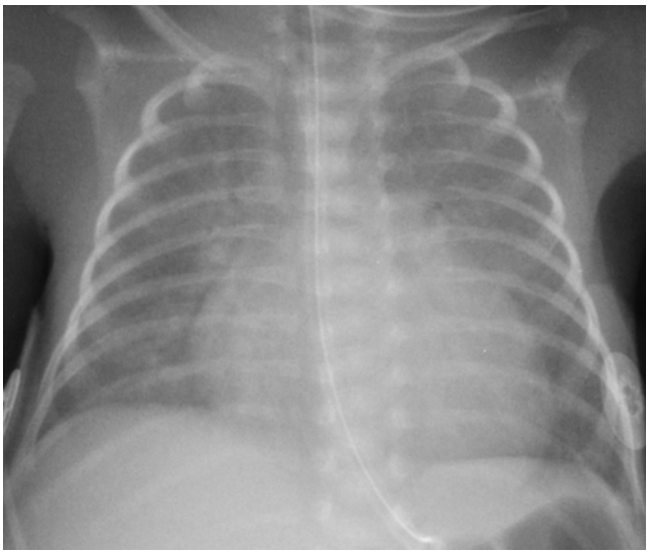


Fig. 20.10 Chest radiograph of a patient with a large PDA demonstrates cardiomegaly and pulmonary edema. *PDA* patent ductus arteriosus

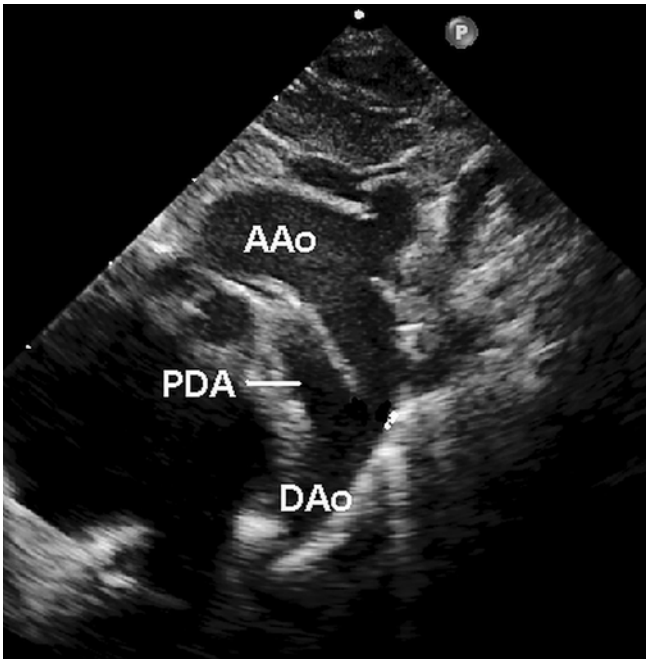


Fig. 20.11 Echocardiogram with a suprasternal long axis view of the aortic arch demonstrating a large PDA. *AAo* ascending aorta, *DAo* descending aorta, *PDA* patent ductus arteriosus

Clinical Features

Children with a small PDA have a minimal left to right shunt and are usually asymptomatic. Diagnosis is usually established on a routine physical examination with the detection of a systolic or a continuous murmur. Infants with a large PDA manifest symptoms of congestive cardiac failure similar to other lesions with a significant left to right shunt. The pulse pressure is wide and the peripheral pulses may be bounding. There is hyperdynamic precordial activity and a systolic or continuous murmur is appreciated in the left upper sternal border.

Survivors of this initial phase of congestive cardiac failure may show improvement in symptoms due to the development of pulmonary vascular disease and a decrease in left to right shunt. Symptoms of pulmonary vascular disease can emerge as early as the second year of life. With irreversible pulmonary vascular disease and reversal of shunt, cyanosis appears initially with exertion and subsequently at rest. Pulses are less bounding and the precordium quieter. There is marked accentuation of the second heart sound and the previously heard systolic murmur may be shorter or disappear. A decrescendo diastolic murmur in the left sternal border indicates pulmonary regurgitation and a holosystolic murmur, suggests tricuspid regurgitation.

The chest radiograph is usually normal in children with a small PDA. Infants with a large PDA have significant cardiomegaly, prominent pulmonary vascular markings or pulmonary edema (Fig. 20.10). A decrease in peripheral markings but prominent central pulmonary arteries herald the development of pulmonary vascular disease. The ECG is normal in children with small PDA. There is evidence of left atrial and left ventricular enlargement in infants with a large PDA. Progressive right ventricular forces may indicate the development of pulmonary vascular disease.

A diagnosis of PDA is easily established by echocardiogram (Fig. 20.11). The size of the PDA can be gauged by employing standard methods. Flow patterns across the ductus arteriosus can be evaluated by Doppler techniques. Left atrial and left ventricular enlargement indicates at least a moderate sized PDA. Cardiac catheterization is not required to establish a diagnosis of PDA but is indicated if pulmonary vascular disease is suspected. Hemodynamic assessment after test occlusion with a balloon catheter and assessment of responsiveness to pulmonary vasodilator therapy are necessary to guide management decisions.

Natural History

Spontaneous closure of the ductus arteriosus beyond 3 months is unusual [116]. A significant number of patients with large PDA's develop cardiac failure and do not survive infancy if left untreated. Symptoms generally improve beyond this period in survivors due to the development of pulmonary vascular disease. More than 40 % of patients with clinically significant untreated PDA succumb by 45 years of age [116].

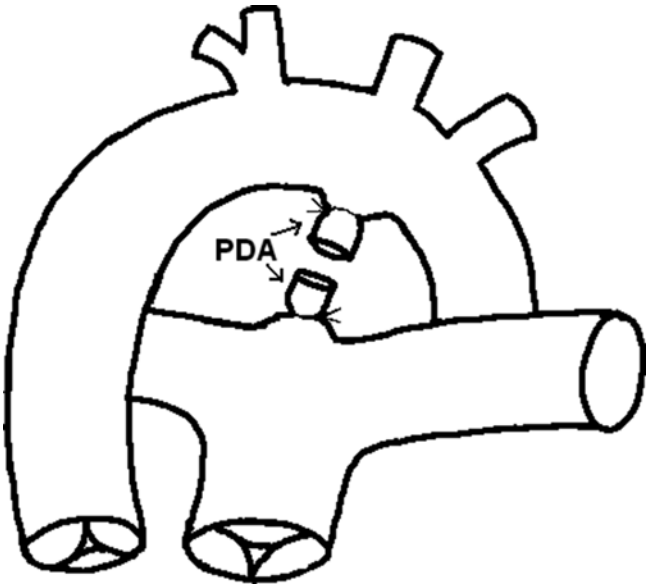


Fig. 20.12 Surgical ligation of a PDA

Management

Elimination of the left to right shunt by surgical or transcatheter techniques is recommended for all patients with a clinical PDA. Gross in1939 first performed ligation of the PDA [117]. Since then surgical techniques and indications have evolved. Surgical transection or division (Fig. 20.12) is now reserved for patients with a very large PDA or in whom repair of other defects is required. Surgery is also recommended in premature infants in whom pharmacological closure has been futile or is contraindicated. The approach is usually through a posterolateral thoracotomy though newer muscle sparing and videoscopic techniques have recently been employed [118, 119]. The surgical mortality is very low [120]. Postoperative complications include injury to the recurrent laryngeal nerve or phrenic nerve, chylothorax and pneumothorax. Recanalization of the ductus may occur with single suture ligation without division.

The transcatheter approach has emerged in recent decades as the preferred therapeutic option for most patients with a PDA. Infants with a very large ductus arteriosus or those who are low birth weight and those who have an unfavorable ductal anatomy may be unsuitable candidates for device closure. Transcatheter closure is recommended in all patients with a clinical PDA irrespective of hemodynamic burden or symptomatology [26]. Controversy persists regarding the management of the "silent" PDA; closure in these patients may decrease the risk of endarteritis [121–125]. Small PDA's can be closed with occluding coils [126–128]. Larger PDA's require specialized devices such as the Amplatzer duct occluder (Fig. 20.13) [129–131]. The catheter-based techniques demonstrate impressive results with high success rates and no mortality [132, 133]. Complications such as device embolization, persistent hemolysis, residual shunt, flow impairment in adjacent vessels and recanalization occur rarely [26, 133].



Fig. 20.13 Angiogram of the descending aorta in the lateral projection demonstrating the placement of an Amplatzer Duct Occluder in the PDA position

Aortopulmonary (AP) Window

Aortopulmonary window is a congenital communication between the ascending aorta and the pulmonary artery. It is a rare anomaly and accounts for 0.2–0.6 % of all cases of congenital heart disease [134].

Embryology

A developmental disturbance in conotruncal septation leads to this uncommon anomaly. Neural crest cells are probably not involved, as their removal does not cause this defect [135].

Anatomy

Mori classifies the defect into three types based on the location [136]:

Type I: the defect is located in the proximal aortopulmonary septum, midway between the semilunar valves and the pulmonary bifurcation; this type is the most common.

Type II: the defect is more distal and also involves the right pulmonary artery, which arises from the ascending aorta.
Type III: the defect is large and affects the entire aortopulmonary septum and extends from the semilunar valves to the pulmonary bifurcation.

Aortopulmonary window is frequently associated with other cardiac malformations [137]. Common associations include an aortic origin of the right pulmonary artery, interruption of the aortic arch type A, Tetralogy of Fallot and anomalous origins of the left or right coronary arteries from the pulmonary artery.

Pathophysiology

The pathophysiology is very similar to other lesions that are accompanied by a large left to right shunt. Pulmonary blood flow increases as pulmonary vascular resistance declines; cardiac failure develops early. There is aggressive progression of pulmonary vascular disease in patients with unrepaired lesions. Severe pulmonary vascular disease can develop in childhood [17, 138].

Clinical Features

The clinical features are similar to lesions with a large left to right shunt, i.e. VSD or a large patent ductus arteriosus. Symptoms of congestive cardiac failure emerge in the early weeks of life in patients with large defects. The precordium is hyperdynamic and peripheral pulses are bounding. A loud S2 indicates pulmonary hypertension. A loud systolic murmur or a machinery murmur is best appreciated in the upper left sternal border. A mid diastolic murmur at the apex suggests a functional mitral stenosis due to excessive flow.

Similar to other lesions with large left to right shunts, cardiomegaly and prominent pulmonary vascular markings are present on chest radiograph. Right or biventricular hypertrophy is usually evident on 12-lead ECG. Two-dimensional echocardiogram and color flow mapping can establish diagnosis (Fig. 20.14). Doppler Echocardiography can be used to estimate right ventricular pressure if tricuspid or pulmonary regurgitation are present. Diagnostic cardiac catheterization is not required in most cases. It should be reserved for patients in whom an echocardiographic diagnosis cannot be established with confidence or when pulmonary hypertension is suspected. A hemodynamic evaluation should be performed in the older infant or child with a delayed diagnosis to rule out irreversible pulmonary hypertension.

Natural History

The natural history depends in part on the severity of associated cardiovascular lesions. Death occurs in early childhood in most patients with large unrepaired lesions. Patients usually succumb to cardiac failure or progressive pulmonary vascular disease. Adult survivors are rare [17].

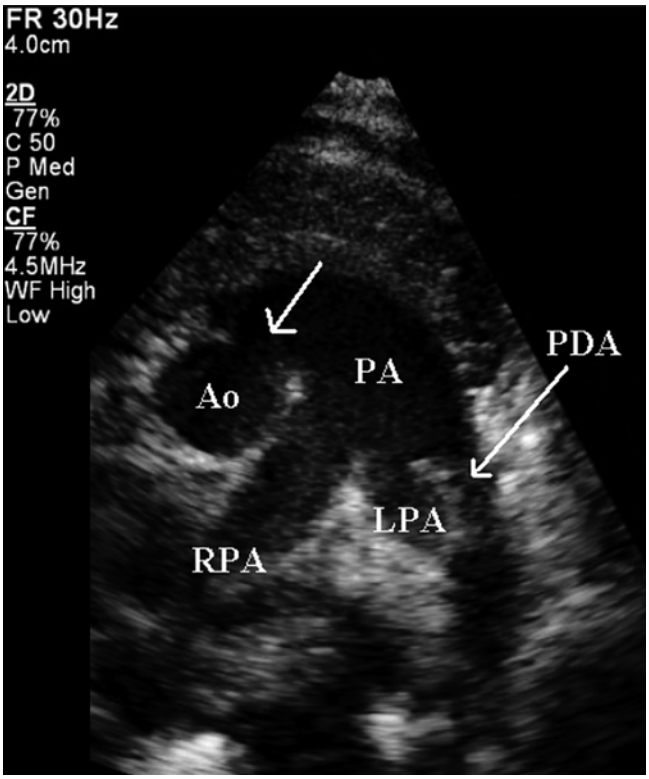


Fig. 20.14 Echocardiogram with a high right parasternal short axis view demonstrating an aortopulmonary defect (*arrow depicts*) between the descending aorta and main pulmonary artery. *Ao* aorta, *PA* pulmonary artery, *RPA* right pulmonary artery, *LPA* left pulmonary artery, *PDA* patent ductus arteriosus

Management

Surgery should be performed as soon as a diagnosis of aortopulmonary window is established. Surgery is performed through a median sternotomy under cardiopulmonary bypass. The defect is repaired with a native pericardial or synthetic patch. Associated lesions are repaired concurrently. A 90 % survival is reported even in patients with associated lesions [139, 140].

Long-term prognosis is excellent following early repair [139–142]. Patients are at risk for pulmonary hypertensive crises due to chronic pulmonary over-circulation. Sedation, avoidance of acidosis, hypoxemia and hyperbia and carly use of inhaled nitric oxide may mitigate this risk.

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Cyanotic CHD Lesions with Decreased Pulmonary Blood Flow

21

John M. Costello and Peter C. Laussen

Abstract

Infants with congenital heart defects associated with cyanosis and decreased pulmonary blood flow are a heterogenous group of patients. The complex aspects of the provision of intensive care for this patient population are largely concentrated in the newborn period, which is the focus of this chapter. An approach to the initial evaluation and stabilization of the cyanotic neonate with suspected congenital heart disease is provided. The anatomy, pathophysiology and clinical presentation, preoperative evaluation, surgical or transcatheter intervention, and postoperative care and outcome for tetralogy of Fallot with pulmonary stenosis are discussed. The concept of restrictive right ventricular physiology is covered in detail. The salient features of complex variants of tetralogy of Fallot are also noted, including pulmonary atresia, absent pulmonary valve syndrome and atrioventricular canal defect. A similar approach is used to discuss patients with pulmonary valve stenosis, pulmonary atresia with intact ventricular septum, and Ebstein's anomaly of the tricuspid valve. With each lesion, esoteric nuances related to the physiology and perioperative care are noted that may contribute to improved outcomes for this complex group of patients.

Keywords

Cyanosis • Ebstein's anomaly • Pulmonary atresia • Pulmonary stenosis • Tetralogy of Fallot • Tetralogy of Fallot with pulmonary atresia • Hyperoxia test • Prostaglandin E1

Initial Evaluation and Stabilization of the Cyanotic Neonate

In cyanotic neonates, an initial evaluation is undertaken in order to determine whether the etiology of hypoxemia is cardiac or non-cardiac in origin. A brief review of the maternal, family and gestational histories, and a directed physical examination may provide clues that favor either cardiac or pulmonary disease. A chest radiograph (CXR) should be obtained and inspected for heart size, signs of parenchymal lung disease, increased or decreased pulmonary vascular markings, and sidedness of the aortic arch. For example, a very large heart and decreased pulmonary arterial markings on CXR suggests severe Ebstein's anomaly of the tricuspid valve, whereas a normal heart size and decreased pulmonary blood flow may be found in some patients with tetralogy of Fallot or pulmonary atresia with intact ventricular septum.

Most cyanotic newborns require an urgent echocardiogram to determine whether or not congenital heart disease is present. If an echocardiogram cannot be immediately obtained, however, a hyperoxia test may be performed to assist with triage. This test involves obtaining an arterial blood gas from the right radial artery while the neonate is in

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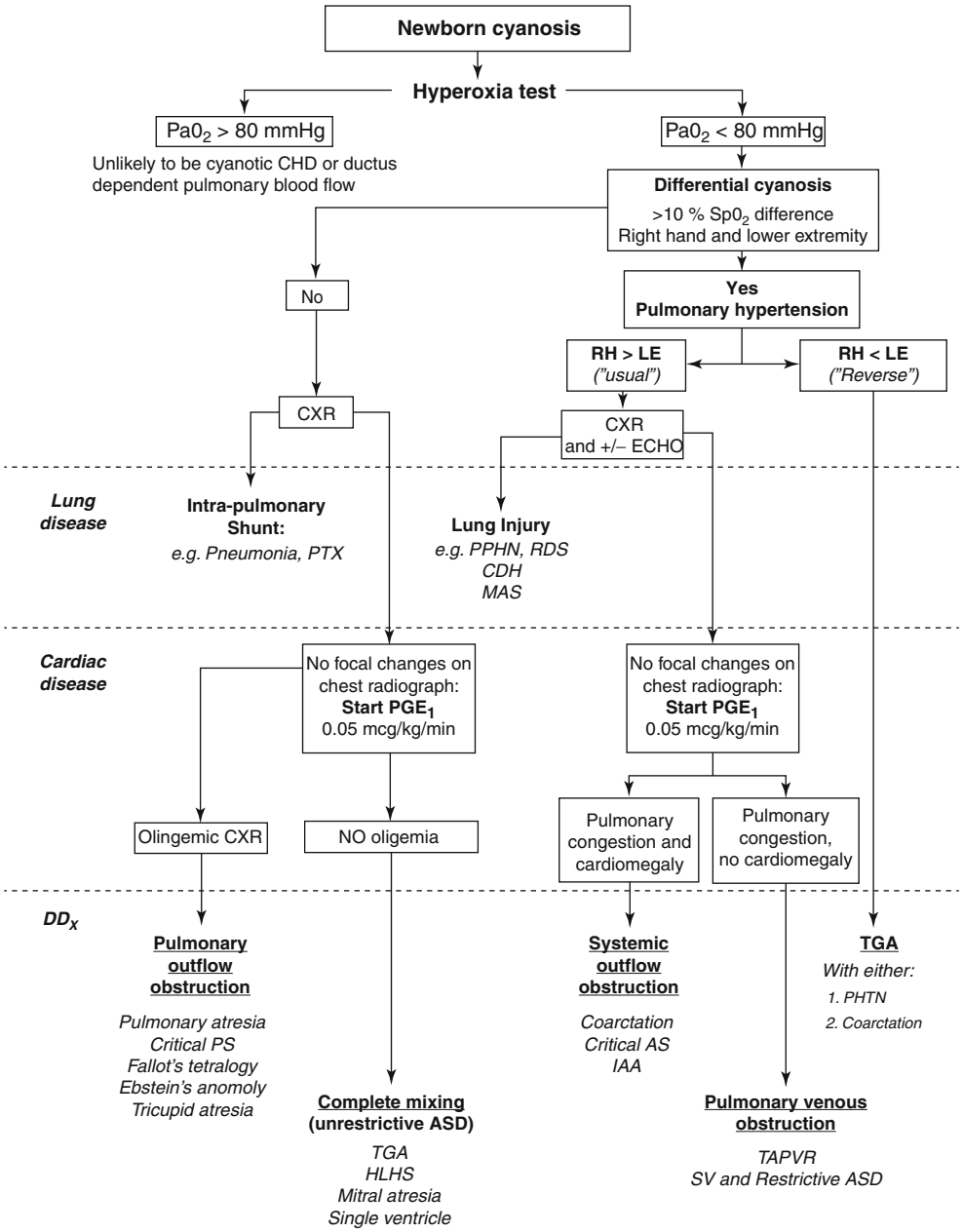


Fig. 21.1 Algorithm for initial assessment of cyanotic newborns. *AS* aortic stenosis, *ASD* atrial septal defect, *CXR* chest radiograph, *CDH* congenital diaphragmatic hernia, *CHD* congenital heart disease, *ECHO* echocardiogram, *HLHS* hypoplastic left heart syndrome, *IAA* interrupted aortic arch, *LE* lower extremity, *MAS* meconium aspiration syndrome, *PTX* pneumothorax, *PGE$_1$* prostaglandin E$_1$, *PPHN* primary pulmonary hypertension, *PHTN* pulmonary hypertension, *PS* pulmonary stenosis, *RH* right hand, *SV* single ventricle, *TAPVR* total anomalous pulmonary venous return, *TGA* d-transposition of the great arteries

room air, and a second blood gas is obtained after the patient receives 10 min of 100 % inspired oxygen. The initial PaO_2 measured while the neonate is breathing room air is often between 25 and 40 mmHg. In 100 % FiO_2, the PaO_2 will usually rise to >80 mmHg in patients with pulmonary disease (provided that significant pulmonary artery hypertension is not present), but remain unchanged or only increase slightly in most neonates with cyanotic heart disease. The pCO_2 is typically mildly decreased in newborns with cardiac disease and mildly elevated in those with pulmonary disease. Note that the hyperoxia test cannot be used in isolation to exclude critical congenital heart disease, as some neonates with left sided obstructive lesions may have a PaO_2 > 60 mmHg in any extremity or a PaO_2 > 150 mmHg in the right arm. An algorithm that incorporates hyperoxia test findings into the initial triage of cyanotic newborns is shown in Fig. 21.1.

The initiation of PGE_1 should be considered in cyanotic neonates with known or suspected congenital heart disease [1]. If pediatric cardiology consultation is readily available and severe cyanosis (SaO_2 < 75–80 %) and metabolic acidosis (pH < 7.3) are not present, then the echocardiogram may be obtained prior to initiation of a prostaglandin E_1 (PGE_1) infusion. If the neonate has mild cyanosis and the echocardiogram reveals anatomy that does not likely require prompt surgical or transcatheter intervention (e.g., a neonate with tetralogy of Fallot and mild pulmonary stenosis), then observation without

Table 21.1 Side effects of prostaglandin E_1 infusion

Respiratory	Respiratory depression,[a] apnea[a]
Cardiovascular	Hypotension,[a] tachycardia,[b] tissue edema[a]
Central nervous system	Fever,[a] seizures[b]
Endocrine/metabolic	Hypocalcemia,[b] hypoglycemia,[b] cortical hyperostosis[c]
Gastrointestinal	Diarrhea,[b] gastric outlet obstruction[c]
Hematologic	Inhibition of platelet aggregation[b]
Dermatologic	Flushing,[b] harlequin rash[b]

[a]Common
[b]Rarely of clinical significance
[c]With long-term use

PGE_1 is warranted. If it is unclear from the initial post-natal echocardiogram whether early intervention is needed, then it is preferable to withhold PGE_1 and monitor the neonate's systemic oxygenation as the ductus arteriosus constricts. However, if pediatric cardiology consultation and echocardiography are not readily available or a prolonged transport is anticipated and the neonate is profoundly cyanotic, then PGE_1 should be administered without delay. PGE_1 allows adequate time for interhospital transport, detailed cardiac anatomic investigation, evaluation of non-cardiac co-morbidities, and semi-elective scheduling of most cardiac interventions. Neonates who present with severe cyanosis and shock can be given time for recovery of end-organ function prior to cardiac intervention. A PGE_1 dose of 0.05–0.1 mcg/kg/min is used when the ductus arteriosus is severely constricted or functionally closed and severe cyanosis exists. A lower dose of 0.01 mcg/kg/min will safely maintain ductal patency.

The most common side effect of PGE_1 is apnea, which occurs in a minority of neonates [2]. Note that elective tracheal intubation of neonates on PGE_1 for transport has been associated with a greater incidence of complications, and thus the risk of apnea related to PGE_1 is not an absolute indication for empiric intubation [3]. Aminophylline may minimize the occurrence of apnea and need for intubation in neonates receiving PGE_1 [4]. Other common side effects of PGE_1 are listed in Table 21.1. Uncommonly, the initiation of PGE_1 may contribute to further clinical deterioration. For example, in neonates with congenital absence of the ductus arteriosus (e.g., tetralogy of Fallot with absent pulmonary valve syndrome; some infants with pulmonary atresia, a ventricular septal defect, and major aortopulmonary collateral arteries), PGE_1 may lower systemic vascular resistance, decrease pulmonary blood flow and thus exacerbate cyanosis. In contrast to neonates with ductal dependent systemic blood flow, the ductus arteriosus in those with right ventricular outflow tract obstruction is often somewhat elongated, restrictive, and follows a tortuous course from the aorta to the pulmonary artery. Less diastolic runoff from the aorta occurs, and the risk for necrotizing enterocolitis may be diminished. Thus it is reasonable to introduce enteral feedings in stable neonates with ductal dependent pulmonary blood flow who are receiving PGE_1, provided that a reasonable diastolic blood pressure (>30 mmHg) is present [5].

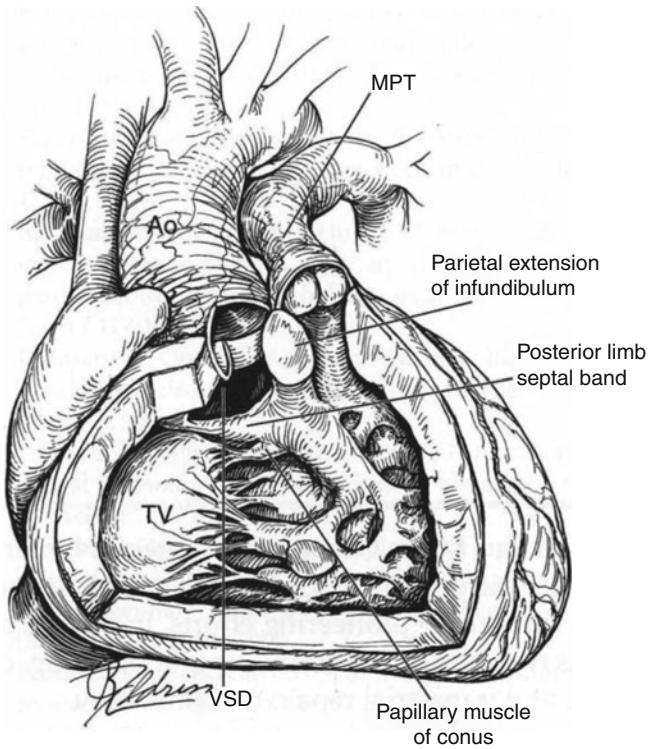


Fig. 21.2 Pathologic anatomy of tetralogy of Fallot. A nonrestrictive malalignment ventricular septal defect (VSD) with aortic override is evident. The papillary muscle of the conus is shown along with the hypertrophied parietal and septal bands, which cause right ventricular outflow tract obstruction. An infundibular "chamber" and a stenotic, hypoplastic main pulmonary trunk (MPT) and valve are shown. *Ao* aorta, *MPT* main pulmonary trunk, *TV* tricuspid valve, *VSD* ventricular septal defect (Reprinted from: Hirsch and Bove [71]. With permission from Elsevier)

Tetralogy of Fallot

Anatomy

Tetralogy of Fallot is the most common cyanotic congenital heart defect. The primary anatomic features of tetralogy of Fallot with pulmonary stenosis are an anterior malalignment VSD, right ventricular outflow tract obstruction, an overriding aorta and right ventricular hypertrophy (Fig. 21.2). Although most commonly a single VSD exists, additional muscular VSDs may be present in 3–15 % of patients. Right ventricular outflow tract obstruction may exist in the infundibulum, at the pulmonary valve, and in the main and branch pulmonary arteries. Patients with tetralogy of Fallot have a

spectrum of severity of right ventricular outflow tract obstruction, ranging from minor infundibular and pulmonary valve stenosis (favorable) to pulmonary atresia. The aortic arch may be right sided in 25 % of cases, which is important if placement of a systemic to pulmonary shunt is planned. The proximal coronary artery anatomy must be defined as the left coronary artery arises from the right coronary artery and cross the right ventricular outflow tract in 5 % of cases and may impact upon the surgeon's ability to place an infundibular patch [6]. More complex variants of tetralogy of Fallot are discussed below.

Pathophysiology and Clinical Presentation

The clinical presentation of patients with tetralogy of Fallot with pulmonary stenosis is determined to a great extent by the degree of anterior malalignment of the conal septum into the right ventricular outflow tract. The amount of blood that shunts right-to-left through the VSD, and thus the extent of cyanosis, varies with the severity of right ventricular outflow tract obstruction and the systemic vascular resistance. Pulmonary vascular resistance usually falls soon after birth and usually has minimal influence on intracardiac shunting because of the right ventricular outflow obstruction. Infants with a minimal degree of obstruction to pulmonary blood flow (i.e., "pink TETs") are usually asymptomatic and fairly well oxygenated (SaO_2>90 %) soon after birth. These patients may be discharged from the hospital with close follow-up. Occasionally a "pink TET" will mimic the pathophysiology of an infant with a large VSD and develop congestive heart failure during the first few weeks of life as pulmonary vascular resistance falls. More commonly, however, progressive right ventricular outflow tract obstruction and worsening cyanosis develop. Neonates with tetralogy of Fallot and more severe right ventricular outflow tract obstruction may develop excessive cyanosis upon closure of the ductus arteriosus. Such patients may be stabilized with PGE_1 and referred for early surgical intervention.

Any stimulus that transiently increases metabolic demand or lowers systemic vascular resistance in a patient with unrepaired tetralogy of Fallot, such as exercise or crying, may lead to transient worsening cyanosis. This physiology is to be expected and is generally self-limited. Patients with unrepaired tetralogy of Fallot are at risk for developing "tet spells." These spells are potentially life-threatening events marked by significant prolonged and severe hypoxemia, hyperpnea and irritability, which may progress to loss of consciousness, seizures and even death. Although tet spells can occur at any age, the incidence seems to increase after 6–12 months of age. Thus true tet spells are uncommon in the current era in developed countries as many patients with tetralogy of Fallot now undergo surgical repair within the first 6 months of life.

Table 21.2 Treatment options for tet spells, presented in the general sequence that they are administered

Intervention	Effect on pathophysiology
Knee-chest position or squatting	↑ Systemic vascular resistance
Oxygen	↑ Blood oxygen content
Volume	↑ Right ventricular preload (30 cc/kg crystalloid)
Opioids or benzodiazepines	↓ Agitation, ↓ hyperpnea
Ketamine	↓ Agitation, ↑ systemic vascular resistance
Beta-blocker	↓ Infundibular spasm, ↓ heart rate
Sodium bicarbonate	↓ Metabolic acidosis
Phenylephrine	↑ Systemic vascular resistance
CPB or ECMO	Rescue therapy when above measures fail

CPB cardiopulmonary bypass, *ECMO* extracorporeal membranous oxygenation

During a tet spell, dynamic infundibular spasm with resultant increased right ventricular outflow tract obstruction and decreased systemic vascular resistance lead to a progressive cycle of decreased pulmonary blood flow, increased right to left shunting across the VSD, worsening cyanosis, and eventually, metabolic acidosis. Tet spells can be triggered by any event that provokes significant patient agitation and a decline drop in systemic vascular resistance, including placement of intravenous catheters or sedation. Treatment is directed toward decreasing patient agitation and heart rate, increasing systemic vascular resistance and pulmonary blood flow, and correcting metabolic acidosis (Table 21.2). Because of the potential morbidity associated with a tet spell, their occurrence is an indication for urgent surgery.

Preoperative Evaluation

Complete anatomic information for patients with tetralogy of Fallot is usually obtained by transthoracic echocardiography [6]. If uncertainty persists about the coronary artery anatomy, some surgeons may request a cardiac catheterization, although the coronary anatomy can usually be determined by intraoperative inspection [7]. If needed, details about the pulmonary artery anatomy may be clarified by CT angiography, MRI, or cardiac catheterization. Approximately 15 % of patients with tetralogy of Fallot have DiGeorge syndrome, and those with a right aortic arch, pulmonary atresia or absent pulmonary valve syndrome are at great risk [8, 9]. About 7 % of patients undergoing tetralogy of Fallot repair have trisomy 21 [10].

Surgical or Transcatheter Intervention

Indications for surgical intervention for older infants with tetralogy of Fallot include increasing cyanosis or the

occurrence of a hypercyanotic episode [11]. Many centers recommend primary complete repair for asymptomatic patients with tetralogy of Fallot before 6 months of age to alleviate cyanosis, minimize the occurrence of hypercyanotic episodes, prevent progressive infundibular stenosis, and alleviate right ventricular pressure overload. Uncertainly exists regarding the optimal surgical strategy for symptomatic neonates. One approach is to perform a complete neonatal repair, thereby avoiding the potential morbidity associated with a systemic to pulmonary artery shunt (shunt thrombosis, pulmonary artery distortion, overcirculation) [11, 12]. Alternatively, a systemic to pulmonary shunt may be placed in symptomatic neonates and young infants, with the belief that doing so may minimize the need for an extensive ventriculotomy and transannular patch during definitive repair at 6–24 months of age [13–15]. Data from 2002 to 2007 obtained from the Society of Thoracic Surgeons (STS) Congenital Heart Surgery Database indicates that approximately half of 344 neonates with tetralogy of Fallot and pulmonary stenosis were palliated, with the remaining patients undergoing complete repair [16].

Complete repair of tetralogy of Fallot includes VSD closure, resection of muscle bundles in the right ventricular outflow tract, a pulmonary valvotomy or leaflet resection, and, if necessary, patch augmentation of the pulmonary valve annulus (i.e., a transannular patch) and proximal pulmonary arteries. In many cases, the operation may be accomplished using a transatrial-transpulmonary approach, thus avoiding the short and long-term sequelae of a right ventriculotomy or transannular patch [7, 12]. A small (i.e., 3 mm) atrial septal defect may be left patent in neonates given their risk of developing restrictive right ventricular physiology as discussed further below.

Postoperative Care

As with any postoperative admission, the receiving clinicians should assess the adequacy of tetralogy of Fallot repair when the patient arrives from the operating room. Information is synthesized from a number of potential sources, including intraoperative transesophageal echocardiogram, measurements of right ventricular and pulmonary artery pressure and any gradient between those two sites, and pulmonary artery oxygen saturation data [13, 17]. Significant pulmonary regurgitation or residual VSDs, right ventricular outflow tract obstruction or pulmonary artery stenosis may complicate the post-operative course. The inability of the right heart to provide adequate preload to the left ventricle, along with adverse effects of ventricular –interdependence and abnormal septal position, may result in left ventricular dysfunction and low cardiac output, particularly in neonates.

Table 21.3 Factors that may contribute to restrictive right ventricular physiology following neonatal right ventricular outflow reconstruction

Risk factor	Etiologies
Diastolic dysfunction	Poorly elastic, hypertrophied right ventricle; right ventriculotomy; right ventricular muscle bundle resection; myocardial ischemia-reperfusion injury; non-contractile VSD patch
Deceased right ventricular preload	Tricuspid stenosis
Myocardial ischemia	Injury to conal branch of coronary artery crossing RVOT
	Inadequate coronary perfusion pressure
Volume load	Residual ventricular septal defect (VSD) or pulmonary regurgitation
Increased right ventricular afterload	Residual stenosis of the right ventricular infundibulum, pulmonary valve or pulmonary arteries

RVOT right ventricular outflow tract, *VSD* ventricular septal defect

One of the postoperative issues relatively unique to complex right heart reconstructions is the potential for the development of restrictive right ventricular physiology. In addition to tetralogy of Fallot, restrictive right ventricular physiology may also develop following surgical repair of pulmonary atresia or truncus arteriosus. Neonates are particularly at risk. In afflicted patients, restrictive physiology has been defined as persistent antegrade flow from the right ventricle into the pulmonary artery during diastole as documented using pulsed Doppler echocardiography, suggesting that the right ventricle end diastolic pressure is elevated. The primary underling cause is impaired elastance of the right ventricle. A variety of factors are contributory as outlined in Table 21.3. Patients with restrictive right ventricular physiology have increased right atrial filling pressure (e.g., 10–15 mmHg) and systemic venous hypertension. Note that the right atrial pressures are not as elevated as one might expect due to high capacitance of the neonatal systemic venous circulation. Hepatic congestion, ascites, increased chest tube losses and pleural effusions may develop. Because of the phenomenon of ventricular-interdependence, changes in right ventricular diastolic function and septal position will in turn affect left ventricular compliance and function. Left ventricular preload and stroke volume are ultimately compromised. Restrictive right ventricular physiology may manifest with a low cardiac output state. Tachycardia, hypotension, poor perfusion and a narrow pulse pressure may be present, along with oliguria and a metabolic acidosis.

Anticipatory treatment for restrictive right ventricular physiology begins in the operating room (Table 21.4). Although any atrial septal defects are usually closed at the time of surgery in older patients, in neonates and young infants undergoing a two ventricular repair involving right heart reconstruction, it is beneficial to leave a small

Table 21.4 Treatment options for restrictive right ventricular physiology

Physiologic goals	Specific treatment strategies	Notes
Optimize ventricular preload	Target right atrial pressure of 10–15 mmHg	
	Drain ascites	
	Leave patent foramen ovale to preserve left ventricular preload	
	Maintain atrioventricular synchrony; treat arrhythmias	
Inotropic support	Judicious use of dopamine, milrinone and/or epinephrine	
Lusitropy	Milrinone	
Optimize myocardial oxygen supply & demand	Maintain coronary perfusion pressure	
	Heart rate control	
	Judicious use of inotropes	
Maintain low right ventricular afterload	Use lowest possible mean airway pressure to maintain FRC of lungs	
	Avoid acidosis	
	Drain pleural effusions, pneumothoraces, or hemothoraces	
Minimize systemic oxygen consumption	Maintain normothermia	
	Provide adequate sedation and analgesia	
	Consider muscle relaxant	

FRC functional residual capacity

(i.e., 3 mm) atrial communication [18]. In the face of diastolic dysfunction and increased right ventricular end diastolic pressure, the resultant right-to-left atrial shunt will maintain preload to the left ventricle and therefore cardiac output. Patients may be mildly desaturated initially following surgery (SaO_2 85–95 %) but as right ventricular elastance and function improves (usually within a few days), the amount of shunt decreases and both antegrade pulmonary blood flow and SaO_2 increase. If an atrial communication does not exist and significant and refractory restrictive right ventricular physiology develops in the early postoperative period, the atrial septum may be opened in the cardiac catheterization laboratory.

Several other strategies must be used to manage restrictive right ventricular physiology, and each should be implemented with the overarching goal of maintaining adequate systemic oxygen delivery while minimizing myocardial oxygen consumption. As tachycardia and wall stress influence myocardial oxygen consumption, therapies that influence these variables need to be used judiciously. Preload must be maintained despite elevation of the right sided filling pressures. In selected cases, low dose epinephrine (e.g., 0.05–0.1 mcg/kg/min) may be beneficial provided that excessive tachycardia does not occur. Milrinone may be beneficial due to its inotropic, lusitropic and vasodilatory properties, however care must be taken to ensure that coronary perfusion pressure is adequate to avoid right ventricular subendocardial ischemia. Efforts are warranted to maintain low right ventricular afterload. Hypoxemia, hypothermia, and acidosis may contribute to elevated pulmonary vascular resistance and should be avoided. Hypo- or hyperinflation of the lung may also increase right ventricular afterload and impede pulmonary blood flow and promote pulmonary regurgitation. Higher airway pressures may also limit right ventricular preload. As proof of this principle, a brief trial of negative pressure ventilation early following tetralogy of Fallot repair has been shown to improve mix venous oxygen saturation and pulmonary blood flow [19]. Thus during mechanical ventilation, goals are to maintain functional residual capacity, limit mean airway pressure and avoid hypoxia and respiratory acidosis. Using intermittent positive pressure ventilation, a short inspiratory time, a low positive end expiratory pressure (e.g., 4–5 cm H_2O) and adequate tidal volume (e.g., 10 mL/kg) and FiO_2 are desirable for most patients. Any significant pleural effusions and other factors that many contribute to elevated pulmonary vascular resistance should be promptly addressed. Sedation and paralysis are often necessary for the first 24–48 h to minimize the stress response and associated myocardial workload. Right ventricular compliance generally improves in a few days, at which point the patient may be weaned from mechanical ventilation.

Loss of sinus rhythm may be poorly tolerated following tetralogy of Fallot repair. Loss of atrioventricular synchrony will increase right atrial pressure and compromise cardiac output and blood pressure. In the setting of restrictive right ventricular physiology, supraventricular arrhythmias may lead to the loss of the contribution of atrial systole to antegrade pulmonary blood flow. Junctional ectopic tachycardia (JET) is the most common arrhythmia seen early following tetralogy of Fallot repair, whereas ventricular tachycardia is (somewhat surprisingly) rarely seen, at least in infants [11, 20]. Details regarding the diagnosis and management of early postoperative arrhythmias are found in subsequent chapters. Of note, a right bundle branch block pattern is common on the post-operative ECG but usually of little short term significance.

Neonates with tetralogy of Fallot and pulmonary stenosis who have a systemic to pulmonary artery shunt placed are at risk for developing pulmonary overcirculation. Total pulmonary blood flow from the shunt plus the native flow across the right ventricular outflow tract may be excessive. In this scenario, efforts to increase pulmonary vascular resistance may be useful. Supportive care is generally required for a few days until the circulatory system adapts to the new volume load. Acute shunt thrombosis and pulmonary artery distortion are also potential complications of this procedure.

Tetralogy of Fallot: Complex Variants

Tetralogy of Fallot with pulmonary atresia is also referred to as pulmonary atresia with ventricular septal defect. At the best end of the spectrum, a newborn may have tetralogy of Fallot, pulmonary atresia, good-sized central pulmonary arteries that are supplied by a patent ductus arteriosus. Occasionally the central pulmonary arteries are discontinuous. Regardless of the details of the anatomy, in neonates with pulmonary atresia all systemic venous return must shunt right to left at the atrial or ventricular level, resulting in complete mixing with pulmonary venous return in the left heart. PGE_1 is used to maintain ductal patency followed by early neonatal surgical intervention. Options include palliation with a systemic to pulmonary shunt or primary repair. A right ventricle to pulmonary artery conduit is typically used to reconstruct the right ventricular outflow tract, although in selected cases with short-segment pulmonary atresia and adequate pulmonary arteries, the operation may be performed using a transannular patch. Postoperative management concepts are similar to those discussed for tetralogy of Fallot with pulmonary stenosis.

In a more complicated variant of tetralogy of Fallot with pulmonary atresia, the central pulmonary arteries may be diminutive and one or more major aortopulmonary collateral vessels (MAPCAs) are present. In approximately 15–25 % of cases there are no central pulmonary arteries [21, 22]. The MAPCAs are variable in number and usually arise from the descending aorta, although their origin may be from the ascending aorta, aortic arch, bracheocephalic vessels or coronary arteries (Fig. 21.3) [21]. There may be multiple stenoses and diminished total cross-sectional area of the pulmonary vascular bed. In neonates with tetralogy of Fallot, pulmonary atresia and MAPCAs, pulmonary blood flow may be quite variable depending upon the size and number of MAPCAs and the severity of stenoses within these vessels [22]. Generally such patients are not dependent upon PGE_1. Although cardiac MRI provides adequate visualization of central pulmonary arteries and the proximal course of important MAPCAs, cardiac catheterization is ultimately required to clarify distal pulmonary artery anatomy and identify all sources of pulmonary blood flow to each lung segment. Indications for initial surgical intervention in neonates with tetralogy of Fallot, pulmonary atresia and MAPCAs include excessive cyanosis, refractory congestive heart failure, or diminutive central pulmonary arteries in need of a reliable source of blood flow to promote growth. In the absence of symptoms, elective surgical intervention may occur within the first 2–6 months of life to maximize the growth potential of the central pulmonary arteries. The ultimate goal of intervention is to optimize the effective cross-sectional area of the pulmonary arterial vascular bed, eliminate any MAPCAs that represent dual blood supply in order to minimize the risk of pulmonary vascular obstructive disease to lung segments, and thus limit right ventricular hypertension following eventual VSD closure. Although primary complete repair in early infancy is possible in selected patients (16), in many cases, a staged series of surgical and transcatheter interventions are required, the timing and conduct of which must be individualized based on underlying anatomy and physiology at presentation [21]. If the central pulmonary arteries are small but confluent, the initial operation must include the establishment of a reliable source of antegrade blood flow, which will promote growth of these vessels over time. Options include placement of a systemic to pulmonary shunt, creation of an aortopulmonary window, or placement of a right ventricular to pulmonary artery conduit [21, 23–25]. The latter approach may be advantageous in that it provides easy antegrade transcatheter access to the distal pulmonary arteries for subsequent balloon angioplasty. If the central pulmonary arteries are absent, they can be constructed using pericardium or pulmonary allograft [21]. Intervention for each MAPCA is customized depending upon its size, the presence or absence of proximal stenosis within the vessel, and a determination as to whether it represents redundant blood supply to individual lung segments. Redundant MAPCAs can be coil occluded in the cardiac catheterization laboratory or ligated at the time of surgery to eliminate left to right shunting and

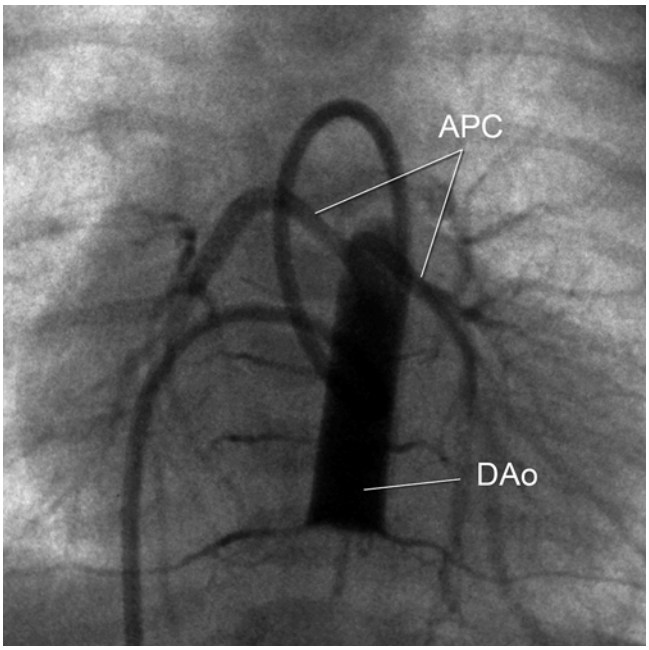


Fig. 21.3 Angiogram in the descending aorta of tetralogy of Fallot with pulmonary atresia demonstrating major aortopulmonary collateral arteries. *APC* aortopulmonary collateral arteries, *DAo* descending aorta

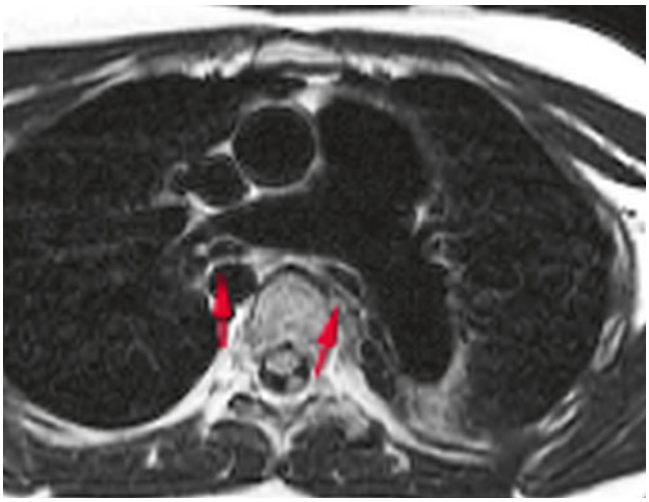


Fig. 21.4 Black blood axial magnetic resonance image in a patient with Tetralogy of Fallot with absent pulmonary valve syndrome. Note the dilated right and left pulmonary arteries with compression of the right and left mainstem bronchi (*arrows*) (Courtesy of Cynthia Rigsby MD, Department of Medical Imaging, Children's Memorial Hospital, Chicago, Illinois)

prevent the development of pulmonary vascular disease. If a MAPCA represents the sole source of pulmonary blood flow to a lung segment, the proximal end of the MAPCA is removed from its source and incorporated into the native or newly constructed central pulmonary arteries, such that blood flow to the lung is supplied from a single source (unifocalization procedure) [21, 26]. Once the pulmonary vascular bed has been optimally recruited, intracardiac repair is completed including VSD closure and (if not previously completed) right ventricular outflow tract reconstruction. The incidence of early postoperative right ventricular failure may be decreased by placement of a fenestrated VSD patch in patients with an inadequate pulmonary vascular bed, which serves to preserve systemic cardiac output at the expense of mild postoperative cyanosis [24].

Approximately 4 % of patients with tetralogy of Fallot have absent pulmonary valve syndrome. In addition to the usual anatomic features of tetralogy of Fallot, such patients have rudimentary pulmonary valve leaflets. The pulmonary arteries are often severely dilated related to to-and-fro flow across the right ventricular outflow tract that was present in utero and continues postnatally (Fig. 21.4). In some patients, severe respiratory compromise may manifest soon after delivery due to bronchial compression by the aneurismal pulmonary arteries. Prone positioning may be beneficial as gravity may allow the pulmonary arteries to fall off of the airways, and extracorporeal membrane oxygenation may be considered in refractory cases as a bridge to surgery. Additional imaging of the pulmonary arteries by CT or MRI may facilitate surgical planning. Early surgery is then indicated, which would typically include plication or replacement of the central pulmonary arteries and placement of a valved right ventricular to pulmonary artery conduit [27, 28]. The postoperative course may be complicated by respiratory insufficiency and prolonged mechanical ventilation secondary to distal bronchomalacia. Those patients without respiratory compromise in the early neonatal period may have their repair delayed until later in infancy.

Tetralogy of Fallot is associated with an atrioventricular canal defect in approximately 2–5 % of cases. Evaluation and management strategies are similar to those used in simple tetralogy of Fallot with pulmonary stenosis [29]. Given the usual issues regarding right ventricular dysfunction following tetralogy of Fallot repair, the presence of residual tricuspid regurgitation following division of the common atrioventricular valve may be poorly tolerated [30].

Outcomes

Surgical outcomes in the current era are excellent for tetralogy of Fallot with pulmonary stenosis [7, 11–14]. Not surprisingly, mortality risk increases with greater anatomical and procedural complexity. Multicenter data collected between 2002 and 2007 by the European Association for Cardiothoracic Surgery (EACTS) and the Society of Thoracic Surgeons (STS) Congenital Heart Surgery Databases indicate that the unadjusted hospital mortality risk following a valve-sparing tetralogy of Fallot repair is 1.4, 2.7 % for patients requiring a transannular patch, and 4.2 % for those requiring a right ventricular to pulmonary artery conduit [31]. STS mortality rates for neonatal palliation or repair of tetralogy of Fallot with pulmonary stenosis are higher: 6.2 and 7.8 %, respectively [16]. Patients undergoing a unifocalization or complete repair of tetralogy of Fallot with pulmonary atresia and MAPCAs experience approximately a 10 % mortality rate for either operation [31]. Mortality rates for tetralogy of Fallot with concurrent absent pulmonary valve syndrome or atrioventricular septal defect are 9.1 and 9.7 %, respectively [31]. Twenty-five to thirty percent of neonates undergoing repair of tetralogy of Fallot and pulmonary stenosis require reintervention during the first decade after the operation, whereas nearly all neonates with tetralogy of Fallot and pulmonary atresia or absent pulmonary valve syndrome will require reintervention during that time period [32].

Pulmonary Valve Stenosis

Anatomy

Pulmonary valve stenosis occurring in isolation is common, representing about 10 % of all congenital heart defects. Pulmonary stenosis also may be associated with other lesions

Table 21.5 Classification and outcomes for balloon dilation for pulmonary valve stenosis

	Mild PS	Moderate PS	Severe PS	Critical PS
RVP	<40 mmHg; <50 % LVP	40–80 mmHg; 50–100 % LVP	>80 mmHg; ≥LVP	>LVP
Cyanosis	None	Rare, mild	Common, mild	≥Moderate
Ductal dependent PBF	No	No	No	Yes
Tricuspid valve size	Normal	Normal	Normal	Low-normal range
≥mild TR	None	Uncommon	+	++
RVH	None	Mild	Moderate	Moderate-Severe
Antegrade RVOT flow	+++	+++	++	Trivial
Probability of successful balloon valvuloplasty[a]	Not indicated	High	90 %	64–85 %

LVP left ventricular pressure, *PBF* pulmonary blood flow, *PS* pulmonary stenosis, *RVH* right ventricular hypertrophy, *RVOT* right ventricular outflow tract, *RVP* right ventricular pressure, *TR* tricuspid regurgitation
[a]Success defined as the lack of need for early surgery [33, 39]

including VSD, transposition of the great arteries, Ebstein's anomaly, or atrioventricular canal defect. This section will focus on isolated pulmonary valve stenosis, as the associated lesions are discussed elsewhere. Stenotic pulmonary valves have one to three thickened cusps that often dome in ventricular systole. The pulmonary valve annulus may be hypoplastic and infundibular hypertrophy may be present. In utero, the stenotic pulmonary valve imposes high afterload on the right ventricle, causing it to hypertrophy. A patent foramen ovale or atrial septal defect is commonly associated with pulmonary valve stenosis.

Pathophysiology and Clinical Presentation

Pulmonary valve stenosis has a wide spectrum of severity and may be classified as mild, moderate, or severe as outlined in Table 21.5. This classification system assumes that cardiac output is normal, and may not be applicable to patients with right ventricular dysfunction. The phrase critical pulmonary valve stenosis may be used to describe the neonate who is symptomatic with cyanosis and right ventricular failure. In such patients, a pinhole orifice exists in the pulmonary valve and nearly all systemic venous return shunts right to left across the atrial septum, where mixing occurs with pulmonary venous return. When compared with infants having severe pulmonary stenosis, those with critical pulmonary stenosis may have smaller tricuspid valves and right ventricles, more tricuspid regurgitation, more right ventricular hypertrophy, and the absence of significant antegrade flow across the right ventricular outflow tract with resultant right to left shunting through an atrial communication (Table 21.5) [33]. As the transcatheter management for older children with pulmonary valve stenosis is technically straightforward and rarely results in complications requiring intensive care, the remainder of this section will focus on the neonate with critical pulmonary valve stenosis.

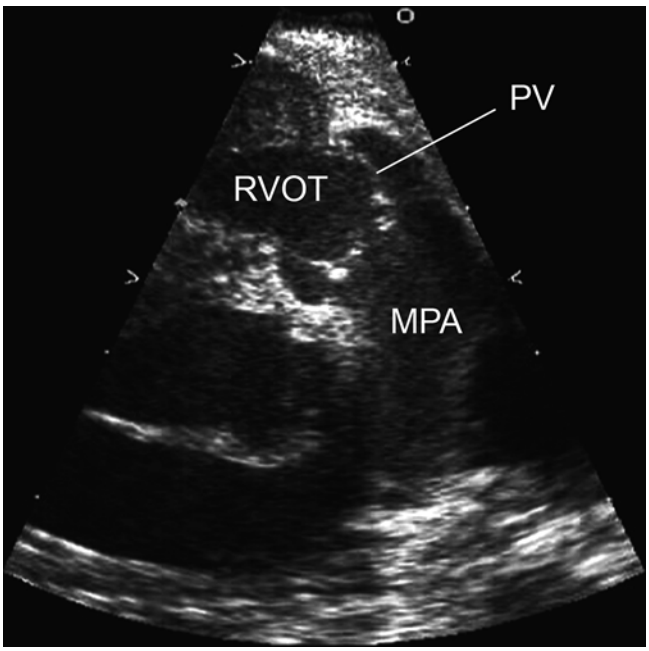


Fig. 21.5 Two-dimensional echocardiogram demonstrating the thickened doming leaflets in a neonate with pulmonary valve stenosis. *MPA* main pulmonary artery, *PV* pulmonary valve, *RVOT* right ventricular outflow tract

Preoperative Evaluation

PGE_1 should be used for neonates with critical pulmonary valve stenosis. Echocardiographic evaluation of pulmonary valve stenosis in the neonatal period is focused on the size and function of the tricuspid valve, right ventricle, and pulmonary valve (Fig. 21.5). In the presence of a widely patent ductus arteriosus and poor right ventricular function or pulmonary hypertension, color-Doppler flow may not be seen across a patent pulmonary valve, a condition known as functional pulmonary atresia. RVP is quantified by Doppler interrogation of the tricuspid regurgitation jet. The Doppler

gradient across the pulmonary valve may be influenced by right ventricular function and by the main pulmonary artery pressure and thus cannot be interpreted in isolation.

Surgical or Transcatheter Intervention

Neonates with severe or critical pulmonary valve stenosis require prompt referral for balloon valvuloplasty [34, 35]. Surgical valvotomy is now reserved for those neonates who fail transcatheter intervention [36]. During the catheterization, a series of balloons with a final diameter of approximately 120–140 % of the pulmonary valve annulus size are used to dilate the stenotic pulmonary valve [33, 34]. Although perforation of the right ventricular outflow tract and other complications inherent to neonatal cardiac catheterization may occur, in the current era the vast majority of procedures are completed without major adverse events [33, 35]. PGE_1 may be discontinued following successful valvuloplasty and the patient returned to the intensive care unit.

Postoperative Care and Outcome

The most common problem encountered following balloon dilation of critical pulmonary valve stenosis is cyanosis, which may recur as the ductus arteriosus constricts several hours following discontinuation of PGE [37]. In such patients, right ventricular hypoplasia and poor compliance exist, leading to right to left atrial shunting. In this scenario, PGE_1 may be resumed to maintain ductal patency and adequate pulmonary blood flow for several days, thus providing time for right ventricular compliance to improve [38]. Right ventricular systolic dysfunction, anemia, tricuspid stenosis, or residual pulmonary stenosis may also contribute to cyanosis following the initial intervention. Patience is required while caring for these neonates and $SaO_2 > 75$ % and $PaO_2 > 35$–40 mmHg are acceptable in the short term. Several trials of observation off PGE_1 may be required. Surgical intervention is ultimately required in 15–25 % of neonates with critical pulmonary stenosis, either for technical failure of the balloon valvuloplasty (often due to a dysplastic pulmonary valve) or persistent cyanosis [34, 37, 38]. A systemic to pulmonary shunt will provide effective pulmonary blood flow until right ventricle compliance and size improves. If infundibular hypertrophy or residual pulmonary valve stenosis is contributing to the cyanosis, an infundibular patch or pulmonary valvotomy may be required [33]. Mortality for neonates with critical pulmonary stenosis in experienced centers is <5 % [33, 34, 39]. The long term outlook for these patients is generally very favorable, although some will ultimately require pulmonary valve replacement.

Pulmonary Atresia with Intact Ventricular Septum

Anatomy

Pulmonary atresia with intact ventricular septum is an uncommon lesion characterized by a membranous or muscular obstruction of the pulmonary valve, associated with variable degrees of hypoplasia of the right ventricle and tricuspid valve. The left and right pulmonary arteries are usually of normal size. MAPCAs are quite uncommon, in contrast to patients with tetralogy of Fallot with pulmonary atresia. Right ventricle to coronary artery fistulae are present in nearly half of cases, particularly in those with more significant tricuspid valve and right ventricular hypoplasia [40–42]. In 9–34 % of patients with pulmonary atresia and intact ventricular septum, stenoses, interruptions or ostial occlusions are present in one or more coronary vessels. The myocardium supplied by these compromised coronary arteries is thus dependent on flow from the right ventricle through the coronary fistulae, a condition known as right ventricular dependent coronary circulation (RVDCC) [40, 42–44]. Ebstein's anomaly of the tricuspid valve is found in approximately 10 % of cases [42].

Pathophysiology and Clinical Presentation

All neonates with pulmonary atresia and intact ventricular septum have ductal dependent pulmonary blood flow, and PGE_1 is required to maintain ductal patency. Complete intracardiac mixing occurs, as all systemic venous return to the right atrium flows through an obligatory atrial communication to the left atrium. The right ventricle is decompressed by tricuspid regurgitation or egress through the coronary fistulae to the aorta. If tricuspid regurgitation is limited, suprasystemic RVP and marked right ventricular hypertrophy are usually present.

Preoperative Evaluation

The initial echocardiogram must delineate the size and function of the tricuspid valve and right ventricle, and the anatomy of the right ventricular outflow tract. A judgment must be made as to whether the right heart structures are adequate, or have the potential to be adequate in the future, to support a two-ventricular circulation [45]. Right ventricle to coronary artery fistulae may be identified by echocardiogram using color Doppler. Neonates with a tricuspid valve Z score of ≤ -2.5 are very likely to have RVDCC [41]. If coronary fistulae are seen by echocardiogram, the

coronary anatomy should be precisely defined by cardiac catheterization (Fig. 21.6) [45]. If stenoses, interruptions or ostial occlusions exist such that a significant amount of myocardium is dependent upon flow from the right ventricle through the coronary fistulae, then surgical or transcatheter decompression of the right ventricle is contraindicated [42, 46].

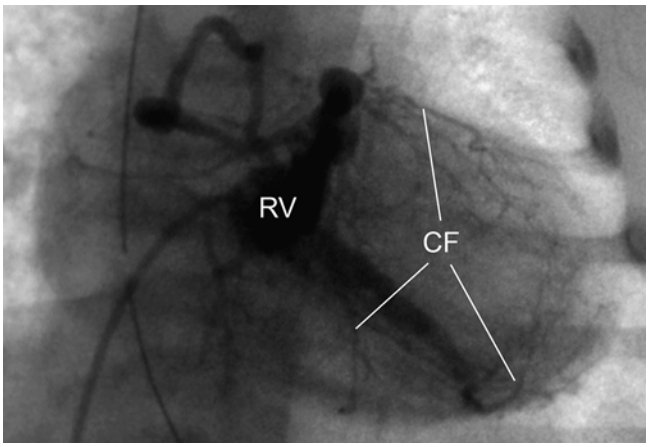


Fig. 21.6 Angiographic injection in the right ventricle of a neonate with pulmonary atresia with intact ventricular septum demonstrating multiple fistulous connections to the coronary circulation. *RV* right ventricle, *CF* coronary fistula

Surgical or Transcatheter Intervention

Provided that the tricuspid valve and right ventricle are of reasonable size and there is no evidence for RVDCC, it is reasonable to pursue a two-ventricular repair [47]. Right ventricular decompression may be accomplished by placement of a right ventricular outflow tract patch to encourage right ventricular growth and allow regression of right ventricular hypertrophy [44, 45]. The atrial septal defect is left open to allow for decompression of the right heart and maintenance of systemic cardiac output, and usually a systemic to pulmonary shunt is concurrently placed to ensure adequate pulmonary blood flow. Alternatively, the right ventricle may also be decompressed in neonates with membranous pulmonary atresia by transcatheter perforation of the pulmonary valve using a stiff wire or radiofrequency ablation catheter followed by balloon valvuloplasty (Fig. 21.7). At best, however, transcatheter intervention avoids the need for early surgical intervention in only approximately one-third of patients [47–49]. If RVDCC exists, relief of right ventricular outflow obstruction is contraindicated, and the initial operation is a systemic to pulmonary artery shunt as the first stage of single ventricle palliation [50]. Cardiac transplantation may be considered for the unusual infant with severe RVDCC and myocardial dysfunction that precludes single ventricle palliation [51].

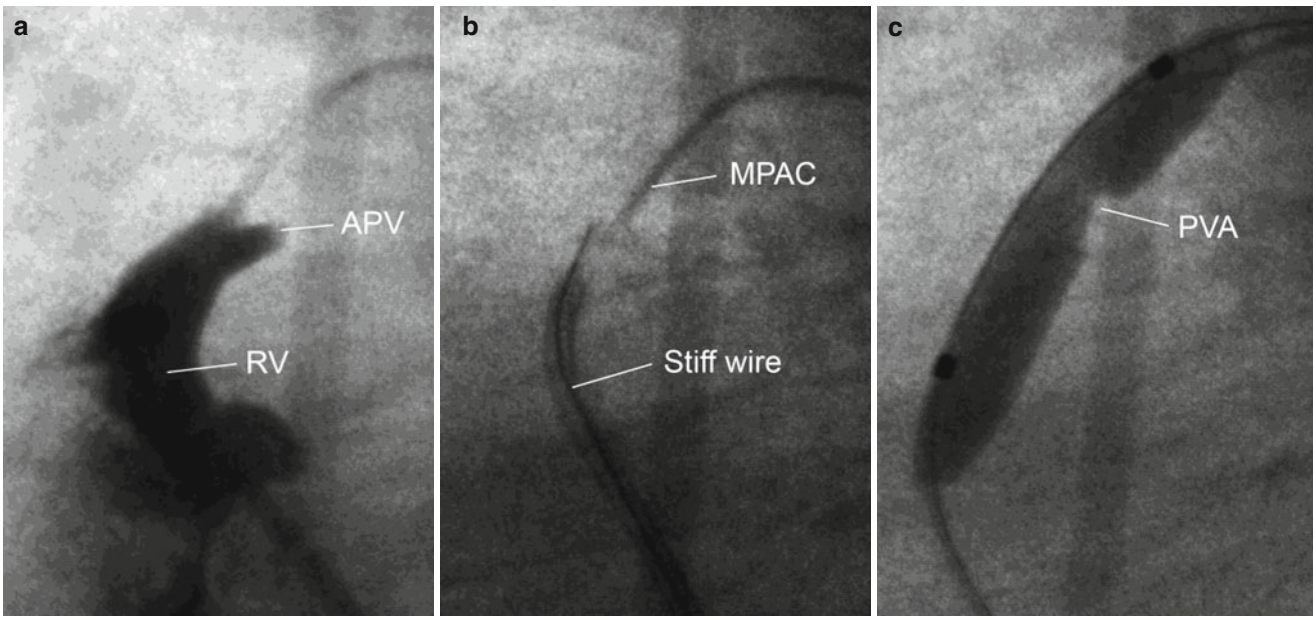


Fig. 21.7 A series of images obtained during therapeutic cardiac catheterization in a neonate with pulmonary atresia and intact ventricular septum. (**a**) Angiogram in the right ventricle demonstrating no antegrade flow across the pulmonary valve. (**b**) A stiff wire is being advance across the atretic pulmonary valve, using a catheter in the main pulmonary artery as a target. (**c**) Following perforation of the pulmonary valve, a balloon is advanced across the right ventricular outflow tract and inflated. Note the waist in the balloon that defines the location of the pulmonary valve annulus. *APV* atretic pulmonary valve, *MPAC* main pulmonary artery catheter, *PVA* pulmonary valve annulus, *RV* right ventricle

Postoperative Care and Outcome

In patients palliated with a systemic to pulmonary shunt, there exists the potential for pulmonary overcirculation (high Qp:Qs), poor systemic perfusion, low diastolic blood pressure and inadequate coronary perfusion. In this setting, maneuvers are indicated to increase pulmonary vascular resistance and thus "balance" the circulation, such as use of increased mean airway pressure and the avoidance of supplemental oxygen and respiratory alkalosis. Following placement of a right ventricular outflow patch in the neonatal period, supportive care as described above for patients with tetralogy of Fallot and restrictive right ventricular physiology may be necessary. Rarely, a circular shunt may develop following placement of a right ventricular outflow tract patch and systemic to pulmonary shunt (as described in detail in the Ebstein's anomaly section). However, this is uncommon in patients with pulmonary atresia and intact ventricular septum due in part to the elevated right ventricular end diastolic pressure that serves to limit pulmonary regurgitation.

In shunted neonates with RVDCC, care should be taken to avoid excessive systemic vasodilation. Norepinephrine or vasopressin may be needed to maintain coronary perfusion pressure. Close ECG monitoring for ST segment changes is required, and if any signs of myocardial ischemia develop, prompt echocardiography should be obtained to evaluate for wall motion abnormalities. If RVDCC was unrecognized and a right ventricular outflow track was opened, myocardial ischemia, ventricular dysfunction and arrhythmias are likely to develop immediately following the procedure [43]. Recreation of pulmonary atresia by ligation of the main pulmonary artery may performed in attempt to salvage such patients.

Following initial neonatal right ventricular decompression, palliated patients with pulmonary atresia and intact ventricular septum are evaluated for interval growth of right-sided heart structures and right ventricular compliance. During cardiac catheterization, test occlusions of the atrial septal defect and systemic to pulmonary shunt may performed to determine whether cyanosis and systemic venous hypertension develop. If not, closure of the atrial communication and takedown or coil occlusion of the shunt are performed to separate the systemic and pulmonary circulations. One-and-one half ventricular repair and Fontan palliation are options for older patients whose right heart has not developed adequately to support the entire circulation [44].

Mortality for patients with pulmonary atresia and intact ventricular septum in early infancy is approximately 10 %, and patients with RVDCC or Ebstein's anomaly are at greater risk [49]. Using appropriate staged interventions in patients with pulmonary atresia and intact ventricular septum, 5-year survival rates greater than 80 % may be achieved [44, 47].

Ebstein's Anomaly

Anatomy

Ebstein's anomaly is a rare congenital heart lesion, representing less than 1 % of all cases of congenital heart disease. The septal and posterior leaflets of the tricuspid valve are displaced to a variable extent into the anatomic right ventricle and variably adherent to the ventricular septum [52]. The anterior leaflet, while not significantly inferiorly displaced, may be fenestrated and redundant or "sail-like" and cause obstruction of the right ventricular outflow tract. The tricuspid valve chordae tendinae and papillary muscles may be abnormal, the true tricuspid valve annulus may be dilated, and tricuspid regurgitation may be severe. The functional right atrium may be quite enlarged because of tricuspid regurgitation and the fact that the inlet portion of the right ventricle is "atrialized" by the inferiorly displaced tricuspid valve leaflets. Atrial septal defects (commonly) and anatomic pulmonary valve stenosis or atresia are associated with Ebstein's anomaly. Left-side heart abnormalities including ventricular non-compaction are occasionally present. One or more accessory conduction pathways may exist at the tricuspid valve annulus, creating the necessary substrate for atrioventricular reentrant tachycardia. In newborns, pulmonary hypoplasia has been associated with advanced Ebstein's anomaly and thought to contribute to cyanosis and mortality [53]. However, a recent report suggests that although lung compression may be severe, true lung hypoplasia and immaturity are uncommon [54].

Pathophysiology and Clinical Presentation

Many patients with Ebstein's anomaly do not develop symptoms until adolescence or early adulthood, when a combination of right-sided congestive heart failure, cyanosis, arrhythmias and sudden death may develop [55]. The fundamental problem is the presence of an abnormal right ventricle and regurgitant tricuspid valve leading to impaired blood flow through the right heart. However, newborns with severe Ebstein's anomaly (i.e., severe tricuspid regurgitation, right ventricular hypoplasia, myocardial dysfunction and severe cardiomegaly) may present with hydrops fetalis or severe cyanosis and heart failure soon after birth [56]. Right to left shunting at the atrial level occurs and may be due to pulmonary hypertension, pulmonary valve stenosis or atresia, or right ventricular outflow tract obstruction by the sail-like anterior leaflet of the tricuspid valve. In some neonates, functional pulmonary atresia exists, which develops when the pulmonary artery pressure is greater than the pressure that the Ebsteinoid right ventricle can generate, and the pulmonary

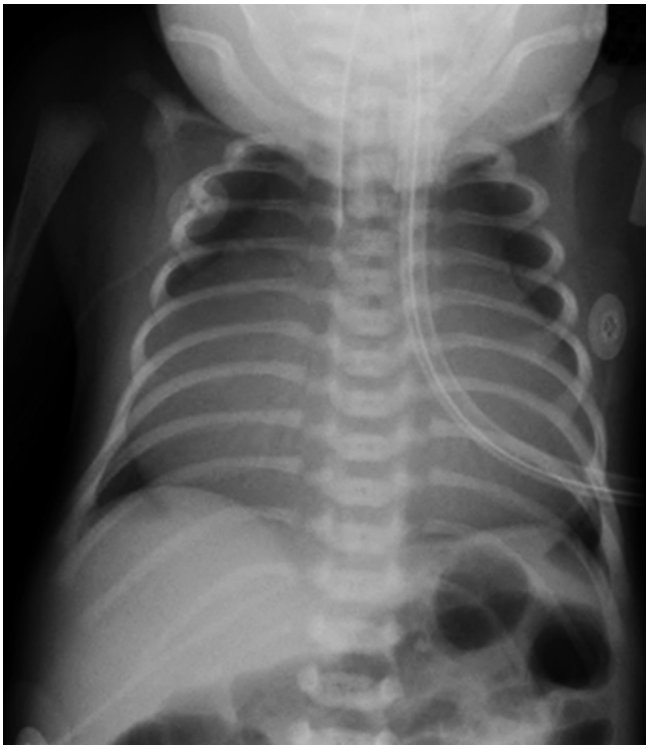


Fig. 21.8 Chest radiograph of a neonate with severe Ebstein's anomaly

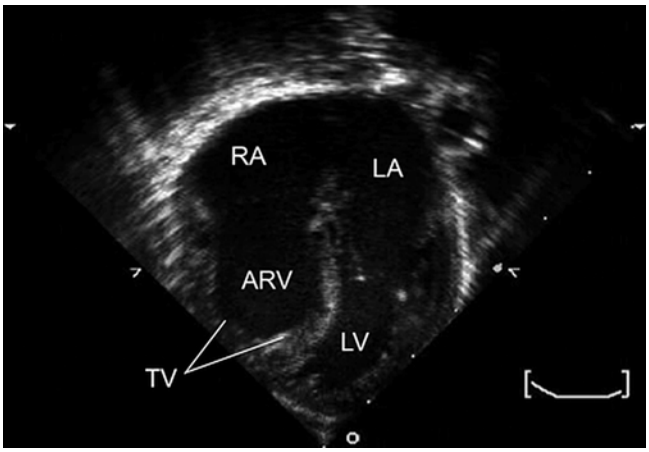


Fig. 21.9 Two-dimensional echocardiogram demonstrating severe Ebstein's anomaly of the tricuspid valve in a neonate. *ARV* atrialized right ventricle, *LA* left atrium, *LV* left ventricle, *RA* right atrium, *TV* tricuspid valve

valve leaflets fail to open. Severe tricuspid regurgitation and extreme right atrial enlargement may result in pooling of venous return in the compliant right atrium with limited shunting across the atrial septal defect to the left atrium. The reduced preload to the left ventricle may contribute to underdevelopment of the left side of the heart and a low cardiac output state. Biventricular function may also be diminished by myocardial fibrosis [56, 57]. Neonates with Ebstein's anomaly presenting with significant cyanosis (<75–80 % systemic saturation) should initially receive PGE_1. The lungs may be compressed by severe cardiomegaly (Fig. 21.8), and thus mechanical ventilation with judicious use of positive end expiratory pressure may be useful [56].

Preoperative Evaluation

The size of the right atrium, anatomy and function of the tricuspid valve, and the right ventricular outflow tract are assessed by echocardiography (Fig. 21.9). Using echocardiographic measurements from the apical four-chamber view, the ratio of the right atrium and atrialized right ventricle to the area of the functional right ventricle, left atrium and left ventricle of greater than one is a strong independent predictor of mortality [55–58]. Other predictors of mortality in the neonatal period include the presence of cyanosis, right ventricular outflow tract obstruction and left ventricular systolic dysfunction [55, 57, 58]. The electrocardiogram may show signs of right atrial enlargement, first degree atrioventricular block, and partial or complete right bundle branch block. The electrocardiogram should be inspected for preexcitation, as some patients with Ebstein's anomaly have accessory atrioventricular conduction pathways that create the necessary substrate for supraventricular tachycardia.

Surgical or Transcatheter Intervention

Decision making for symptomatic neonates with severe Ebstein's anomaly is complex and requires a complete understanding of the evolving physiology. If pulmonary atresia is present, early consideration must be given to determining whether it is anatomic or functional. If functional atresia is suspected, discontinuation of PGE_1 may lead to ductal constriction. The resultant decreased pulmonary artery pressure may allow the pulmonary valve leaflets to open [59]. Anatomic pulmonary atresia may warrant attempted balloon dilation or placement of a systemic to pulmonary shunt. In patients without pulmonary atresia, pulmonary vascular resistance may fall, and systemic to pulmonary runoff may occur through the ductus arteriosus leading to a low output state. Increased pulmonary venous return leads to elevated left atrial pressure, which may inhibit right to left atrial shunting and thus contribute to systemic venous hypertension. In this scenario PGE_1 should be discontinued with the hope that ductal constriction will lead to decreased pulmonary artery pressure, thereby promoting increase antegrade flow across the right ventricular outflow tract and abating symptoms of heart failure. Persistent patency of a large

ductus arteriosus may warrant surgical ligation, which may result in dramatic improvement. The judicious use of mechanical ventilation, supplemental oxygen, and inhaled nitric oxide may also facilitate a decline in pulmonary vascular resistance, thereby promoting antegrade flow across the right ventricular outflow tract [57, 59, 60]. If cyanosis decreases, surgical intervention on the tricuspid valve can then be deferred.

For symptomatic neonates who fail medical management, there is no single reparative or palliative procedure that has been associated with widespread success. For neonates with both cyanosis and heart failure, one surgical option is to place a systemic to pulmonary artery shunt, over sew the tricuspid valve annulus and perform an atrial septectomy as the first stage procedure toward Fontan palliation [61]. Plication of the right atrium is usually necessary to reduce its size and volume, and promote right to left shunting across the atrial septum. Alternatively, a two ventricular repair may be attempted consisting of a reduction atrioplasty, fenestrated closure of the atrial septum and complex tricuspid valvuloplasty [62]. Heart transplantation may also be considered, but despite early listing it may be difficult to medically manage these patients while waiting for a donor graft to become available. Despite aggressive care, a subset of neonates with severe Ebstein's anomaly has persistent low cardiac output and profound cyanosis resulting in early mortality [57, 60].

Older children and adults with Ebstein's anomaly may develop worsening right heart dilation, symptoms of right sided heart failure, atrial or ventricular arrhythmias, cyanosis or paradoxical emboli, all of which warrant consideration for intervention [52]. Significant right ventricular volume overload due to severe tricuspid regurgitation may cause septal shift thereby compromise left ventricular function. A number of techniques for tricuspid valve repair with or without plication of the atrialized right ventricle have been reported [63, 64]. Tricuspid valve replacement is also an option [63, 65, 66]. In addition to tricuspid valve repair, a bi-directional Glenn operation may reduce the volume load to the right heart [67, 68]. Electrophysiological study and radiofrequency or surgical ablation may be indicated for patients with supraventricular tachycardia, which is most commonly atrial flutter/fibrillation or accessory pathway-mediated tachycardia [69].

Postoperative Care and Outcome

Neonates with Ebstein's anomaly who require early surgical intervention are at significant risk for developing a low cardiac output state, and a number of factors may be contributory [53, 57, 60]. In neonates with a ductus arteriosus or systemic to pulmonary shunt and tricuspid and pulmonary regurgitation, circular shunting may contribute to a low cardiac output state. A circular shunt implies the presence of aortic blood flowing through the ductus arteriosus or shunt, retrograde through the main pulmonary artery to the right ventricle and tricuspid valve, across the atrial communication and out the left ventricle and aorta, with resultant inadequate systemic blood flow (Fig. 21.10). Thus, blood may leave the aorta and return to the aorta without crossing a capillary bed, creating a significant volume load and systemic steal [59]. In this situation, an emergent reoperation may be required to ligate the ductus arteriosus, limit the shunt size, ligate the main pulmonary artery or reduce tricuspid regurgitation with a valvuloplasty [59]. Although the lungs may appear small on CXR, judicious airway pressures should be used and excessive mean airway pressures avoided, as overdistension of the lungs may increase pulmonary vascular resistance and limit left ventricular preload. Supraventricular tachycardia (usual mechanism is atrioventricular reentry) may cause a severe low cardiac output state, and early radiofrequency ablation may be necessary if medical control is unsuccessful.

In general, good outcomes are achieved for neonates with Ebstein's disease who do not require early intervention, intermediate outcomes for those in whom only a systemic to pulmonary shunt is performed, and suboptimal outcomes

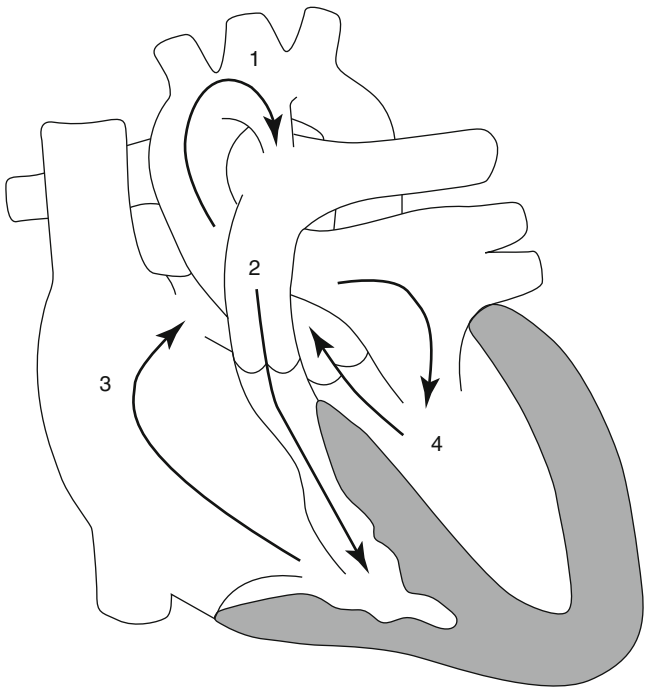


Fig. 21.10 Line diagram depicting the "circular shunt" in Ebstein's anomaly of the tricuspid valve with pulmonary insufficiency. There is ineffective blood flow from the aorta to the aorta (*1*), without traversing a capillary bed. This occurs through the patent ductus arteriosus to the pulmonary artery (*2*) to the right ventricle through pulmonary insufficiency to the right atrium through the regurgitant tricuspid valve across the foramen ovale (*3*) to the left atrium and the left ventricle (*4*) and return to the aorta (*1*) (Reprinted from Wald et al. [59]. With permission from Elsevier)

(mortality approaching 50 %) for patients undergoing tricuspid valve repair or closure (right ventricular exclusion) [70]. In a single-center series of 49 neonates diagnosed with Ebstein's disease or dysplasia of the tricuspid valve, surgical interventions were performed in 13 and transcatheter balloon dilation of the pulmonary valve in 3 (2 of whom subsequently required surgery) [58]. Of these 49 neonates, 71 % survived to hospital discharge, and of the 14 neonates who underwent surgical or transcatheter intervention, 6 (43 %) survived. Only one of six neonates who required extracorporeal membrane oxygenation support in this series survived [58]. In one report, a conservative management strategy that recognized the potential pitfalls of prolonged ductal patency and the potential for circular shunting was associated with an overall neonatal mortality rate of 7 % [59].

Postoperative issues following a tricuspid valve repair or replacement for older children with Ebstein's anomaly include low cardiac output related to the inability of the right ventricle to provide adequate preload to the left heart, myocardial ischemia due to kinking of the right coronary artery during plication annuloplasty procedures, right ventricular systolic and diastolic myocardial dysfunction and arrhythmias [63]. Early postoperative treatment strategies therefore include maintenance of adequate preload to both ventricles (using an atrial fenestration if needed), judicious use of inotropes and maintenance of low afterload to the right ventricle. Surgical mortality is less than 5 % in experienced centers in the current era [63, 64].

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Cyanotic Lesions with Increased Pulmonary Blood Flow

22

Nazima Pathan and Duncan J. Macrae

Abstract

Cyanosis may present in neonates for a number of reasons including pulmonary and cardiac. Cardiac cases of cyanosis are often due to inadequate flow of blood to the lungs, however in some cases, there may be unrestricted and/or increased pulmonary blood flow in the presence of cyanosis. Lesions where pulmonary flow is increased in the presence of cyanosis include Transposition of the great arteries, Truncus arteriosus, Total Anomalous Pulmonary Venous Connections, and single ventricle lesions without obstruction to pulmonary vascular flow. In such cases, early recognition and management are of great importance to prevent long term damage to the pulmonary vasculature. This review describes the anatomy, pathophysiology and clinical management of such cases.

Keywords

Cyanosis • Pulmonary blood flow • Transposition of the great arteries • Truncus arteriosus • Total anomalous pulmonary venous connections

Introduction

Cyanosis is clinically defined as an excess of deoxygenated hemoglobin (at least 3 g/dL) in the circulation, and presents with bluish discoloration of skin, nail beds and mucous membranes. The physical signs of cyanosis typically occur when systemic saturations fall to 80–85 %. The development of cyanosis will also depend on factors affecting the hemoglobin-oxygen dissociation curve, such as the hemoglobin concentration, blood pH, pCO2 levels, temperature, the ratio of adult to fetal hemoglobin and levels of 2,3 diphosphoglycerate. While cardiac causes of cyanosis are often due to inadequate flow of blood to the lungs (as in Tetralogy of Fallot or critical pulmonary stenosis), it may also occur when there is inappropriate mixing of systemic and pulmonary blood. If systemic venous return is pumped back into the aorta, mixing of deoxygenated and oxygenated blood (a right to left shunt) reduces blood oxygen saturation in the systemic circulation, and reduces the *effective* pulmonary blood flow (the volume of deoxygenated blood entering the lungs). In some lesions, oxygenated blood may also be pathologically pumped back into the lungs as well as into the systemic circulation (increasing the proportion of *ineffective* pulmonary blood flow). Here the total volume of blood flowing to the lungs is increased, and yet there is a reduction in effective pulmonary blood flow and the child develops cyanosis. Lesions where pulmonary flow is increased in the presence of cyanosis include Transposition of the great arteries, Truncus arteriosus, Total Anomalous Pulmonary Venous Connections, and single ventricle lesions without obstruction to pulmonary vascular flow.

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The severity of cyanosis in these children will be dependent on pulmonary vascular resistance. In the early postnatal period, a temporarily raised pulmonary pressure may result in reduced pulmonary blood flow and cyanosis will be prominent. As pulmonary vascular resistance normally falls a few days after birth, there is some improvement in cyanosis, though due to the mixing effect of the lesion some desaturation persists. Eventually, the excessive pulmonary vascular flow will result in pulmonary hypertension and congestive cardiac failure.

Transposition of the Great Arteries

Transposition of the great arteries (TGA) is the most common cyanotic congenital lesion in neonates (Tetralogy of Fallot is the most common cyanotic congenital heart lesion overall), comprising 5 % of all congenital heart defects and 10 % of all neonatal cyanotic lesions. The reported incidence is between 20 and 30 per 100,000 live births.

Anatomy

TGA is defined by the discordant origin of the arterial trunks from the ventricles, so that the pulmonary artery arises from the anatomic left ventricle and the aorta from the anatomic right ventricle. Figure 22.1 illustrates the anatomy of TGA. In the absence of associated shunts such as an ASD, VSD, or PDA, the systemic and pulmonary circulations would exist in parallel rather than in series, and the condition would be rapidly fatal. This defect is distinct from congenitally corrected TGA where both the atrio-ventricular and ventriculo-arterial connections are discordant. Further qualification of TGA type includes the 'simple' versus 'complex' transposition. A simple transposition is defined by VA discordance in the absence of associated malformations. Complex TGA may be complicated by hemodynamically significant ventricular septal defect (VSD), obstruction to Left Ventricular Outflow tract (LVOT) flow (e.g., Coarctation or interrupted arch), Obstruction to Pulmonary blood flow, and Coronary artery abnormalities.

An associated anterior malaligned VSD may be associated with override of the pulmonary outflow tract over the right ventricle, up to the degree of a double outlet right ventricle physiology with subpulmonary septal defect. In addition, anterior malalignment is associated with subaortic stenosis and may commonly co-exist with obstruction to LV outflow (aortic arch hypoplasia, coarctation or interrupted aortic arch). This may have serious consequences due to further restriction of oxygenated blood to the systemic circulation and may influence the operative plan and outcome.

Obstruction to pulmonary blood flow is more common in TGA with VSD (particularly a posteriorly maligned outlet VSD), which may be associated with subpulmonary stenosis, annular hypoplasia and pulmonary valve atresia. Coronary artery arrangements are abnormal in up to 33 % of TGA cases. The origin and course must be defined. In addition to variability of proximal origin, the distal course and distribution of each of the coronary artery branches may be abnormal and may include an intramural course. Less common associated malformations in children with TGA, include left juxtaposition of the atrial appendages (often associated with RV hypoplasia) and common AV canal (a rare occurrence, which may be associated with visceral heterotaxy or atrial appendage isomerism).

Pathophysiology

In TGA the systemic and pulmonary circulations are in parallel rather than in series, so that the systemic blood flow will remain unoxygenated since pulmonary venous return is not delivered to the body. Survival is dependent on the presence of an inter-circulatory shunt. Initially the ductus arteriosus and foramen ovale (or associated ASD or VSD) may allow mixing and sustain systemic oxygenation. However, eventually the unrestricted pulmonary blood flow will, even in these cases, lead to pulmonary overcirculation and hypertension unless surgical correction is undertaken.

Clinical Presentation and Diagnosis

Antenatally there is usually an uncomplicated obstetric course. Some babies may be severely cyanosed at birth, particularly those with restrictive flow across the atrial foramen ovale, and/or where pulmonary vascular resistance is elevated. There may be prenatal cerebral hypoxia, as oxygenated blood is preferentially streamed into the lower body rather than into the brain. Magnetic Resonance (MR) spectroscopy demonstrates alterations in parietal white matter, suggesting a maturational (*in utero*) rather than a post-natal insult.

Antenatal diagnosis enables early transfer to a cardiac surgical center, improved pre-operative stabilization and better surgical outcome [1]. However, overall antenatal detection rates remain relatively low (around 20 % in many first world centers), but is improved in centers where sonographers are trained in two-outlet echocardiography views in addition to the four chamber view which may appear normal.

Neonates with previously undiagnosed TGA may present with increasing cyanosis and metabolic acidosis, and in need of resuscitation, at day 2–3 of life as the ductus arteriosus begins to close. High pre-operative lactate is an important predictor of adverse neurological outcome, underpinning the importance of early diagnosis and resuscitation.

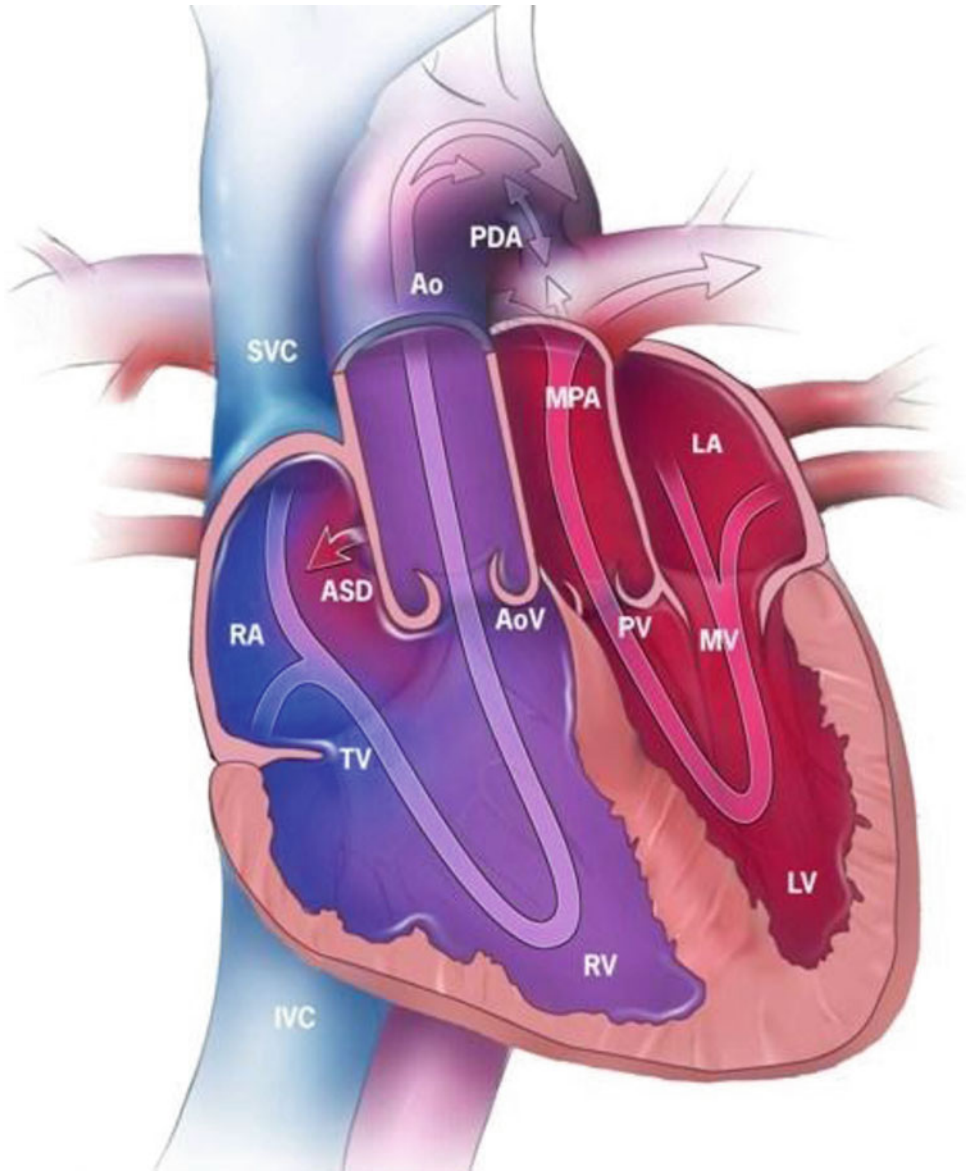


Fig. 22.1 Anatomy of Transposition of the Great Arteries. Deoxygenated blood from the systemic venous return enters the right heart. Since the aorta arises inappropriately from the right ventricle, the blood entering the systemic circulation fails to pass through the pulmonary circulation. Oxygenated blood arriving from the lungs returns to the pulmonary bed via the pulmonary artery which arises from the left ventricle. The circulations therefore exist in parallel and are dependent on shunts (not shown) to maintain some mixing of oxygenated and deoxygenated blood and allow oxygenated blood to enter the systemic circulation, such as a patent ductus arteriosus, patent foramen ovale or ventricular septal defect). *RA* right atrium, *RV* right ventricle, *LA* left atrium, *LV* left ventricle, *SVC* superior vena cava, *IVC* inferior vena cava, *MPA* main pulmonary artery, *Ao* aorta, *TV* tricuspid valve, *MV* mitral valve, *AoV* aortic valve, *ASD* atrial septal defect, *PDA* patent ductus arteriosis (Reprinted from Centers for Disease Control and Prevention [31])

While cross sectional echocardiography may quickly diagnose the presence of d-TGA in a newborn, coronary arterial anatomy is less easily defined, but is important to address to prepare for the increased risk of a more complicated surgical repair and adverse post-operative outcome. In addition, assessment should include the presence and nature of any VSD's, the quality and size of the aortic arch and the nature of the pulmonary valve (which will become the systemic neoaortic valve following the arterial switch procedure).

Pre-operative Care

In most cases, current treatment for a neonate with a diagnosis of TGA involves treatment with intravenous prostaglandins from birth to maintain the patency of the ductus arteriosus. The neonate should be transferred early to a cardiac surgical center. In cases of profound hypoxia or acidosis, atrial septostomy may be required [2]. However some neonates may suffer from pulmonary hypertension of the

newborn. In this case, severe cyanosis may develop due to inadequate pulmonary blood flow despite atrial septostomy and/or maintenance of ductal patency. In these cases the use of pulmonary vasodilator therapy such as inhaled nitric oxide may be indicated until pulmonary vascular resistance falls.

Surgical Intervention

The arterial switch operation, first successfully undertaken by Jatene et al. [3] and modified by Lecompte [4] replaced the previous atrial baffle procedures introduced by Mustard [5] and Senning [6]. While these latter operations had relatively good initial outcome, long term morbidity including right ventricular failure, atrial rhythm disturbances and sudden death resulted in a 20 % mortality by the age of 18 years in those who survived the operation.

The arterial switch procedure includes closure of septal defects, division of the PDA, transfer of the coronary arteries and then transfer of the aorta and pulmonary arteries to the left and right ventricles respectively. With improvements in surgical techniques, anesthesia and bypass techniques and post-operative care (including delayed sternal closure where necessary, the use of inodilators such as milrinone, and the availability of extracorporeal support) mortality is now low (<3 %, lower for simple TGA). Better operative outcomes are achieved if surgery is undertaken when the pulmonary vascular resistance has fallen (generally by day 7 or 8 of life) [7], using prostaglandin infusion to maintain the ductal patency or where necessary a BAS to maintain oxygenation and hemodynamic stability until surgical repair.

Some children may not present until a few weeks after delivery. In such cases, where the pulmonary pressures have dropped, the left ventricle will have decompressed and may not be in good enough condition to pump against the higher systemic vascular resistance. In these cases, there may be a less straightforward post-operative course, though most centers still undertake an ASO until 2–3 months of age. Alongside BAS, some surgeons may opt to precondition the LV and improve LV muscle mass by placing a pulmonary artery band as an interim measure, but there is an increased risk of aortic regurgitation [8].

Infants with TGA born prematurely or with low body weight (<2 kg) present a challenge due to the increased difficulty of repair and poorer tolerance of cardiopulmonary bypass. With improved surgical training, many centers report good outcomes of early repair in this group of children, though others opt to delay surgery by maintaining duct patency and waiting for increased body weight. However some reports suggest that mortality during the growth phase is a greater risk than in the case of early repair [9, 10].

Another important operative consideration is the anatomy of the coronary arteries. Atypical arrangement may lead to increased risk of kinking or torsion following transfer to the neo-aorta. Careful pre-operative assessment and mobilization of the coronary buttons before insertion into the neo-aorta is now commonly achieved without complication, but a high degree of attention to the development of myocardial ischemia must be maintained in those individuals with abnormal coronary arrangement. Since ST elevation and raised plasma markers of myocardial injury (BNP and cardiac Troponin I) are commonly elevated post-operatively, specific indication of ischemia is difficult to define. Some markers that should raises suspicion include high left atrial pressure, increased arterial-venous oxygenation difference (over 30–40 %), and evidence of poorly contracting and stiff ventricles. In these cases, re-exploration and coronary repair should be considered.

Post-operative Care

Most patients have an uncomplicated recovery from the arterial switch operation. Use of inodilators such as milrinone have improved outcome [11]. Complications include those associated with cardiac bypass procedures such as systemic inflammatory activation, low cardiac output state and capillary leak [12]. Support with low dose inotropic medication and/or the use of judicious fluid boluses may be needed. Careful assessment for coronary insufficiency is needed. Where surgery is prolonged or where the lesion has associated complications delayed sternal closure may be indicated to allow time for tissue edema to settle and myocardial function to recover.

Complications

Long term outcomes following ASO are good. Mortality is higher in those with complex TGA [13]. Some centers report close to 100 % survival at 5 years for simple TGA, around 96 % for complex TGA. Aside from the early post-operative complications described above, a number of late complications that may need further intervention are recognized.

Rhythm disturbances that may continue for some time after TGA repair include AV block, SVT and VT, with increased risk in those babies with associated VSD [14]. Stenosis of the branch pulmonary arteries is seen in up to 30 % of survivors following the arterial switch operation. Careful PA reconstruction to avoid pulling forwards and stretching of the pulmonary artery over the aortic root during repair may reduce this risk. In cases of significant stenosis, balloon dilatation or stenting of the pulmonary arteries may be required [15].

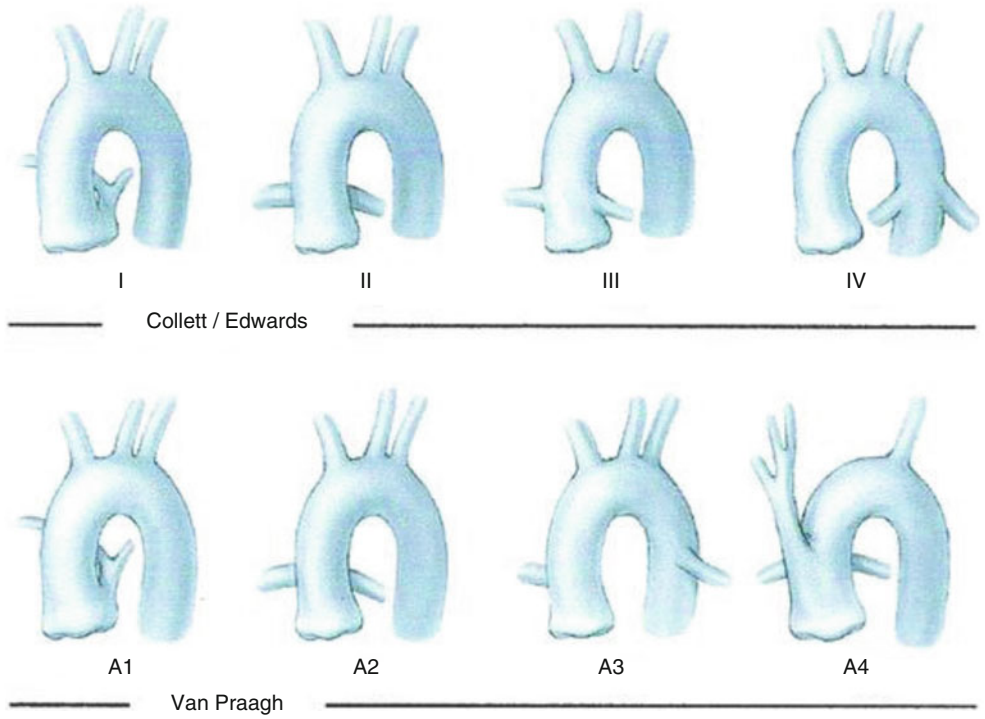


Fig. 22.2 Anatomical arrangements in Truncus arteriosus. The classification of TA based on Collet and Edwards (*top row*) and Van Pragh and Van Pragh (*bottom row*) are shown (Reprinted from Louis [32]. With permission from Springer Science + Business Media)

Significant coronary abnormalities are reported in around 10 % of patients following the arterial switch procedure. Evaluation of coronary ischemia may be difficult in the long term. Due to denervation of the heart during the procedure, angina pain is not felt, and patients may present with pallor, sweating, reduced exercise tolerance and sudden death. The position and shape of the aortic sinuses may be sub-optimal due to dilatation of the neo-aortic root following surgery. This may adversely affect coronary diastolic flow and reduce coronary flow reserve. Exercise stress testing is generally undertaken post-operatively in early teenage years to screen for coronary artery insufficiency, with additional imaging by MRI, CT or coronary angiography where indicated to inform clinicians of the need for further intervention.

The risks of surgery and bypass on the developing neonatal brain are of increasing clinical interest. While major neurological abnormalities are uncommon, developmental delay, attention disorder and IQ are thought to be affected in children undergoing neonatal surgery for this and other congenital cardiac lesions, particularly where the intra- and post-operative course is prolonged [16].

Truncus Arteriosus

Truncus arteriosus is an uncommon lesion, accounting for under 3 % of all congenital heart lesions.

Anatomy

The lesion is defined by failure of early embryologic common arterial trunk to separate into aorta and pulmonary arteries. It is associated with a ventricular septal defect just below the large semilunar truncal valve. This valve may have between two and six leaflets and typically functions very well, but the arising truncal artery supplies the pulmonary, systemic, and coronary circulations. The artery separates into pulmonary artery and aorta a short distance above the valve, though the pattern may vary, as shown in Fig. 22.2.

A classification proposed by Collett and Edwards in 1949 [17] is based on the nature of origin of the pulmonary artery from the common arterial trunk.

Type I: The PA arises almost immediately as the truncal artery emerges from the common semilunar valve, with the ductal portion continuing to form the aorta.

Type II: The left and right pulmonary arteries arise separately from the posterior wall of the truncal artery.

Type III: This is similar to type II although the origins of the two pulmonary arteries are further apart.

Type IV: There is no pulmonary artery, instead the blood supply to the lungs is via collateral arteries. It is argued that this type should not be classified as a truncal lesion and is more in line with a pulmonary atresia with ventricular septal defect.

An alternative classification system was proposed by Van Pragh and Van Pragh in 1965 [18]. This is based on the nature of the conotruncal septum.

Type A1: The truncal septum is partially developed so pulmonary artery and aorta co-exist.

Type A2: There is no truncal septum so that left and right pulmonary arteries arise separately from the truncal artery.

Type A3: One of the pulmonary arteries is absent from the truncal artery.

Type A4: The truncus arteriosus is associated with an interrupted aortic arch.

More recently, Russell et al. have proposed a simplified categorization based on whether the common arterial trunk has aortic or pulmonary dominance, based on analysis of autopsy specimens from individuals with a diagnosis of truncus arteriosus [19]. The lesion may be Pulmonary or Aortic dominant. In Pulmonary dominance, the common trunk trifurcates into right and left branch pulmonary arteries, with ductal continuation to the descending aorta. The ascending aorta may emerge from common trunk as a side branch. In addition the aortic arch may be interrupted or hypoplastic. In Aortic dominance, the common trunk resembles an ascending aorta continuing on to a normal aortic arch. The branch pulmonary arteries emerge from the left posterior aspect of the trunk. The pulmonary artery origins may be adjacent to one another, or one pulmonary artery may arise via the arterial duct. In some cases, a sinusal origin of the pulmonary arteries is observed, and very rarely a balanced pattern of origin is observed.

Associated Lesions

A number of associated lesions may co-exist that affect the prognosis and surgical plan. These include interventricular communication, truncal valvar override and origin of the truncal artery (which may be balanced or arise exclusively from either the right or the left ventricle). There may be variation in the truncal valve, including the number of leaflets (ranging from 2 to 5 or more), and degree of stenosis or insufficiency (mild, moderate or severe). In some cases, the right and left pulmonary arteries may cross over each other.

Pathophysiology

The right and left ventricles become pressure and volume overloaded, particularly where the truncal valve is stenotic or regurgitant. The low pressure in the pulmonary circulation leads to excessive runoff of cardiac output into the lung and reduced systemic flow, compromising blood supply to vital organs including the heart, gut and brain.

The defect is commonly associated with chromosomal microdeletion at 22q11 (Di George syndrome), where there is often associated T lymphopenia and immune paresis [20]. Children with this genetic defect appear to be at greater risk of adverse outcome.

Clinical Presentation

Initially the newborn with Truncus Arteriosus may not be symptomatic due to elevated pulmonary vascular resistance. As this pressure drops, and pulmonary flow increases, clinical presentation with features of congestive heart failure are seen. These include tachypnea, tachycardia, poor feeding and sweating. Cyanosis may be minimal unless there is stenosis of the pulmonary valve.

Pre-operative Care

Some degree of stabilization is needed prior to surgery, including management of heart failure, and assessments of the pulmonary vascular resistance and the nature of the truncal valve, along with associated anomalies. Chromosomal evaluation should be undertaken since children with DiGeorge syndrome will require blood products to be irradiated to reduce the risk of Graft versus Host disease following transfusion.

Surgical Intervention

Complete surgical correction is generally undertaken in the first few weeks of life [21]. The pulmonary arteries are removed from the vessel to leave the truncal vessel as a 'neo-aorta'. A valved conduit is placed to supply the pulmonary arteries from the right ventricle and the VSD is closed [22].

Post-operative Care

The main issues facing the critical care clinician include management of post-operative pulmonary hypertension and low cardiac output state. Delayed sternal closure may be employed to allow time for tissue edema to settle. If there are intra-operative concerns about pulmonary hypertension, the surgeon may leave a small intra-atrial communication to decompress the right ventricle. This may result in cyanosis due to right to left shunting and must be differentiated from pulmonary causes of cyanosis post-operatively. Post-operative arrhythmias that may be seen include right bundle branch block, heart block and junctional arrhythmias.

Prognosis

The mortality risk is 10 % if the truncal valve is functionally normal with good long term results, although the valved conduit may require upsizing as the child grows. The risk of adverse outcome is increased if there are associated anomalies such as interrupted aortic arch or if there is post operative pulmonary or truncal valve regurgitation [23]. Long term survival and functional status are generally very good in infants undergoing repair of truncus arteriosus [24, 25].

Total Anomalous Pulmonary Venous Connections (TAPVC)

TAPVC is rare, accounting for 2–3 % of congenital cardiac defects.

Anatomy

In total anomalous pulmonary venous drainage, oxygenated blood from the pulmonary veins drains into the systemic circulation rather than into the left atrium [26]. The connections are most often with the left innominate vein, superior vena cava, coronary sinus or portal vein, and occasionally the pulmonary veins drain directly into the right atrium. From here blood flows either back into the lungs (via the right atrio-ventricular valve and the right ventricle) or into the systemic circulation (via the foramen ovale). The mixing of oxygenated and deoxygenated blood leads to cyanosis.

Classification is based on the location to which the pulmonary veins drain, which may be supradiaphragmatic (supra-cardiac), intra-cardiac or infra-diaphragmatic (infra-cardiac), and if there is a degree of pulmonary vein stenosis, there may be obstruction to pulmonary venous return and pulmonary venous hypertension. In supracardiac TAPVC, the four pulmonary veins drain via a common vein into the right superior vena cava, left superior vena cava, or their tributaries. In intra-cardiac TAPVC, the pulmonary veins connect directly to the right heart (such as to the coronary sinus to the right atrium). In infradiaphragmatic TAPVC, the common pulmonary vein travels inferiorly through the diaphragm, and connects to the systemic circulation at the level of the portal venous system. In some cases, there may be mixed connections, where the right and left pulmonary veins drain to different sites (e.g., left pulmonary veins into the left vertical vein to the left innominate, right pulmonary veins directly into the right atrium or coronary sinus). Classification of TAPVC is illustrated in Fig. 22.3.

Pathophysiology

As a result of the mixture of pulmonary and systemic venous flow, right atrial and right ventricular volume loading develops in children with TAPVC. Most patients with isolated total anomalous pulmonary venous connection have a patent foramen ovale with some degree of restriction to trans-atrial flow. In the absence of pulmonary venous obstruction, a three to five fold increase in pulmonary blood flow is seen in early infancy. As a result, systemic arterial oxygen saturations may be as high as 90 %, although right heart volume load or right heart failure soon becomes evident. If the foramen ovale is restrictive, right atrial pressure elevates, resulting in pulmonary venous congestion, increased pulmonary blood flow and pulmonary arterial hypertension. If obstruction of pulmonary venous flow is present due to pulmonary venous stenosis, then pulmonary venous congestion occurs. Reflex pulmonary arterial vasoconstriction may also occur. Here an increase in pulmonary vascular resistance leads to a decrease in pulmonary blood flow and systemic desaturation.

Clinical Presentation

In non obstructive TAPVC, infants may present with symptoms of congestive cardiac failure at around 4–6 weeks of life with poor feeding, tachypnea and tachycardia. In contrast, where the TAPVC drainage is obstructed, babies will present within the first few days of life with cyanosis and heart failure due to pulmonary venous congestion.

Pre-operative Care

Babies with TAPVC will need stabilization and treatment of heart failure. Where cardiac function is impaired, inotropic support may be needed. If there is a restrictive PFO, systemic flow may be compromised and balloon atrial septostomy undertaken, although in most cases a full surgical repair is performed. In obstructed TAPVC, prostaglandin E1 infusion may help to decompress the pulmonary circuit and may open the ductus venosus, helping to decompress the pulmonary circulation and reduce pulmonary venous obstruction.

Surgical Intervention

Obstructed TAPVC is a surgical emergency to establish flow of oxygenated blood from pulmonary veins, into the left atrium and thence to the systemic circulation. In unobstructed TAPVC, surgery is performed once the child is clinically stable, within the first month of life. Surgical repair is achieved by anastomosis of the pulmonary venous confluence with the

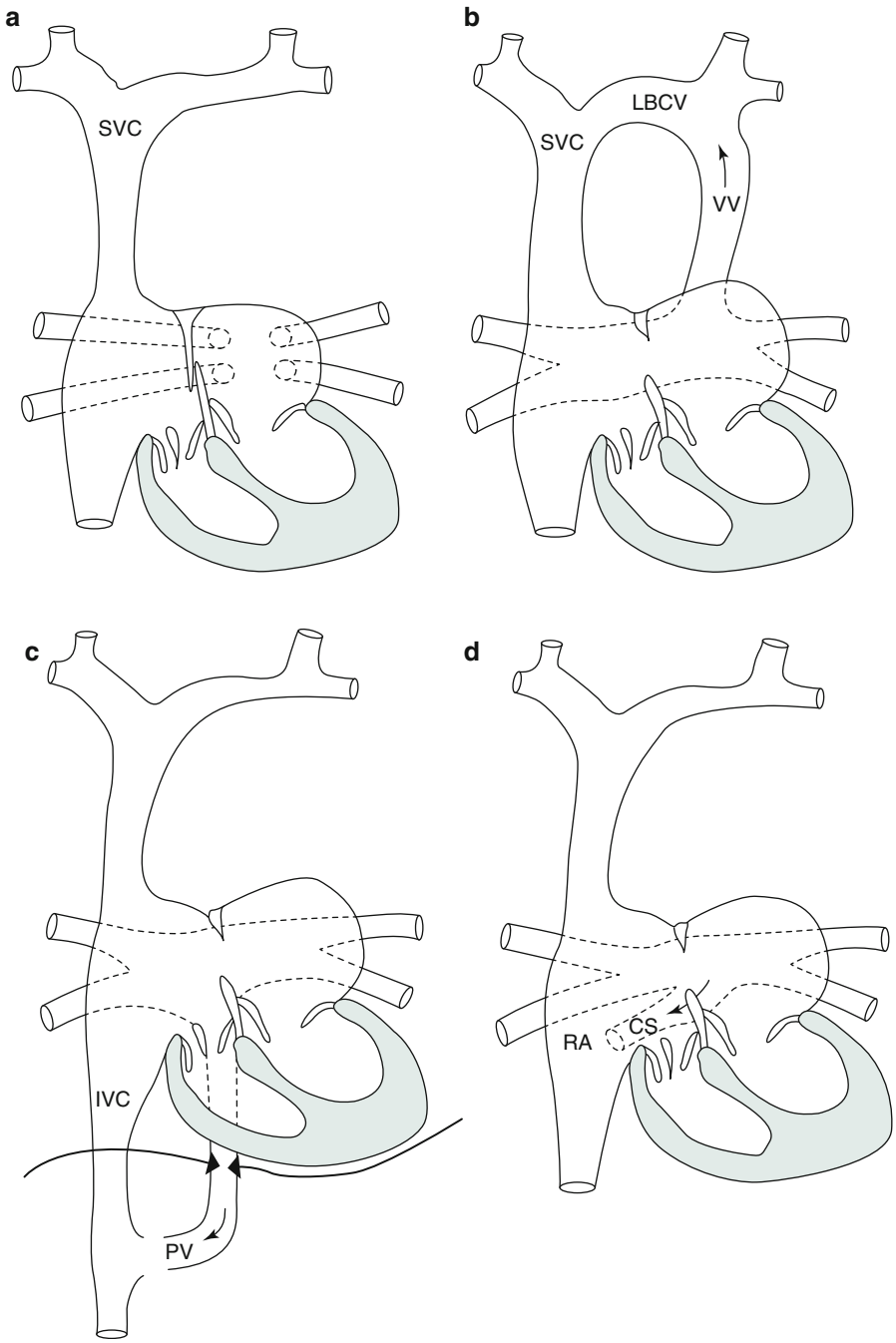


Fig. 22.3 Types of total anomalous pulmonary venous connection (TAPVC). Diagram of the various anatomical levels of anastomosis of the venous confluence in total anomalous pulmonary venous connection (TAPVC). (**a**) Normal, (**b**) Supracardiac, (**c**) Infracardiac and (**d**) Cardiac (see text). Superior vena cava (*SVC*), vertical vein (*VV*), left brachiocephalic vein (*LBCV*), inferior vena cava (*IVC*), portal vein (*PV*), right atrium (*RA*), coronary sinus (*CS*) (Reprinted from Kastler [33]. With permission from Springer Science+Business Media)

left atrium. Repair is often undertaken using bicaval cannulation and low flow hypothermic perfusion to avoid prolonged circulatory arrest [27]. The use of sutureless techniques for the repair of pulmonary vein stenosis appear to have good outcomes compared to previous methods. By suturing the left atrium or atrial appendage to the pericardium surrounding the pulmonary venous confluence, it avoids suturing and distortion of the pulmonary veins with a reduced risk of post-operative pulmonary venous obstruction [28, 29].

Post-operative Care

Monitoring of pulmonary pressures is an important part of post-operative care, since pulmonary hypertension is a risk in the post-operative period, especially in cases of obstructed TAPVC [30]. Monitoring with intra-pulmonary artery catheters in such cases will help guide therapy. Measures to reduce pulmonary pressures may include sedation, adequate oxygenation, and maintenance of low-normal pCO2 levels

(respiratory alkalosis) through hyperventilation. Additionally inhaled nitric oxide and ECMO may be required in resistant cases. Having been underfilled pre-operatively, a restrictive pattern in the left ventricle stroke volume may be a problem, which may benefit from use of intravenous inodilators such as milrinone and delayed sternal closure may be indicated. The left sided structures may be relatively small and sensitive to volume boluses which should be given judiciously with monitoring of left atrial pressures.

Prognosis

With earlier diagnosis and improvements in peri-operative care, outcomes have improved in the last few years with mortality rates less than 10 % reported (in case series including obstructed TAPVC) compared to early surgical mortality rates of up to 25 %.

In children with TAPVC and an associated single ventricular physiology, the mortality rates remain high. Mortality of over 60 % by 1 year has been reported and late pulmonary venous obstruction is also a significant morbidity risk, seen in over 50 % of survivors.

Lesions with Physiology of Single Ventricle and Unobstructed Pulmonary Blood Flow

In infants with single ventricle physiology, the work of balancing pulmonary and systemic circulations may be profoundly impacted by obstruction to systemic flow, for example mitral or aortic valve stenosis/atresia in the setting of a functionally univentricular heart (Double inlet left ventricle, hypoplastic left heart for example). In these cases, due to mixing of pulmonary and systemic inflow, there is cyanosis, but outflow is largely directed to the pulmonary circulation. Early intervention to protect the pulmonary vasculature is important in order to enable palliation or reconstruction and future establishment of a Fontan circulation. The medical and surgical plan will be dependent on the lesion but will usually involve a three-staged approach. In the first few days of life, and depending on the individual lesion, surgeons may with placement of a shunt to establish unobstructed flow between the single ventricle and the aorta to improve systemic blood supply. Regulation of pulmonary blood flow by placement of a band across the pulmonary artery may be necessary. The later stages involve diverting pulmonary venous return into the lungs via the caval circulation, initially a superior vena Cavopulmonary anastomosis (Glenn shunt) and later routing of inferior vena caval supply to the pulmonary arteries (Fontan circulation) to allow the univentricular heart to solely supply the systemic circulation. Outcomes of these operations have improved over the last few years, and are discussed in more detail in the relevant chapters elsewhere in this book.

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Congenital Heart Disease: Left Ventricular Outflow Tract Obstruction

23

John R. Charpie, Dennis C. Crowley, and Ranjit Aiyagari

Abstract

Left ventricular outflow tract obstruction represents a wide spectrum of disease, including subvalvar aortic stenosis, valvar aortic stenosis, supravalvar aortic stenosis, coarctation of the aorta, and interrupted aortic arch. In some cases, these disorders may manifest in the fetal and early neonatal period, requiring early medical management or urgent surgical or catheter-based intervention. Patients presenting later often have chronic left ventricular pressure overload, compensatory hypertrophy with altered ventricular diastolic properties, and arterial hypertension. Most of these conditions are easily diagnosed by physical examination, electrocardiography, chest radiography, and two-dimensional echocardiography with Doppler. Diagnostic catheterization may be helpful if the diagnosis is in question, for precise determination of pressure gradients, or for providing further anatomic detail via angiography. The threshold for invasive therapy varies with the location of the obstruction and its natural history. Catheter-based intervention is commonly utilized for valvar aortic stenosis and coarctation, with success rates varying based on disease type and location. Surgical intervention is indicated for interrupted aortic arch, certain types of valvar aortic stenosis and coarctation deemed not suitable for catheter-based intervention, and for subvalvar and supravalvar aortic stenosis of adequate severity. Lifelong follow-up is generally recommended, as recurrence requiring reintervention may occur.

Keywords

Aortic stenosis • Coarctation • LVOT obstruction

Valvar Aortic Stenosis

Isolated valvar aortic stenosis (AS) accounts for 3–6 % of all congenital heart disease [1]. This defect comprises a spectrum of aortic valve pathologies ranging from a bicuspid, or bicommissural, valve, which often has minimal hemodynamic significance, to less common abnormalities including fusion of all three leaflets (unicuspid, or unicommissural, valve) or myxomatous, thickened, dysplastic valve leaflets. Aortic annular hypoplasia may be more frequently associated with additional left- sided obstructive defects such as mitral valve disease, coarctation of the aorta and hypoplastic left heart syndrome.

Aortic valve abnormalities occur approximately four times more often in males than females, and associated cardiac anomalies are present in nearly 20 % of patients,

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including patent ductus arteriosus, coarctation of the aorta, and ventricular septal defects. Although familial cases have been described, there is no known genetic predisposition to valvar aortic stenosis, with the exception of monosomy X (Turner syndrome), which confers an elevated risk of AS.

Valvar AS is a progressive disease which results in obstruction to egress of blood from the heart, producing a pressure gradient from the left ventricle to ascending aorta. There is an obligatory increase in left ventricular pressure in order to maintain adequate systemic blood flow. Chronic pressure overload on the left ventricle will stimulate myocardial hypertrophy leading to altered diastolic properties of the ventricle and eventual elevation of the end-diastolic and left atrial pressures. Left ventricular systolic function and cardiac output are generally well maintained. Another consequence of significant left ventricular hypertrophy may be subendocardial ischemia that is usually manifest only during times of increased myocardial oxygen demand, as with exercise. Subendocardial ischemia may be a stimulus for ventricular tachyarrhythmias that can arise in this setting. Endocardial fibroelastosis (EFE), a condition observed in some infants, in particular those with *in utero* severe AS and chronic subendocardial ischemia, may impair both systolic and diastolic myocardial performance.

Clinical Presentation

The majority of children with valvar AS are asymptomatic with normal growth and development. The diagnosis is often made by detection of a murmur on routine physical examination. Symptoms, if present, are dependent on the severity of the lesion and the age of the patient. Older children may experience exercise intolerance and easy fatigability. Chest pain and syncope are much less common, but are generally considered more ominous signs related to more severe stenosis. Most significant is the small but finite risk of sudden death in patients with moderate or severe AS. In contrast to older children, infants and toddlers may exhibit tachypnea, tachycardia, poor feeding and delayed growth due to congestive heart failure. Infants with ductal-dependent ("critical") AS may present in frank cardiogenic shock following closure of the ductus arteriosus.

In many patients, classical cardiac exam findings confirm the diagnosis of valvar AS. Vital signs are usually normal, except for a decreased arterial pulse pressure with severe stenosis. Patients with significant hypertrophy may have a prominent left ventricular impulse, and most patients will have a suprasternal notch thrill, even with mild stenosis. Auscultation often reveals a systolic ejection click heard at the left lower sternal border or apex. However in severe AS, restricted mobility of the valve leaflets may preclude an audible ejection click. With progression of AS, left ventricular ejection may be prolonged causing abnormally delayed closure of the aortic valve after pulmonic closure resulting in paradoxical splitting of the second heart sound.

Valvar AS presents with a systolic ejection murmur that begins immediately following the ejection click and is often best heard at the right upper sternal border with radiation to the carotid vessels. The severity of the stenosis can be estimated by the intensity of the murmur. Murmurs of grade 2 or less are very rarely heard with severe obstruction, whereas a grade 4 murmur (with a thrill) is often associated with gradients of >50 mmHg [2]. It is important to note that this clinical correlation between intensity and severity assumes a normal cardiac output. Neonates and infants with severe AS and diminished ventricular function often have very soft murmurs due to the markedly diminished cardiac output. An early diastolic murmur of aortic insufficiency may be heard in some patients. Additionally, a fourth heart sound, representing decreased ventricular compliance, may be heard in occasional patients with severe AS.

The electrocardiogram (ECG) may be quite variable in patients with AS. Children and adults may demonstrate left ventricular hypertrophy on ECG, although the degree does not correlate with the severity of AS [3]. Left ventricular hypertrophy and inverted T waves in the lateral precordial leads (strain pattern) may be the most reliable index of severe AS. In contrast to older children and adults, infants with severe AS often exhibit right ventricular hypertrophy on ECG. The chest radiograph is generally normal in most patients with AS. Patients with severe AS, particularly infants, may exhibit cardiomegaly and increased pulmonary vascular markings consistent with congestive heart failure.

Two-dimensional echocardiography allows visualization of aortic valve size and morphology and demonstration of impaired valve leaflet mobility. The echocardiogram also permits assessment of the rest of the left ventricular outflow tract, the degree of left ventricular hypertrophy, and quantification of left ventricular function. Doppler interrogation across the aortic valve estimates the peak instantaneous pressure gradient from left ventricle to ascending aorta, using the simplified Bernoulli equation [gradient $= 4 \times (\text{velocity})^2$]. The Doppler-derived mean gradient across the aortic valve has been shown to correlate reasonably well with the peak systolic gradient measured at cardiac catheterization [4].

Cardiac catheterization remains the gold standard for determination of the degree of AS. However, due to advances in echocardiography, catheterization is rarely required for determination of valve gradients in isolated valvar AS, and is generally reserved for patients with associated lesions (e.g. multiple levels of left ventricular outflow obstruction), and for catheter-based intervention.

Management

Neonates and infants with severe AS and symptoms of congestive heart failure require intervention, regardless of the estimated gradient, because diminished ventricular function and

systemic blood flow may underestimate the true gradient across the aortic valve. Furthermore, these neonates often require initiation of prostaglandin E_1 (PGE_1) at 0.01–0.03 mcg/kg/min to maintain ductal patency and augment systemic blood flow while awaiting surgical or catheter-based palliation. Patients who present in cardiogenic shock from ductal closure generally require higher doses of PGE_1 at 0.05–0.1 mcg/kg/min to re-open the ductus arteriosus. Additional supportive measures, such as mechanical ventilation and inotropic support, are often beneficial to treat severe congestive heart failure in infancy.

Beyond infancy, treatment guidelines are individualized based on patient and physician preference. Generally, patients with trivial AS (gradient <25 mmHg) do not require intervention nor activity restrictions, although follow-up is recommended for possible progression. Mild AS (gradient of 25–49 mmHg) also generally does not require treatment in the absence of symptoms. Although recreational activities are not usually restricted, some clinicians would discourage participation in competitive athletics due to the possibility that the AS gradient might be worse with strenuous exercise. Most physicians would recommend intervention for patients with moderate AS (gradient of 50–75 mmHg), particularly in the presence of ECG changes or symptomatology at rest or with exercise. Severe AS (gradient >75 mmHg), even in the absence of symptoms, requires intervention due to a significant risk of arrhythmias and sudden death.

Balloon aortic valvuloplasty (BAV) was first introduced as a therapeutic option for valvar AS in the mid-1980s [5, 6]. In many congenital heart centers, BAV has now become the procedure of choice replacing open surgical valvotomy. Although BAV may be associated with severe arrhythmias, vascular complications, stroke and even death (particularly in patients with severe AS), registry data show that BAV compares favorably with surgical valvotomy [7]. Furthermore, as catheter technology continues to advance with the introduction of lower profile balloons, the incidence of vascular complications, even in neonates, is improving. The hemodynamic result achieved by BAV appears to be no different from surgery [8, 9], with a similar reduction in valve gradient. However, aortic insufficiency remains a potential complication of the procedure, with some series describing at least moderate insufficiency following BAV in 10 % of patients [10]. Furthermore, despite adequate reduction in the AS gradient following successful valvuloplasty, progression of the disease is highly likely and thus BAV is generally considered a palliative and not a curative procedure. Consistent with this, freedom from reintervention after BAV for congenital AS is 72 % at 5 years, 54 % at 10 years, and only 27 % at 20 years. Open surgical valvotomy consists of a commissurotomy of the valve leaflets performed on cardiopulmonary bypass. This surgical approach has been shown to be effective at relieving the valve gradient in nearly all patients [11], although AS may still progress with time. Similar to BAV, valvotomy also may be associated with progressive aortic insufficiency.

For patients in whom BAV has failed to relieve the gradient, or in patients with significant residual aortic insufficiency, replacement of the aortic valve may be the only option. Traditionally, aortic valve replacement has consisted of placing a mechanical prosthesis in the aortic valve position. These mechanical valves have been shown to have excellent long term durability. However, they carry a significant risk of thromboembolic complications, necessitating life-long anticoagulation (generally with warfarin) and the attendant bleeding risks. Anticoagulation with warfarin is also contraindicated in patients who become pregnant, necessitating transition to other agents such as low molecular weight heparin. Furthermore, mechanical valves are not manufactured in small sizes and have no potential for growth, making them a less desirable option for young children.

Aortic valve replacement using the native pulmonary valve in the aortic position (autograft) with homograft replacement of the pulmonary valve has been advocated as a viable surgical option for aortic valve disease in children [12]. This procedure enjoys the dual benefits of avoiding the need for anticoagulation and allowing for native growth of the autograft, with the trade-off of having to replace the pulmonary valve. While impressive early surgical results have been reported in young children and adolescents [13], mid-term results suggest that reintervention is required in 25 % of patients at 6.5 years follow-up, both for right and left ventricular outflow tract procedures [14]. More long-term data is required to establish the role of this procedure as a primary treatment strategy for AS in infants and children.

Tissue valves (bioprostheses) provide an additional replacement option that generally does not requiring anticoagulation. However, bioprosthetic valves have no or limited growth potential and their long-term durability are also limited, especially during adolescence, often necessitating replacement within a decade.

Postoperative Management

The postoperative course for patients following either surgical aortic valvuloplasty or valve replacement is generally uneventful and patients are often extubated within 24 h. Rarely, patients can return from the operating room in low cardiac output. It is important to re-evaluate these patients for significant residual aortic stenosis and/or new aortic insufficiency, and exclude any additional levels of left ventricular outflow obstruction that may not have been recognized preoperatively, such as aortic coarctation or significant subaortic stenosis. In the absence of significant residual or unrecognized heart disease, patients may benefit from low-dose inotropic support with β adrenergic agonists. In addition, with significant left ventricular hypertrophy, cardiac output may be preload-dependent and responsive to intravascular volume repletion. Postoperative hypertension is

frequently observed, and these patients may benefit from β adrenergic antagonists that slow the heart rate (allowing time for adequate ventricular filling) and simultaneously decrease afterload on the ventricle. Afterload reduction may also be an important adjunctive therapy if there is any residual or new aortic insufficiency.

For patients with mechanical valves in the aortic position, heparin infusion may be delayed for 36–48 h due to bleeding risk. Anticoagulation with warfarin is generally started when the patient begins feedings.

Coarctation of the Aorta

Coarctation of the Aorta (CoA) is a common congenital heart defect which may be isolated, but it is frequently associated with bicuspid aortic valve (80 %), and with a variety of other lesions such as ventricular septal defect and multiple left heart abnormalities. In isolated CoA, the obstruction is usually fairly discrete and is located just opposite the patent ductus arteriosus (juxtaductal). There is usually some degree of transverse arch or isthmus hypoplasia that may be significant. Rarely, CoA is located in the abdominal aorta near the renal arteries.

The pathophysiology of CoA depends on age and severity. In the infant with severe CoA, there is an abrupt increase in left heart afterload following ductal closure leading to left ventricular (LV) failure. If the narrowing is less severe or if ductal closure is incomplete, there is a gradual increase in afterload with compensatory LV hypertrophy, and activation of the renin-angiotensin system leading to upper body hypertension.

Clinical Presentation

Clinical presentation is variable. Symptoms in infancy often include poor feeding, tachypnea, and other signs of congestive heart failure (CHF). Neonates with severe CoA may present in shock at the time of ductal closure in the first few weeks of life. Older children are often completely asymptomatic. Symptoms of left heart disease such as dyspnea on exertion, fatigue, chest pain, and decreased blood flow to the legs (claudication) are anticipated but rarely seen in the late presenting patient.

Classic CoA in the older patient has the exam findings of upper extremity hypertension with decreased femoral pulses and brachiofemoral pulse delay. There is a normal to mildly increased LV impulse. S1 and S2 are normal. A systolic ejection murmur is heard over the left upper sternal border and left upper back, and if collaterals are present the murmur may be continuous. An apical click is frequently present because of a bicuspid aortic valve, but an aortic stenosis murmur is unusual. In the infant with severe CHF or shock, pulses will be globally decreased, and a gallop rhythm is often present. There is frequently absence of a murmur or blood pressure gradient because of severely diminished cardiac output. With abdominal CoA there are decreased femoral pulses, no click or murmur over the precordium, and a bruit heard over the abdomen or lower back.

The diagnosis of CoA is usually made clinically, but the echocardiogram is often confirmatory. In the infant with CHF or shock, the echocardiogram permits an immediate diagnosis, localizes the obstruction, rules out associated lesions, assesses ductal patency, and evaluates ventricular function. In the asymptomatic or older patient the echocardiogram can localize the area of narrowing, and assess LV hypertrophy and function. Although occasionally helpful, Doppler gradient measurements tend to overestimate the severity of CoA, and therefore are less reliable than cuff pressures for approximation of direct catheterization measurement [15].

Chest x-ray may be helpful for localizing the coarcted area. Plain film reveals the aortic knob, CoA waist, and dilated descending aorta forming the "3" sign. Rib notching from increased intercostal artery collateral flow may be seen in late childhood and adolescence.

When the area of CoA cannot be localized by echocardiogram or chest x-ray, MRI and/or CT scan are useful modalities for defining the anatomy. Cardiac catheterization is rarely necessary unless there are associated lesions whose severity cannot be assessed by echocardiogram, or unless catheter intervention is anticipated. ECG may show LV hypertrophy with significant CoA, but is generally non-specific. It may be useful in deciding on intervention in the borderline patient.

Management

In the infant with severe CHF or shock, intubation and ventilation, treatment with PGE_1, fluid resuscitation, pH correction, and inotropic and pressor agents are indicated. Surgical intervention may be delayed to allow for end organ recovery if renal and/or hepatic failure occurs [16]. Although urgent surgery would seem to be indicated if ductal patency cannot immediately be established, significant clinical improvement may still be observed with mechanical ventilation and inotropic treatment alone. In the less severely ill infant or child with preserved LV function but early symptoms of CHF, one can temporize with digoxin and diuretics until elective surgical intervention. Surgical correction usually involves resection of the coarcted segment with direct or extended end-to-end re-anastomosis (with arch mobilization) depending on the degree of arch hypoplasia.

Intervention is indicated in the older asymptomatic patient if the blood pressure cuff gradient is greater than 30 mmHg, or if upper body hypertension or significant LV hypertrophy are present. Patients with gradients less than 30 mmHg can

be followed without intervention, but most develop hypertension in early or late adolescence. In native CoA, surgical intervention is usually recommended, although balloon dilation is employed by several centers with good results [17]. In recurrent CoA after initial surgical repair, catheter-directed intervention with balloon angioplasty has been successful [18]. In the older teenage patient with recurrence or mild CoA with hypertension, intravascular stent placement has been advocated [17, 19].

Postoperative Care

Postoperative care focuses on controlling hypertension which is mainly observed in older patients, but can be seen at any age. The rapid onset and short half-life of esmolol make it ideal for the control of the catecholamine surges that are seen in these patients. Good pain control and sedation also are necessary, especially if a lateral thoracotomy was performed. In the past, gastrointestinal problems such as mesenteric arteritis were occasionally seen in the older patients. This seems to be a rare complication now. Pre-treatment with beta blockers for a short term prior to surgery has been shown to be effective at blunting postoperative hypertension. In infants who present in shock, postponement of enteral feeding for 5–7 days post repair may help reduce the rare incidence of necrotizing enterocolitis.

Interrupted Aortic Arch

Interrupted aortic arch (IAA) is a rare but serious congenital heart lesion that is frequently associated with ventricular septal defect (and posterior deviation of the ventricular septum), subaortic narrowing, and patent ductus arteriosus [20]. It also can be seen in concert with more complex lesions such as truncus arteriosus, complete atrioventricular septal defect, single ventricle, or aorto-pulmonary window. A high proportion of patients with IAA also have a genetic defect known as CATCH 22, with half having a chromosome 22q11 deletion, and a smaller fraction having the DiGeorge syndrome phenotype [21].

IAA is generally divided into three subtypes based on the anatomic level of interruption. Type A IAA occurs distal to the left subclavian artery (in the region of a classical thoracic coarctation); type B interruption is between the left carotid artery and left subclavian artery, and type C is between the right and left carotid arteries. The diameter of the ascending aorta is usually correlated to the number of vessels that are located proximal to the interrupted segment. Thus, the smallest ascending aorta is often seen in type C IAA with an anomalous right subclavian artery where the right carotid artery is the only vessel arising from the ascending aorta.

The pathophysiology of IAA is similar to severe CoA with an acute increase in biventricular afterload and absent systemic blood flow to the trunk and lower extremities occurring with ductal closure in the first week of life. With a patent ductus arteriosus, systemic blood flow is preserved, with the right ventricle supplying the lower body.

Clinical Presentation

Unless detected by routine *in utero* ultrasound, or if a murmur is appreciated early after birth prompting further work-up (including echocardiogram), the most common presentation is cardiogenic shock with severely diminished cardiac output and metabolic acidosis. If ductal patency is present, the physical findings in an infant with IAA may be subtle and are similar to a newborn with hypoplastic left heart or CoA. Usually, however, there is a murmur from subaortic stenosis, and occasionally differential cyanosis with lower oxygen saturations in the legs than in the arms. This finding is often obscured by the large intra-cardiac left to right shunt through the ventricular septal defect which raises pulmonary artery and hence lower extremity saturations. Following ductal closure, the lack of any perfusion to the lower body leads to severe acidosis, ischemic organ injury, and death unless treatment is initiated immediately.

As with CoA, the echocardiogram is a useful diagnostic test in both the asymptomatic patient, and following resuscitation of the infant presenting in shock. The findings of a ventricular septal defect with posterior deviation of the outlet ventricular septum, and a small ascending aorta strongly support the diagnosis. Precise localization of the area of interruption is usually straight forward, and the size of the patent ductus can be verified. ECG is not diagnostic and may appear normal. Chest x-ray has variable findings, but cardiac enlargement and increased pulmonary vascular markings are most common. Cardiac catheterization is generally not indicated since the arch may not be seen well with this study. MRI or CT scan may be quite helpful in further delineating the anatomy if the arch is not well-visualized by ultrasound.

Management

Immediate treatment with PGE_1 is warranted as soon as the diagnosis of IAA is suspected because of the dire consequences to the patient if ductal closure occurs. For this reason, PGE_1 should be considered as part of the treatment algorithm for suspected septic shock in the first month of life prior to evaluation with echocardiogram. Once the diagnosis of IAA is entertained, DiGeorge syndrome precautions should be instituted including irradiated blood products and careful monitoring of serum calcium levels while chromosome studies are pending.

Definitive treatment for IAA is surgical with a few potential options to consider. One initial option is aortic arch repair and pulmonary artery banding, although there remains a risk of progressive worsening subaortic stenosis using this palliative technique. A second surgical option, particularly with aortic annular hypoplasia, is a combined Norwood-Rastelli operation using the pulmonary valve as the neoaortic valve. Lastly, advances in neonatal cardiopulmonary bypass and myocardial preservation techniques make primary aortic arch repair with ventricular septal defect closure the most common and attractive alternative [22, 23].

Postoperative Care

The early postoperative care of the patient with IAA is supportive and the use of inotropic agents nearly universal. Because of the complex nature of the underlying anatomic substrate, early echocardiographic evaluation might be considered to look for possible residual lesions such as ventricular septal defects and subaortic stenosis, which might impact on morbidity and have long-term consequences. One additional consideration is the possibility of (left) mainstem bronchial compression following IAA repair which may complicate ventilator weaning and extubation. Again, until CATCH 22 has been ruled-out, irradiated blood precautions and calcium monitoring must be re-instituted postoperatively.

Supravalvar Aortic Stenosis

Supravalvar Aortic Stenosis (SVAS) is a rare congenital heart lesion. It presents as a sporadic type, a familial autosomal dominant type, or in association with a genetic defect (Williams Syndrome) due to a microdeletion in the elastin gene at 7q11.23 [21, 24]. The fixed area of narrowing is usually at the sino-tubular junction just above the sinuses of Valsalva. Frequently there is tethering of the aortic valve leaflets causing interference of flow to the coronary arteries or coronary ostial stenoses. In the familial type, and with Williams syndrome, multiple vessels may have stenoses, especially the peripheral pulmonary arteries, neck vessels, and renal arteries.

The overall pathophysiology is one of left ventricular pressure overload. Additionally, since the coronary arteries are below the obstruction there can be chronic coronary artery hypertension and the development of accelerated coronary arteriosclerosis. The natural history of the disorder is usually progressive with worsening left ventricular hypertrophy and coronary changes in the first few years of life [25].

Clinical Presentation

SVAS usually presents with the discovery of a murmur. Symptoms are rare in infancy unless coronary obstruction is present, potentially causing anginal pain. Angina in infancy, leading to fussiness around the stress of eating, may be misdiagnosed as colic. Other symptoms with SVAS are similar to those of other forms of left ventricular outflow tract obstruction and symptoms progress during childhood. These may include dyspnea on exertion, presyncope or syncope with exertion, congestive heart failure, or even sudden death, especially if coronary involvement is present.

Classically SVAS has the findings of a systolic ejection murmur over the right 2nd and 3rd intercostal spaces with radiation especially to the right carotid area. S1 and S2 are normal, and clicks are rare. An increased left ventricular impulse and suprasternal notch thrill are often present. There also is frequently an increased blood pressure in the right arm, even without other vessel narrowing, due to the Coanda effect [26], which is caused by the SVAS jet directed into the first branch off the ascending aorta. One has to be cognizant of the possibility of multiple vessel stenoses which may make for quite variable pulses and even generalized hypertension if the renal arteries are involved. Abnormal "Elfin" facies and degrees of mental retardation are recognizable in the patients with Williams syndrome.

ECG may show LV hypertrophy depending on the degree of stenosis with varying degrees of RV hypertrophy if peripheral pulmonary artery stenosis is present. ST-T wave changes are ominous especially if LV hypertrophy is not present, suggesting coronary involvement. Chest X-ray is usually normal and cardiac enlargement is a late finding in severe cases. Echocardiography is an important tool to examine the degree of LV hypertrophy and ventricular function, and can outline the SVAS anatomy. It is also useful in the evaluation of the degree of right heart involvement and peripheral pulmonary artery stenosis [27].

Cardiac catheterization is usually indicated to measure right and left heart pressures especially if peripheral pulmonary artery stenosis is suspected. Angiography of the pulmonary arteries, ascending aorta and neck vessels, and descending aorta in the area of the renal arteries, should be performed because of the risk of multi-vessel disease. Stenting of the pulmonary arteries may be of benefit prior to correction of the left sided lesion. The ability to predict less than systemic RV pressure at the time of relief of the left sided obstruction probably reduces the risks of surgical interventions. MRI and/or CT assessment of anatomy, combined with Echo/Doppler studies of the peripheral and renal vessels, may be used instead of catheterization if significant right heart and coronary lesions are not suspected.

Management

Medical management is usually reserved for patients felt to be inoperable. Surgical intervention of isolated SVAS is indicated for gradients of greater than 25–30 mmHg or if LV hypertrophy is present by EKG/Echo. Stenting of stenotic pulmonary and peripheral vessels has been advocated [17], but stenting or balloon intervention of SVAS is rarely indicated because of the proximity of the aortic valve and coronary arteries. These modalities, however, might be considered in the rare case of membranous stenosis.

Postoperative Care

In isolated SVAS the postoperative care is straight forward and supportive. If multi-vessel involvement is present, especially unrelieved peripheral pulmonary artery stenosis with systemic or suprasystemic RV pressure, or uncorrected carotid artery stenoses, maintenance of a generous systemic arterial pressure is probably beneficial.

Subvalvar Aortic Stenosis

Subvalvar aortic stenosis (SAS) encompasses a variety of lesions that produce fixed, or occasionally dynamic, anatomic obstruction to egress of blood across the left ventricular outflow tract (LVOT). The etiology of SAS is incompletely understood and probably multifactorial. Associated cardiac malformations occur in approximately 50 % of patients with SAS [28–31] including bicuspid aortic valve, ventricular septal defect, coarctation of the aorta, mitral valve abnormalities, atrioventricular septal defect, and interrupted aortic arch, suggesting that a congenital factor is involved.

A variety of classification schemes for SAS have been proposed based on morphological, histological, or anatomical features. From a management perspective, SAS can be divided into discrete, tunnel and dynamic forms. The discrete form accounts for 70–80 % of SAS and consists of a thin, discrete, fibrous ridge alone or associated with a muscular base circumferentially attached to the LVOT below the aortic valve. In contrast, the tunnel form consists of a diffuse, long segment, fibromuscular narrowing of the LVOT. Subaortic stenosis can also be caused by deviation or malalignment of structures in the LVOT in association with a ventricular septal defect, or due to atrioventricular valve tissue in the subaortic area [32, 33]. Another form of SAS is dynamic LVOT obstruction, usually as a result of hypertrophy of the interventricular septum. Dynamic SAS may be difficult to distinguish from hypertrophic cardiomyopathy with asymmetric septal involvement, but the latter condition may have a familial inheritance pattern and is often more rapidly progressive and generalizable.

Progression of SAS occurs but the rate is variable and the factors influencing it are unknown. Only the gradient at diagnosis is predictive of the rate of progression of LVOT obstruction [33]. Significant LVOT obstruction ultimately results in concentric LV hypertrophy which leads to a vicious cycle of further obstruction and localized fibromuscular growth, in addition to decreased LV compliance and left heart failure.

Aortic regurgitation occurs in more than 50 % of patients with SAS [34, 35] and in some cases it may progress despite surgical intervention [33–36]. The etiology of aortic regurgitation is multifactorial, and in some patients extensions of fibrous tissue onto the valve may result in aortic valve thickening and leaflet distortion. In addition, damage to the valve may result from repetitive trauma and vibrations by the turbulent subaortic systolic jet of blood. A bicuspid aortic valve may also contribute to aortic regurgitation.

Aortic regurgitation contributes a volume overload to an already pressure-overloaded LV. The resultant decreased aortic diastolic pressure may lead to diminished coronary perfusion in the face of an increased LV oxygen demand from pressure and volume overload. This combination may predispose the LV to ischemic injury.

Clinical Presentation

Symptoms from SAS, even with severe stenosis, are rare in infancy and uncommon in early childhood. In addition, symptoms of associated congenital heart defects often mask symptoms of SAS. In most cases, SAS is detected either in the course of follow-up care for associated congenital heart defects or during evaluation of a heart murmur. Symptoms, when present, include dyspnea on exertion, effort syncope and presyncope, angina, orthopnea, congestive heart failure, and sudden cardiac death. Most of these symptoms occur in children and young adults with moderate to severe LVOT obstruction and a peak systolic ejection gradient at cardiac catheterization greater than 50 mmHg.

Somatic growth of the child with SAS is usually normal. Peripheral pulses are symmetric. A palpable carotid thrill and left parasternal thrill are present in approximately one-third of patients with mild SAS, and one-half of patients with moderate to severe SAS. An increased left ventricular apical impulse is present in most patients with SAS. The first heart sound is normal; the second heart sound can be narrowly split or single (because of prolonged LV systole). Paradoxical splitting of the second heart sound suggests LV dysfunction associated with severe SAS. An ejection click is notably absent (differentiating SAS from valvar aortic stenosis). A systolic ejection murmur in the 2nd and 3rd left intercostal spaces with radiation to the suprasternal notch is typically present in isolated SAS. A high-pitched early

diastolic murmur of aortic regurgitation in the same auscultatory area is present in 30–50 % of patients.

Echocardiography provides anatomic definition and localization of SAS, including the extent of LVOT narrowing, degree of LV hypertrophy, and indices of LV systolic and diastolic performance. The peak instantaneous and mean gradient across the LVOT estimated by continuous wave Doppler provide measures of the severity of LVOT obstruction and help guide cardiac intervention. Secondary effects, such as aortic and mitral regurgitation, or poststenotic dilatation of the aorta, may also be assessed by echocardiography. Associated congenital heart defects also may be evaluated.

Chest roentgenogram usually shows mild cardiomegaly, and occasionally a dilated ascending aorta. On ECG, a variable degree of LV hypertrophy is often noted, although occasionally ECG findings may be normal. A prominent Q wave in the left precordial leads may be present (indicating septal hypertrophy), and a left ventricular strain pattern is visible in approximately 25 % of patients indicating severe obstruction.

Cardiac catheterization may be indicated in SAS to assess the anatomy and severity of LVOT obstruction, especially if associated with other congenital heart defects. Careful pullback pressure measurements from the LV to the aorta usually delineate the pressure gradient and exact site of obstruction. Left ventriculography can help to define the type of SAS and reveal aortic valve stenosis. An aortogram is useful to assess the degree of aortic regurgitation if present.

Management

Controversy exists regarding the optimal management and timing of surgery for patients with SAS [33]. Because SAS may be progressive it often requires intervention to relieve LVOT obstruction sometime during the clinical course of the disease. However, the high rate of postoperative recurrence [37] and the persistence or progression of aortic regurgitation after surgery [33, 34, 36] may influence the decision to operate. In most centers, a peak systolic ejection gradient >30 mmHg and presence of mild or more significant aortic regurgitation indicate intervention. Early surgical intervention is usually indicated in tunnel-type and rapidly progressive fibromuscular ridge lesions.

Percutaneous balloon dilation of discrete SAS has been reported [38] and can result in LVOT pressure gradient reduction. However, relief of LVOT obstruction is usually temporary and thus balloon dilation is only a palliative procedure and generally not recommended. Surgery of choice for discrete SAS is complete resection with or without myomectomy through an aortotomy. Patients with significant aortic regurgitation may also require aortic valvuloplasty or replacement. For tunnel-type or more complex SAS (particularly in the neonate), a modified aortoventriculoplasty (modified Konno procedure) alone or in combination with an aortic valve allograft or pulmonary valve autograft (Ross-Konno procedure) may be required to completely relieve LVOT obstruction. In some patients, progressive aortic regurgitation may necessitate aortic valve repair or replacement at the time of surgical intervention for SAS.

Postoperative Care

The postoperative care of patients with simple SAS is usually uneventful and early extubation is often performed. An occasional patient may have significant LV hypertrophy and/or residual SAS, and hence it is imperative to maintain adequate preload and avoid β (beta) adrenergic agents if possible. The incidence of early postoperative hypertension (responsive to β (beta) adrenergic antagonists) is probably less than in patients with valvar aortic stenosis or aortic coarctation. In rare instances, excision of the subaortic membrane may injure the mitral or aortic valves leading to mitral or aortic insufficiency. With more complex LVOT obstruction (usually requiring a Ross-Konno procedure), there is a potential for creation of a ventricular septal defect and a residual left-to-right shunt that may be poorly tolerated in the early postoperative period. Left bundle branch block or even complete heart block can occur secondary to surgical resection in the LVOT, or during closure of an associated ventricular septal defect. Overall surgical mortality is less than 3 % at most centers [33, 36, 39, 40], and postoperative survival rates are more than 85–95 % at 15 years [31]. A high recurrence rate (10–15 % on >10-year follow-up) has been associated with high preoperative LVOT pressure gradients, tunnel-like SAS, incomplete removal of discrete SAS, and young age (<10 years-old) at surgery [40, 41].

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Single Ventricle Lesions

24

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Abstract

The univentricular or single ventricle heart applies to a heterogeneous group of congenital cardiac lesions with wide variability in the pre- and post-operative anatomy and physiology. The management of a child with single ventricle physiology represents a unique challenge to the intensive care physician both in the pre- and post-operative period, as these children often respond differently to common interventions such as supplemental oxygen, mechanical ventilation, and vasoactive infusions differently than children with biventricular physiology. Surgical strategies for patients with a univentricular heart typically include multiple stages of palliation with the goal of separating the systemic and pulmonary circulations and thereby restoring near normal cardiac physiology. Given the complexity of these lesions and their repair, children may be more adversely affected by inter-current illness, experience limitations in activities of daily living, and succumb to complications seen commonly in the inter-stage periods. The unique physiology encountered in single ventricle heart disease represents the *sine qua non* of pediatric cardiac intensive care, and it is therefore imperative that pediatric intensivists have a thorough understanding of its nuances. This chapter will address the important physiologic issues that arise in the care of infants and children with a univentricular heart both before and after surgery.

Keywords

Hypoplastic left heart syndrome • Single ventricle • Univentricular • Norwood • Glenn • Fontan • Hemi-Fontan • Qp/Qs

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Introduction

The univentricular or single ventricle heart applies to a heterogeneous group of congenital cardiac lesions with wide variability in the pre- and post-operative anatomy and physiology (Table 24.1). The management of a child with single ventricle physiology represents a unique challenge to the intensive care physician both in the pre- and post-operative period, as these children often respond differently to common interventions such as supplemental oxygen, mechanical ventilation, and vasoactive infusions compared to children with biventricular physiology. Surgical strategies for patients with a univentricular heart typically include multiple stages of palliation with the goal of separating the systemic and pulmonary circulations and thereby restoring near normal cardiac physiology. Given the complexity of these lesions and their repair, children may be more adversely affected by inter-current illness, experience limitations in activities of daily living, and succumb to complications seen commonly in the interstage periods. The unique physiology encountered in single ventricle heart disease represents the *sine qua non* of pediatric cardiac intensive care, and it is therefore imperative that pediatric intensivists have a thorough understanding of its nuances. This chapter will address the important physiologic issues that arise in the care of infants and children with a univentricular heart both before and after surgery.

Single Ventricle Physiology in the Newborn Before and After Surgery

Regardless of the underlying anatomy, single ventricle physiology is characterized by (i) the complete mixing of systemic and pulmonary venous return, and (ii) partitioning of total cardiac output into the pulmonary blood flow (Qp) and systemic blood flow (Qs). Mixing can occur at the atrial level, the ventricular level, or both. Following mixing, the blood is ejected into the pulmonary or systemic circulations that exist in parallel. The aortic and pulmonary artery saturations are equal and the total ventricular output is the sum of the Qp and Qs. This is in contrast to normal anatomy, a circulation in series, in which the aortic saturation is higher than the pulmonary artery saturation, or to transposition physiology, where the pulmonary artery saturation is higher than the aortic saturation.

The amount of flow to the pulmonary and systemic circuits is determined by their relative resistance, which may be impacted by vasoconstriction or by anatomic obstruction. Obstruction to one of the ventricular outflow tracts exists in most, but not all univentricular hearts. It is less common to have no outflow obstruction, and extremely rare to have obstruction of both the pulmonary and systemic circuits. The factors affecting resistance to Qp and Qs are listed in Table 24.2.

Table 24.1 Anatomic diagnoses commonly associated with single ventricle physiology in the newborn

Physiology	Anatomy
Systemic outflow obstruction	Hypoplastic left heart syndrome
	Critical aortic stenosis
	Critical coarctation of the aorta
	Interrupted aortic arch
	Tricuspid atresia with transposition of the great arteries
	Double inlet left ventricle
	Double outlet right ventricle (some variations)
Pulmonary outflow obstruction	Tricuspid atresia with normally related great arteries
	Pulmonary atresia with intact ventricular septum
	Tetralogy of Fallot with pulmonary atresia
	Critical pulmonary stenosis
	Severe Ebstein's anomaly of the tricuspid valve
	Double outlet right ventricle (some variations)

Not all diagnoses listed are anatomically single ventricle lesions

Table 24.2 Factors affecting resistance to pulmonary and systemic blood flow

Pulmonary	Systemic
Degree of pulmonary stenosis	Degree of aortic stenosis/arch obstruction:
(a) subvalvar	(a) subaortic
(b) valvar	(b) valvar
(c) supravalvar	(c) aortic arch hypoplasia
	(d) coarctation of the aorta
Pulmonary vascular resistance	Systemic vascular resistance
Pulmonary venous and left atrial pressure. where the left atrial pressure is determined by:	Size of the ductus arteriosus
(a) Volume of blood entering the left atrium	
(b) Degree of obstruction to outflow through the left AV valve and atrial septum	
Size of the ductus arteriosus	

It is generally assumed that systemic arterial oxygen saturation (SaO_2) reflects the ratio of Qp to Qs (Qp:Qs) in the un-operated, shunted, or banded newborn single ventricle patient. This assumption is based on manipulation of the Fick principle – Qs and Qp are calculated by the Fick equation:

$$Q_s = VO_2 / \left(CaO_2 - CmvO_2\right) \quad (24.1)$$

$$Q_p = VO_2 / \left(CpvO_2 - CpaO_2\right) \quad (24.2)$$

where VO_2 = oxygen consumption, CaO_2 = arterial oxygen content, $CmvO_2$ = mixed venous oxygen content,

$CpvO_2$ = pulmonary venous oxygen content, and $CpaO_2$ = pulmonary artery oxygen content. By substituting the equations for oxygen content into the above equations, and because arterial and pulmonary artery saturations are identical in single ventricle physiology, one can derive a simplified Fick equation for Qp:Qs:

$$Q_p : Q_s = \left(SaO_2 - SmvO_2\right) / \left(SpvO_2 - SaO_2\right) \quad (24.3)$$

where $SmvO_2$ = oxygen saturation of mixed venous blood, SaO_2 = oxygen saturation of arterial blood, and $SpvO_2$ = oxygen saturation of pulmonary venous blood. If there is normal function of the respiratory tract, $SpvO_2$ can be assumed to be approximately 95 % while breathing room air. If one also assumes that the systemic arterial-venous oxygen saturation difference (SaO_2-$SmvO_2$) is normal (thereby assuming normal oxygen delivery (DO_2)), at approximately 25 %, the above equation can be further simplified:

$$Q_p : Q_s = 25 / \left(95 - SaO_2\right) \quad (24.4)$$

This simplified version of the Fick equation allows estimation of Qp:Qs based upon SaO_2. Given the ease with which SaO_2 can be obtained in clinical practice, the above equation allows the clinician to estimate tissue (DO_2) simply by looking at SaO_2. Thus, one can theoretically assess the effectiveness of any intervention designed to alter Qp:Qs by observing the change in SaO_2. This simplified approach to estimating Qp:Qs is predicated on the previously described assumptions regarding $SmvO_2$ and $SpvO_2$, which may be inaccurate, particularly in the immediate postoperative period. First, the assumption regarding the systemic arterial-venous oxygen saturation difference is only accurate if DO_2 is normal. In shock or in the face of myocardial dysfunction, which is common following surgery, $SmvO_2$ will be low and therefore SaO_2-$SmvO_2$ will be substantially higher than 25 %. When the decrease in $SmvO_2$ is offset by an increase in the amount of well-saturated blood returning from the lungs (increased Qp:Qs), SaO_2 will remain unchanged [1–4]. Furthermore, pulmonary venous desaturation is common after cardiopulmonary bypass (CPB), even in the absence of chest x-ray abnormalities or other clinical indicators of lung problems [3]. As with underestimation of DO_2, overestimation of $SpvO_2$ will result in an underestimation of Qp:Qs.

In order to accurately estimate Qp:Qs, an understanding of the relationship between Qp:Qs, DO_2, and total cardiac output is necessary [5]. Using mathematical modeling and keeping $SpvO_2$ constant at 96 %, Barnea et al. generated a series of curves showing DO_2 as a function of Qp:Qs. Since the total cardiac output pumped by the single ventricle is Qp + Qs, an increase in Qp is accompanied by a decrease in Qs and vice versa *unless* the total cardiac output also increases. The mathematical model was able to demonstrate that the maximum DO_2 occurs between a Qp:Qs of approximately 0.5 and 1 and depends upon the total cardiac output. The slope of each isobar for a given cardiac output is steepest on either side of the maximum DO_2, suggesting small changes in Qp:Qs can be associated with large changes in DO_2. Barnea at al also suggested that DO_2 can be improved to a far greater degree by increasing total cardiac output rather than by altering Qp or Qs individually [5]. Since Qp is generally anatomically limited following the first stage of palliation (see below), the benefit of increasing overall cardiac output may be even greater since additional cardiac output will primarily be directed to the systemic circulation (Qs). One limitation to this type of model for DO_2 is the use of SaO_2 and Qs as interchangeable components of DO_2. Although newborns tolerate cyanosis well, the oxyhemoglobin dissociation curve dictates that once SaO_2 becomes critically low, further decreases can no longer be compensated for by increases in Qs [6]. Nevertheless, when cardiac output is maximized, optimization of Qp:Qs is still very important for improvement of marginal DO_2.

Perinatal Management

Antenatal diagnosis of single ventricle cardiac lesions is now common, and fetal intervention is considered with increasing frequency in patients with certain cardiac lesions. In cases of a fetal diagnosis, opportunities exist for counseling and anticipatory guidance for the postnatal treatment plan and course of events. Critical aortic stenosis with a normal or dilated left ventricle in the fetus can progress to hypoplastic left heart syndrome (HLHS) by late gestation. In an attempt to alter the natural history of this progression, fetal aortic valvuloplasty has been used with some success of a postnatal biventricular outcome [7]. However, the availability of this procedure is limited to a few large centers and to date there have been no randomized trials to clearly establish that HLHS is truly preventable by early intervention.

Atz et al. evaluated the prevalence and timing of diagnosis in potential subjects screened for the Single Ventricle Reconstruction (SVR) trial; a large multicenter trial conducted by the Pediatric Heart Network (a multi-center research collaboration sponsored by the NIH/NHLBI) in patients with HLHS or related single right ventricular lesions with systemic outflow obstruction. Of the 906 patients screened for participation in the trial, prenatal diagnosis was made in 75 % [8], demonstrating that, in the majority of cases, perinatal management of these critically ill neonates can be planned well in advance of delivery. Despite the lack of clear improvement in outcomes following prenatal diagnosis, in the current era, it is generally less common for a neonate to present in shock secondary to an undiagnosed single ventricular lesion. Outcomes for improved survival

following stage I Norwood procedure based on the timing of diagnosis (prenatal vs. postnatal) are conflicting, though the SVR trial demonstrated that patients with a prenatal diagnosis were less likely to have major extracardiac anomalies and a higher gestational age at the time of delivery [8]. In the population screened for participation in this trial, preoperative mortality was 3 % and was associated with a lower gestational age and birth weight, higher rate of extracardiac anomalies, and obstructed pulmonary venous return [8]. Current practices for immediate management in the newborn period with a known prenatal diagnosis include delivery at a high-risk center in close proximity to a pediatric institution specializing in the care of complex congenital heart disease. In the event of an intact or restrictive atrial septum, delivery of the infant is often carried out in a children's hospital, where urgent atrial septostomy or septectomy can be performed. In addition, there have been reports of fetal intervention for this condition [9].

Preoperative Management

General Considerations

The approach of "less is more" appears to be the most beneficial for neonates with single ventricle lesions. Multiple factors such as the systemic and pulmonary vascular resistance, ductal size and degree of outlet obstruction impact the adequacy of Qp, Qs and DO_2. General management of ductal dependent single ventricle lesions includes maintenance of ductal patency by a continuous intravenous prostaglandin E1 (PGE1) infusion until surgical or catheter intervention is undertaken. There does not appear to be a dose response for increasing ductal size, but one likely does exist for occurrence of side effects. These include fever (14 %), apnea (12 %), peripheral vasodilation (10 %), bradycardia (7 %), hypotension (4 %) (Percentages obtained directly from the package insert). The lowest possible dose should be used to minimize the risk of apnea, and is typically 0.01 μg/kg/min. Aminophylline and caffeine can be considered for the treatment of apnea related to PGE1 infusion [10, 11].

Preoperative management of circulation is key to prevent organ dysfunction related to inadequate Qs or Qp. Careful attention should be paid to the associated signs of pulmonary or over-circulation. Pulmonary over-circulation (high Qp:Qs) can be identified by the presence of high arterial oxygen saturations (>90 %), and evidence of poor systemic perfusion. Since the vast majority of neonates with single ventricle physiology have SaO_2>90 %, the decision to intervene should depend on evidence of compromise beyond simply high saturations. Over-circulated infants most commonly have an unrestrictive atrial septum, low pulmonary vascular resistance (PVR) and/or high systemic vascular resistance (SVR). In addition, ventricular wall tension and oxygen consumption are increased in the dilated and volume loaded single ventricle. This may lead to myocardial dysfunction and atrioventricular valve regurgitation. Signs and symptoms of poor systemic perfusion include pallor or duskiness, decreased pulses, and delayed capillary refill, tachypnea, tachycardia, hypotension and feeding intolerance. Other markers of pulmonary over-circulation include elevated metabolic markers of end organ dysfunction (increased lactate and creatinine, and metabolic acidosis), declining cerebral and splanchnic near infrared spectroscopy (NIRS), and declining $SmvO_2$ [12–14]. The development and subsequent progression of a metabolic acidosis is concerning in this patient population, even if mild, and warrants urgent evaluation. Study of the effects of anaerobic metabolism in neonates after the Norwood procedure demonstrated that $SmvO_2$ below 30 % was strongly related to anaerobic metabolism, making it a useful indicator of inadequate tissue oxygen delivery. Unfortunately, SaO_2 showed no significant relation to the development of anaerobic metabolism [1]. Imaging studies such as chest x-ray in a patient with over-circulation may demonstrate pulmonary congestion, increased vascular markings and cardiomegaly.

Management of Pulmonary Over-Circulation

Several strategies to reduce Qp and optimize cardiac output in the infant with pulmonary over-circulation exist. Diuretics are often used in the setting of congestive heart failure and increased Qp. The purpose of diuresis is to decrease intravascular volume, which could have an indirect effect on decreasing Qp.

Hypoxic gas therapy, or subambient oxygen, is achieved by bleeding in nitrogen with oxygen or room air, either into a hood or via the ventilator circuit, resulting in fractions of inspired oxygen from 0.17 to 0.19 [15]. The hypoxic gas results in pulmonary vasoconstriction and thus encourages systemic blood flow. There is however a risk of systemic desaturation from alveolar hypoxemia, with associated atelectasis and apnea. Animal studies have demonstrated that sustained hypoxia can lead to pulmonary hypertension and medial hypertrophy [16, 17]. However, no changes in PVR with the use of supplemental nitrogen were seen in studies in early infancy [18]. The long-term consequences of hypoxic gas therapy on neurodevelopmental outcome are unknown. In a prospective crossover study, Tabbutt et al. compared the effects of hypoxia achieved by adding inspired nitrogen (FiO2 of 17 %), with hypercarbia, achieved by adding 2.7 % carbon dioxide in pre-operative infants with HLHS under conditions of mechanical ventilation with a fixed minute ventilation, sedation and muscle relaxation [19]. They eloquently demonstrated that hypercarbia was associated with an increase in cardiac output and increased mixed cerebral venous oxygen saturation, while there was no change

with hypoxia, although it is important to note that these interventions were applied and studied over a relatively short time frame [19]. Inspired carbon dioxide also provided the added benefit of improving cerebral oxygen saturation, while no effect was seen with nitrogen [20].

PVR can also be increased independently of SVR with the judicious use of positive end-expiratory pressure (PEEP) [21]. When lung compliance is normal, PEEP increases PVR by compressing the inter-alveolar pulmonary arterioles. Compression of the inter-alveolar pulmonary arterioles is accomplished by increasing the PEEP to a level such that it results in an end-expiratory lung volume greater than functional residual capacity (FRC). This is because the nadir of PVR occurs at FRC, rather than at a PEEP of zero. The initial application of PEEP above zero applies radial traction forces to the pulmonary vasculature and aids vascular recruitment. Increased PEEP may also prevent pulmonary venous desaturation by optimizing lung gas exchange and therefore decreases Qp:Qs while simultaneously maximizing the oxygen saturation of pulmonary venous blood. Using PEEP to limit pulmonary blood flow should be accompanied by careful observation for any impediment to systemic venous return by increased intrathoracic pressure. Table 24.3 summarizes the effects of respiratory maneuvers on pulmonary and systemic vascular resistance.

Table 24.3 Effects of respiratory maneuvers on pulmonary and systemic vascular resistance

Treatment	PVR	SVR	Q_p/Q_s
Increase FiO_2	Decrease	Increase	Increase
Increase CO_2	Increase	Decrease	Decrease
Increase pH	Decrease	Increase	Increase
PEEP	Increase	No effect	Decrease

PVR Pulmonary vascular resistance, *SVR* Systemic vascular resistance, *FIO2* Fraction of inspired oxygen, *PEEP* Positive end-expiratory pressure

Lesion-Specific Management

Preoperative management varies upon whether there is systemic outflow tract obstruction, pulmonary outflow tract obstruction, pulmonary venous obstruction, or any combination of these. Each of these are discussed below:

Systemic Outflow Obstruction

Systemic outflow obstruction, also sometimes referred to as ductal dependent systemic blood flow, is characteristic of HLHS (Fig. 24.1), tricuspid atresia with transposed great arteries, double inlet left ventricle (DILV), and other less common anatomic variations [22]. Additionally, prior to intervention, neonates with biventricular lesions that are characterized by ductal dependent systemic blood flow, such as critical aortic stenosis, severe coarctation of the aorta, interrupted aortic arch or Shone's syndrome (hypoplasia of the AV valve, ventricle and outflow tract) also demonstrate single ventricle physiology with systemic outflow obstruction. Many of these lesions are described in the chapter on Left Ventricular Outflow Tract Obstruction. The most important feature of this type of anatomy is that ventricular outflow is directed primarily to the pulmonary artery, and in those with true single ventricle lesions, there is also complete mixing of pulmonary and systemic venous return. Provision of Qs is accomplished by right-to-left shunting across the patent ductus arteriosus (PDA), and is dependent upon the relative PVR and SVR as previously described. In these patients, if ductal closure occurs, systemic outflow is critically reduced and is accompanied by signs and symptoms of profound shock (essentially "obstructive shock").

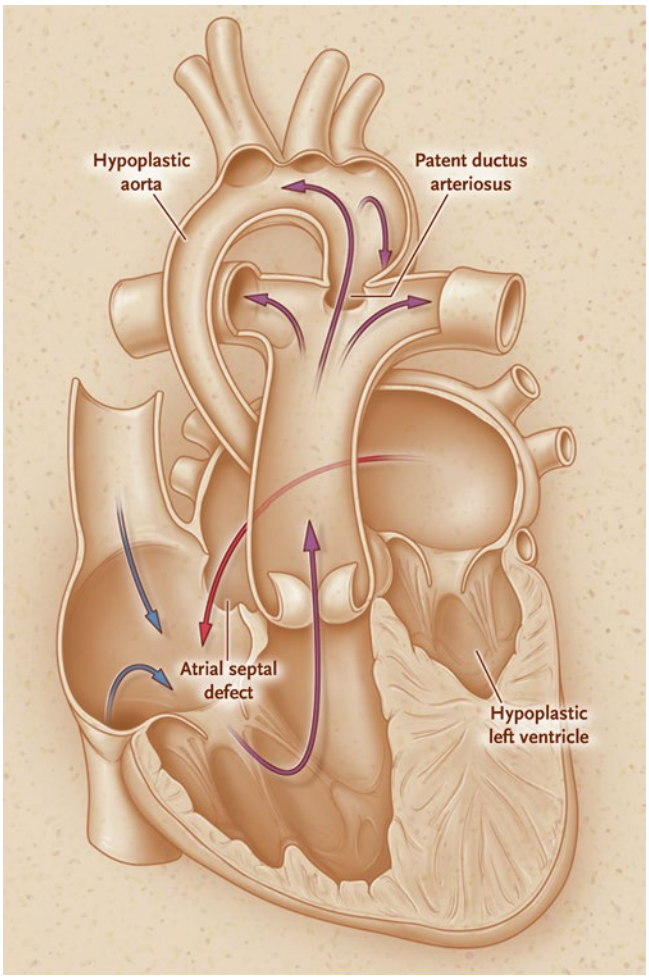


Fig. 24.1 Hypoplastic left heart syndrome. Lesions with ductal dependent systemic blood flow is characterized complete mixing of the systemic and pulmonary venous return. The mixed blood is ejected by the right ventricle into the pulmonary artery. A portion of the blood goes to the lungs, but the remaining portion supplies the systemic circulation via the ductus arteriosus (Reprinted from Ohye et al. [30]. With permission from Massachusetts Medical Society)

Pulmonary Outflow Obstruction

Single ventricle physiology with pulmonary outflow obstruction is characteristic of lesions such as tricuspid atresia with normally related great vessels, pulmonary atresia, and severe Ebstein's anomaly of the tricuspid valve. Pulmonary outflow obstruction is often times referred to as ductal dependent pulmonary blood flow. The salient anatomic features are complete mixing of systemic and pulmonary venous return and ventricular outflow predominantly directed out the aorta. Low Qp in these patients implies an obligate right-to-left shunt, generally at the atrial level and results in deoxygenated blood reaching the systemic circulation and hence, cyanosis. The clinical consequences of low Qp are variable and depend upon the degree of pulmonary outflow obstruction. Most commonly, there is important pulmonary outflow obstruction or even atresia. These patients can be profoundly cyanotic unless an alternate source of Qp is quickly established. Occasionally, patients with only mild obstruction may have inadequate restriction to flow, with excessive Qp and impaired Qs. Treatment for this subset of patients is therefore directed at limiting Qp. Infants with this type of anatomy may be only minimally cyanotic, and can have signs and symptoms of congestive heart failure. For some however, pulmonary outflow obstruction may result in a good balance of Qp and Qs.

Obstructed Venous Return

Unobstructed pulmonary or systemic venous return in infants with single ventricle anatomy frequently depends upon an unrestrictive inter-atrial communication. When one of the AV valves is severely stenotic or atretic, as occurs in HLHS, tricuspid atresia, or pulmonary atresia with intact ventricular septum, a large atrial septal defect is mandatory for decompression of the atrium with the inadequate AV valve. Obstruction of the systemic venous atrium causes increased central venous pressures and third spacing of fluid, eventually limiting systemic cardiac output and producing signs and symptoms of shock. Although a patent foramen ovale allows for some right to left shunting of blood across the atrial septum, it may be inadequate to permit unobstructed flow of all systemic venous return, although in practice, single ventricle lesions with obstructed Qp rarely require intervention on the atrial septum.

Obstruction of the pulmonary venous return causes elevated pulmonary venous pressures and pulmonary hypertension. This phenomenon may be beneficial to a degree in the immediate neonatal period, as it can limit Qp and enhance Qs, thereby increasing DO_2, even if at the expense of SaO_2. Nevertheless, the atrial septum must be opened at the time of the first palliative operation, or shortly afterwards in the case of a hybrid surgical/catheter approach to HLHS, to avoid the long-term consequences of elevated pulmonary vascular resistance. A severely restrictive or intact atrial septum with pulmonary venous hypertension, however, usually requires emergent creation of an atrial level shunt because of profound cyanosis and inadequate cardiac output. These procedures carry a high risk of morbidity and may imply a worse prognosis for further palliative surgery [23].

Other Considerations

Other preoperative considerations include nutrition and feeding. Parenteral nutrition is used in the pre-operative period to provide the newborn with adequate nutrition prior to surgical palliation. While *ad lib* oral feeding is used in some centers prior to the first surgery, caution should be undertaken in patients with pulmonary over-circulation, and avoided in situations of end organ dysfunction because of the risk of nectrotizing enterocolitis.

Surgical Management

The goal to any palliative surgery is to establish (i) unobstructed pulmonary and systemic venous return, (ii) unobstructed Qs, and (iii) a regulated source of Qp. Timing of surgery is institution dependent, but most commonly occurs by 3–7 days of life. There is variability in the type of procedure performed, and is dependent upon whether the patient has ductal dependent Qs or Qp.

Several options for the first stage of palliation exist for patients with ductal dependent systemic blood flow. The Norwood procedure is accomplished with a pulmonary-artery-to-aortic anastomosis (Damus-Kaye-Stansel), an atrial septectomy, and placement of a shunt for provision of Qp. In the current era, provision of Qp can be accomplished using several shunt types, with the modified systemic to pulmonary artery (Blalock-Taussig) shunt (mBTS) (Fig. 24.2a), and the right-ventricle-to-pulmonary artery (RV-PA) (Sano shunt) conduit being the most common (Fig. 24.2b). An alternative approach for the first stage palliation is the hybrid procedure, which is a combined surgical and catheter procedure that includes placement of a PDA stent, banding of the bilateral pulmonary arteries, and an atrial septostomy. The details of these procedures as discussed elsewhere in this book.

HLHS encompasses a continuum of congenital heart lesions producing left-sided obstruction and hypoplasia and generally ranges from severe, with mitral and aortic atresia with a diminutive left ventricle to more mild forms with mitral and/or aortic stenosis and a non-apex forming left ventricle [24]. While biventricular repair may be possible for those infants at the more favorable end of the spectrum (i.e. mitral stenosis, aortic stenosis), the severe end of the spectrum is universally fatal in the absence of intervention, with

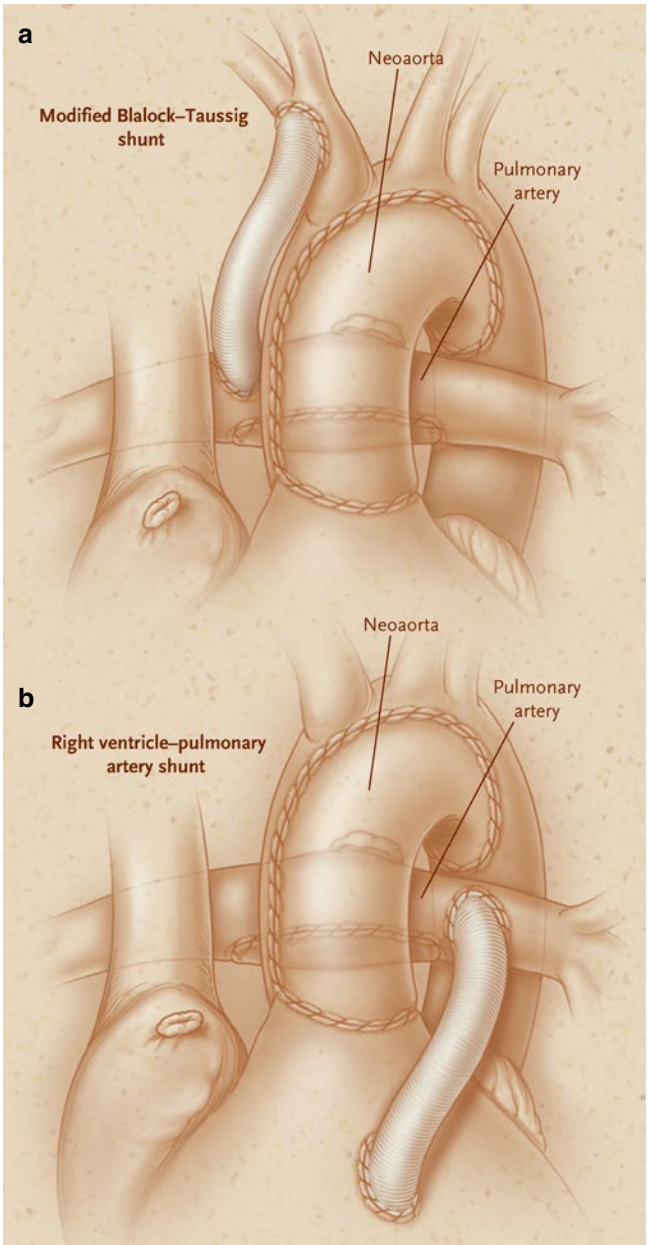


Fig. 24.2 Norwood procedure with a modified Blalock-Taussig shunt (**a**) and right ventricle to pulmonary artery conduit (**b**) (Reprinted from Ohye et al. [30]. With permission from Massachusetts Medical Society)

an average life expectancy of approximately 5 days if left untreated [24, 25]. Controversy exists over whether patients with mild to moderate forms of Shone's syndrome or lesions with similar left-sided inflow or outflow tract obstruction or both should be committed to single ventricle repair, or staged toward a separated two-ventricular repair [26–28]. In patients with borderline left hearts, primary left ventricular rehabilitation with endocardial fibroelastosis (EFE) resection, and mitral and aortic valvuloplasty have resulted in improved LV systolic and diastolic performance and decreased right ventricular pressures [29]. Left ventricular size appears to play an important role as to whether a biventricular repair can be accomplished, but there are no clearly established guidelines. Univentricular palliation following attempted biventricular repair is associated with increased mortality. In addition, a complex biventricular repair with residual lesions may be worse than a successful univentricular palliation.

Even with a staged surgical approach to palliation, HLHS carries a substantial risk of morbidity and mortality. This has however improved over the past decade, and recent data from the SVR trial reported a 12-month transplant free survival of 74 and 64 % in those palliated with a RV-PA conduit and mBTS respectively [30]. Despite this large randomized control trial, there still does not appear to be consensus on which shunt to use, largely because the survival benefit appears to narrow over time [30, 31], and the long-term effects of the ventriculotomy on ventricular function with use of the RV-PA conduit remain to be determined. The SVR trial is the largest prospective randomized trial comparing two different shunt types for initial palliation of patients with a single right ventricle.

Lesions with ductal dependent Qp will typically only require a stable source of Qp, which can be accomplished by use of a mBTS or PDA stent. Placement of the PDA stent is performed in the cardiac catheterization laboratory, and the mBTS is performed in the operating room. Finally, for lesions with excessive Qp, pulmonary artery banding alone may be sufficient. Although variations on each of these operations exist, they represent the spectrum of post-operative anatomy the intensive care physician is likely to encounter.

Since each anatomic arrangement establishes similar physiology, the important differences between them are the means by which each operation accomplishes its goals. The Norwood operation requires cardiopulmonary bypass, cardioplegia and a period of deep hypothermic circulatory arrest, although some techniques can limit circulatory arrest time [32, 33]. The heart, kidneys, brain, and other organs are exposed to a planned period of ischemia followed by reperfusion, which often results in a defined period of myocardial, renal, and perhaps endothelial dysfunction in the post-operative period. Use of the mBTS or PDA stent for provision of either pulmonary or systemic blood flow often results in low diastolic arterial pressure that may compromise coronary perfusion [34, 35]. In addition mesenteric perfusion may also be compromised, thereby increasing the risk of mesenteric ischemia or necrotizing enterocolitis [36–38]. In addition to compromised coronary and mesenteric perfusion, some investigators have suggested that pulmonary artery bands may increase the risk of subaortic obstruction and ventricular hypertrophy when used for palliation of specific lesions [39], though this assertion has also been disputed [39–41]. Both shunts and bands carry the risk of unilateral pulmonary artery obstruction and this should be included in the differential of late cyanosis after either of these

procedures. In the SVR trial, subjects palliated with the RV-PA conduit had a greater number of unintended cardiovascular interventions and complications despite having better overall survival [30]. These interventions were most commonly for shunt and pulmonary artery stenosis, and are congruent with other studies [42–46]. The most prominent risk factors for poor outcome following the Norwood procedure include low birth weight, tricuspid valve regurgitation (pre or post-operative), gestational age <37 weeks, greater number of post-Norwood complications (vocal cord paresis, diaphragm paralysis etc.) [47–49].

Post-operative Management

Many similarities exist for strategies of optimizing Qs and limiting Qp in the pre- and post-operative period. However, one should also consider then the effects of cardiopulmonary bypass and aortic cross clamping on myocardial function and PVR. Lability in PVR may exist due to ongoing inherent changes in the patient. Myocardial ischemia from aortic cross-clamp may lead to globally depressed ventricular function [50]. Post-operative issues may relate to low systemic cardiac output, excessive cyanosis or relatively high oxygen saturations.

Myocardial function (systolic and diastolic), competence of the atrioventricular and semilunar valves, presence of outflow obstruction, and the amount of Qp are crucial to optimizing DO_2 in single ventricle physiology. Early survival is therefore largely dependent upon achieving adequate DO_2 with restricted but sufficient Qp. In post-operative single ventricle patients, it is likely that Qp becomes limited by the size of the systemic to pulmonary artery shunt or pulmonary artery band, and further decreases in downstream resistance are of minimal consequence [51, 52]. More recent data suggest that management of total cardiac output (i.e. Qp + Qs) and SVR may be more effective [4]. Afterload reduction decreases Qp by decreasing SVR and increases the total cardiac output. Sodium nitroprusside, phenoxybenzamine, milrinone and more recently, phentolamine (since phenoxybenzamine is no longer readily available) have been used as systemic afterload-reducing agents, and to block the α-adrenergic receptor mediated vasoconstriction that occurs with drugs such as epinephrine. Agents such as phenoxybenzamine and phentolamine lower SVR, decrease Qp:Qs, and improve DO_2 after the Norwood operation, even though they may be associated with a decrease in systemic blood pressure [4]. Flow tank models of single ventricle physiology demonstrate that decreasing SVR primarily increases total cardiac output while Qp remains constant so that all of the additional cardiac output is directed to Qs [53]. β-adrenergic stimulation of the myocardium in conjunction with systemic vasodilation can further increase total cardiac output (Qp + Qs) without associated vasoconstriction. Other vasodilating agents can potentially be used to accomplish the same goal, although they involve different receptor mechanisms and cellular pathways.

It should be mentioned that not all post-operative single ventricle patients demonstrate pulmonary over-circulation. Elevated PVR can easily persist from the pre-operative period and cause severe cyanosis. This may be more common at altitude. Furthermore, there can be anatomic irregularities in the surgical source of Qp, such as shunt thrombosis, that can impair Qp. When Qp is very low (PaO_2 <30 torr), it can effectively increase pulmonary dead space and impair minute ventilation. The occurrence of respiratory acidosis in this setting is of grave concern because this will further increase PVR, limiting the ability to hyperventilate or alkalinize the patient. Management of high PVR in this population is much the same as in any other population. Alveolar recruitment strategies of ventilation are appropriate when there is atelectasis or pulmonary disease, but otherwise airway pressures should be kept to a minimum. High-frequency ventilation may be effective in inducing hyperventilation at low mean airway pressure [54]. Use of supplemental inspired oxygen, hyperventilation, and alkalosis (i.e. through the administration of sodium bicarbonate) may all be effective. Inhaled nitric oxide and PGE infusion have been used in these patients to selectively lower PVR as well. Raising systemic blood pressure by vasoconstriction may increase Qp and will usually increase SaO_2, but at the expense of decreased systemic perfusion. It is also essential to carefully evaluate the anatomic source of Qp to determine if urgent surgical or catheter based revision is necessary.

Management of Low Total Cardiac Output

It is important to recognize that any operation that converts a patient from unobstructed Qp to limited Qp inherently involves an afterload stress on the ventricle, which may acutely decrease stroke volume and thus cardiac output. Because low total cardiac output (Qp + Qs) in single ventricle physiology causes both low Qs and low SaO_2, it is of critical importance to rapidly diagnose and treat as previously discussed. In the absence of $SmvO_2$ monitoring, low SaO_2 with clinical signs of low cardiac output or shock (e.g., anuria, delayed capillary refill, high ventricular filling pressure, or metabolic acidosis out of proportion to the degree of cyanosis) suggest poor cardiac function, which newborns with single ventricle physiology are particularly at risk for [55–57]. Low Qs, particularly with low diastolic blood pressure (as is commonly observed in a newborn with a large PDA or after placement of a mBTS), or a high end-diastolic ventricular pressure (as is commonly observed with a volume-loaded heart or ventricular dysfunction that normally occurs after

cardiopulmonary bypass) can cause coronary perfusion pressure to become critically low – this further compromises systolic ventricular function, raises ventricular end-diastolic pressure and lowers systemic arterial pressure. If not rapidly corrected, this can result in profound hemodynamic decompensation. Inotropic support that increases Qs may also increase SaO_2 simply by increasing $SmvO_2$. The use of particular inotropic agents may also be associated with a change in Qp:Qs in addition to increases in total cardiac output. Riordan et al. studied the effects of epinephrine, dobutamine, and dopamine in an animal model of single ventricle physiology and found that dobutamine (5 and 15 μg/kg/min) increases Qp:Qs, epinephrine (0.05 and 0.1 μg/kg/min) decreases Qp:Qs, and dopamine (5 and 15 μg/kg/min) has minimal effects on Qp:Qs [21]. In this study, the use of low dose epinephrine (0.05 μg/kg/min) was associated with the greatest increase in PVR/SVR ratio, largely because of a decrease in SVR. This probably reflects the predominance of vascular β-receptor stimulation at this dose compared to α-adrenergic activation at higher dose and illustrates the importance of using vasodilating drugs as an accompaniment to inotropic agents with prominent vasoconstrictor properties. Use of a low dose arginine vasopressin following stage 1 palliation is becoming increasingly common for vasoplegia associated with low cardiac output syndrome following Norwood procedure. It has been shown to improve systolic blood pressure and urine output with decreasing postoperative fluid requirements and lactate in the first 24 h after surgery [58]. However, its use should be cautioned in the setting of ventricular dysfunction due to the increased afterload effects.

Other Management Considerations

Controversy exists over the optimal hemoglobin for patients with single ventricle physiology. The rationale for increasing hemoglobin concentration in the patient with single ventricle physiology are twofold (i) Increased hemoglobin concentration increases $SmvO_2$ and SaO_2 and decreases Qp:Qs, and (ii) DO_2 can be improved by increasing oxygen carrying capacity [59, 60]. The optimal hemoglobin for achieving this has not been established, but hemoglobin in the range of 13–15 mg/dL can have a positive influence on DO_2. Unfortunately there are no randomized controlled trials to guide transfusion goals before the second stage of palliation, and much of what is done is with the understanding of the physiologic mechanisms of oxygen carrying capacity and DO_2. Blackwood et al. examined the relationship between hemoglobin concentration and transfusion with outcome following stage 1 palliation. This prospective inception cohort study demonstrated that a higher hemoglobin nadir on postoperative days 2–5 was associated with higher early mortality, and a greater number of transfusions were associated with a longer duration of mechanical ventilation [61]. No specific cutoff values for the optimal hemoglobin were able to be determined from this study. Hemoglobin transfusion goals are likely different in the interstage periods and achieving a high hemoglobin may be of less importance after the Glenn procedure. Cholette et al. performed a randomized control trial in children following the second stage of palliation. Patients were randomized to a restrictive (hemoglobin <9 mg/dL) or liberal (hemoglobin ≥13 mg/dL) transfusion protocol. There were no differences in mean and peak arterial lactate levels, tissue oxygen delivery or clinical outcomes between the two groups [62], suggesting that a lower hemoglobin level may be well tolerated in this population.

Other post-operative considerations include delayed sternal closure, arrhythmias, afterload reduction, anticoagulation and need for extracorporeal life support (ECLS). Sternal closure after surgery can be associated with cardiac compression, decreased ventricular compliance, decreased cardiac output and thus hemodynamic and respiratory compromise. Delayed sternal closure is used by some centers, with reports of conflicting outcomes. Despite the conflicting results, the Society for Thoracic Surgery database was recently evaluated and delayed sternal closure was used in 74 % of cases. It was associated with prolonged length of stay and higher rate of post-operative infection [63]. Furthermore, delayed sternal closure was associated with increased mortality in the SVR trial [64]. It is well known that significant arrhythmias occur following stage I Norwood procedure, and may increase morbidity and mortality [47, 65, 66]. A recent study of 86 patients following the Norwood procedure reported 63 arrhythmias in 49 patients, and was associated with a higher mortality compared to arrhythmias occurring after the bidirectional Glenn procedure. Supraventricular tachycardia was the most common arrhythmia, occurring in 25 % of cases. Persistent bradycardia characterized by sinus node dysfunction or high grade atrioventricular block had the worst clinical outcome with a 73 % mortality [66]. Arrhythmia onset can occur late after the Norwood procedure (median time of 10 day, range 0–47 days), and male gender may be a risk factor (Gist et al., *unpublished data*).

Afterload reduction using angiotensin converting enzyme inhibitors (ACEi) is commonly used in adult patients with heart failure to reverse ventricular remodeling and preserve ventricular function in children with volume-overload conditions, and is known to improve somatic growth in infants with large left to right shunts [67–70]. Consequently some have believed it might be effective for long-term treatment of patients with post-operative single ventricle physiology. The Pediatric Heart Network conducted a randomized clinical trial investigating the effects of ACEi on somatic growth in infants with single ventricle physiology, with secondary

outcomes examining ventricular function and hemodynamic status. This study failed to demonstrate a beneficial effect of ACEi on improving somatic growth in infants, but was limited by the fact that the majority of patients had normal ventricular function [71].

Shunt patency following stage 1 palliation is of critical importance, and acute thrombosis can result in acute decompensation and death. Common anticoagulation strategies following stage 1 palliation include low dose aspirin (3–5 mg/kg), with an increase in clopidigrel use occurring in the past decade. Despite the use of clopidigrel, there does not appear to be any significant benefit, with no demonstrable reduction in mortality from any cause or shunt related morbidity [72].

ECLS in the single ventricle patient can be technically challenging. Veno-venous cannulation can be utilized if oxygenation is the principle problem. The most common indications for ventriculo-arterial (VA) extracorporeal membrane oxygenation (ECMO) in the single ventricle population after stage 1 palliation include low cardiac output states, secondary myocardial dysfunction and hypoxemia related to inadequate shunt flow. Secondary myocardial dysfunction can manifest as escalating inotropic requirements, refractory arrhythmias, increasing lactate or cardiac arrest [73]. High flows are typically needed (150–200 ml/kg/min) in order to overcome the excessive pulmonary runoff seen in patients with a mBTS or PDA stent. The high flow requires large enough cannula to achieve adequate Qs and manipulation of Qp via the ventilator, a high hematocrit, or permissive hypercapnea. In patients with a closed chest, cannulation via the neck is most commonly performed. Survival from ECMO following the Norwood procedure is variable, ranging from 30 % to 80 %, with the highest survival occurring in patients with isolated shunt obstruction [64, 74–79].

In addition to the immediate and intermediate post-operative considerations, operative complications may have a significant impact on long-term outcome, including length of hospital stay, and interstage issues (see below). The most commonly reported post-operative complications include vocal cord paresis or paralysis, feeding intolerance, bleeding, infection (sepsis, mediastinitis) and diaphragm paralysis [30, 64]. There are many excellent reviews and chapters that discuss the myriad issues pertaining to the evaluation and management of infants with HLHS in great detail – these would be difficult to improve upon and to attempt to do so is well beyond the intended scope of this chapter [30, 47, 66, 71–73, 80–90].

Interstage Management

Feeding intolerance, failure to thrive and poor oral feeding skills are particularly problematic in the interstage period between the Norwood and Glenn procedures. This period carries with it the highest risk of morbidity and mortality. Intensive interstage surveillance programs have been able to decrease morbidity and mortality [47, 91, 92]. Patients with single ventricle physiology following stage 1 generally respond poorly to decreases in preload and acute increases in afterload, both of which are not uncommon in the perioperative setting [93]. This may be more common in the setting of abdominal or laparoscopic surgery. Minimization of the stress associated with the procedure and maintenance of preload have been described as crucial in this setting [93]. Due to the associated comorbidities of reflux, poor feeding oropharyngeal dysfunction and failure to thrive, gastrostomy tube placement with or without Nissen fundoplication has been demonstrated to be beneficial for this population [94–97]. Watkins et al. reported their experience of evaluation of patients undergoing gastrointestinal surgery [98]. The majority of patients were tracheally extubated in the OR. They defined specific hemodynamic parameters for instability, and report many patients experiencing instability with induction, maintenance and emergence. A smaller proportion of patients required escalation of respiratory (23.1 %) or hemodynamic (15.4 %) support [98]. ECMO was needed in two patients (5 %), and there was one death. These data highlight the importance of the need for anticipation of perioperative instability, post-operative pain management and need for escalation of hemodynamic and respiratory support. Anticipation of instability may be best detected using invasive and noninvasive monitoring. These may include an arterial line, an internal jugular central venous line and NIRS.

A Rationale Approach to Single Ventricle Physiology in the Older Infant and Child

The Bidirectional Cavo-Pulmonary Anastomosis (BCPA)

The second and third stages of single ventricle palliation result in re-direction of Qp directly to the pulmonary arteries. This Qp is dependent upon non-pulsatile venous return from the systemic veins. The second stage, also known as the bidirectional cavo-pulmonary anastomosis (BCPA) involves removing the connection of the superior vena cava (SVC) from the heart, and connecting it directly to the pulmonary artery (Fig. 24.3). Other sources of Qp are eliminated or severely restricted. Anatomic variations include the hemi-Fontan. These procedures differ in that the hemi-Fontan includes the attachment of the proximal stump of the SVC to the underside of the pulmonary artery, but this connection is then patched to avoid flow of deoxygenated blood into the right atrium from the pulmonary artery. The BCPA has been remarkable for the relatively low level of associated morbidity, and mortality of less than 3 % [99].

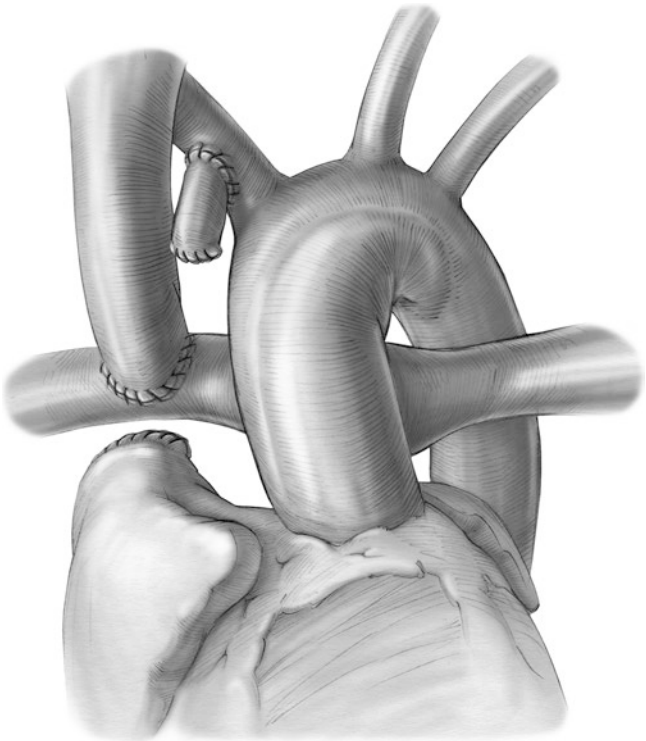


Fig. 24.3 Completion of the bidirectional cavopulmonary (Glenn) anastomosis – the second stage of palliation for hypoplastic left heart syndrome (Courtesy of James St. Louis, MD)

The real hemodynamic advantage of the BCPA compared to shunted or banded single ventricle physiology is in the reduction of the volume load on the ventricle. This occurs because the right-to-left shunt is eliminated and all Qp is effective pulmonary flow. The ventricle now only pumps Qs, not Qp + Qs [100]. Some of the Qs (the portion distributed to the upper body) passes through the lungs before reaching the ventricle again and thus all blood reaching the lungs is deoxygenated. The advantageous consequences of this volume reduction go beyond simply lowering the amount of blood the ventricle needs to pump to maintain adequate systemic cardiac output. There is an acute increase in wall thickness and decrease in cavity dimension that has been associated with improved tricuspid valve function [101], and there is overall improved efficiency of the ventricle. Preload and afterload are both decreased, although there is no measurable increase in ventricular contractile state [102].

Because Qp is supplied by upper body systemic venous return, one consequence of conversion to a BCPA is an acute rise in SVC pressure. Selection of patients with low PVR as candidates for the BCPA minimizes the risk of clinical complications arising from elevated SVC pressure, but SVC syndrome can occur nonetheless. Failure to maintain low SVC pressure following the BCPA can also lead to problems maintaining an adequate SaO_2. Small veno-venous collateral vessels (such as a persistent left SVC or vein of Marshall) may enlarge in size following a BCPA and allow a *pop-off* for desaturated blood in the SVC to bypass the lungs and thus contribute to arterial desaturation [103]. When the anastamosis is performed as part of a hemi-Fontan rather than a bidirectional Glenn, a right-to-left shunt may occur if there is a persistent communication between the SVC and right atrium. Table 24.4 summarizes the key causes of hypoxemia in patients following the BCPA and Fontan procedure.

Table 24.4 Differential diagnosis of hypoxemia after the bidirectional Glenn and Fontan procedure

	Causes
Pulmonary venous desaturation	Pulmonary arteriovenous malformations
	Pleural effusion
	Pulmonary edema
	Infection (Pneumonia)
	Persistent left superior vena cava
Reduced pulmonary blood flow	Superior vena cava obstruction
	Increased pulmonary vascular resistance
	Pulmonary venous hypertension
	Restrictive atrial septum
	Pulmonary artery distortion
Systemic venous desaturation	Anemia
	High oxygen consumption states
	Low systemic cardiac output

Early extubation following the BCPA procedure is optimal. Positive pressure ventilation is known to decrease systemic venous return. In order to minimize the SVC pressure following the BCPA procedure, it is desirable to minimize the positive pressure and PEEP. Less than physiologic PEEP can however result in atelectasis and ultimately result in increased PVR and suboptimal pulmonary blood flow. As previously described in the neonate with single ventricle physiology, favorable hemodynamics are most likely maintained by using ventilator settings that allow the end-expiratory lung volume to approximate FRC, since PVR is lowest at FRC. The beneficial effects of negative pressure ventilation resulting from early extubation will generally be associated with increased pulmonary blood flow. Negative pressure ventilation has been shown to improve cardiac output after the Fontan operation, and would likely have similar effects following the BCPA [104]. When lung disease such as pneumonia or acute respiratory distress syndrome occurs in the patient with a BCPA, higher airway pressures may actually promote Qp and minimize pulmonary artery pressure if the higher airway pressure helps maintain FRC.

A unique aspect of the physiology of the BCPA is that Qp is largely dependent on the resistance of two highly but differentially regulated vascular beds [105]. The cerebral and pulmonary vasculature have opposite responses to changes in carbon dioxide, acid–base status, and oxygen. This can make treatment of elevated pulmonary vascular resistance or low arterial saturation particularly challenging. Hyperventilation

and alkalosis for example, may have limited utility in this setting and can even be detrimental [105–107]. Although they are effective pulmonary vasodilators, hyperventilation and alkalosis cause cerebral vasoconstriction. Since Qp is dependent on venous return via the SVC (largely made up of cerebral blood flow), maneuvers that limit cerebral blood flow may decrease pulmonary flow and exacerbate hypoxemia. Other frequently used techniques for decreasing pulmonary resistance such as deep sedation/anesthesia may also reduce cerebral blood flow and therefore fail to increase Qp even if they successfully reduce resistance. Inhaled nitric oxide, which acts selectively on the pulmonary vasculature, has been reported to be effective in reducing the transpulmonary pressure gradient for patients after the BCPA and may therefore be the best treatment for high pulmonary resistance and hypoxemia [108]. In the patient with normal PVR, mild hypoventilation will generally result in improved cerebral blood flow and thus increased Qp. Patients with a BCPA will also benefit from return to spontaneous ventilation as soon as their clinical state allows.

The persistence of right-to-left shunts due to additional sources of Qp, or aortopulmonary collateral vessels and persistent pleural effusions will result in elevated central venous pressures, a reduction in Qp and a subsequent decline in cardiac output [109, 110]. Changes in ventricular geometry that occur with unloading of the ventricle at the time of the BCPA may decrease the left-to-right shunt across a ventricular septal defect or bulboventricular foramen. When systemic outflow is dependent on flow through a ventricular septal defect or bulboventricular foramen (as in tricuspid atresia with transposed great arteries), acute decreases in ventricular dimension may precipitate effective sub-aortic stenosis. The appearance of an ejection murmur in a patient with susceptible anatomy following bidirectional cavopulmonary anastomosis should prompt a complete assessment for this phenomenon.

Post-operative considerations following the BCPA include the potential complications. Phrenic nerve paralysis resulting in diaphragm paresis/paralysis occurred in 4.7 %, pleural effusion in 2.8 % and chylothorax in 1.9 % [111]. The presence of diaphragm paralysis could have significant implications for early extubation, or for possible reintubation, and warrants urgent evaluation. Risk factors for mortality following the BCPA procedure include an elevated SVC pressure and transpulmonary gradient, AV valve regurgitation and the presence of a systemic right ventricle [112]. The transpulmonary gradient is the difference between the mean pulmonary artery pressure (in the BCPA circuit) and the mean left atrial pressure. A normal transpulmonary gradient is less than 10 mmHg. Table 24.5 outlines the differential diagnosis of elevated pulmonary artery and left atrial pressures following the BCPA or Fontan procedure.

ECLS following the BCPA poses several unique challenges. Specifically, one has to achieve adequate lower body systemic venous drainage for adequate cardiac output, and sufficient cerebral venous drainage to prevent intracerebral hypertension [73]. Since the SVC and IVC flows are completely separated, this requires cannulation of both the atrium and the SVC if one needs to support both oxygenation and cardiac output. Depending on the indications for ECLS, it may be possible to achieve effective results only cannulating one or the other, but once must carefully consider the intended goals and consequences. Effective cardiopulmonary resuscitation for cerebral oxygen delivery in this population is unattainable, and as a result, emergent cannulation often time results in significant neurologic injury. There is a high risk for death and severe neurologic injury whether ECLS is employed for progressive myocardial dysfunction, immediate post-operative ventricular failure or a cardiac catheterization related event [113]. As a result, takedown of the BCPA with provision of pulmonary blood flow by a shunt

Table 24.5 Differential diagnosis of abnormal hemodynamics in patients following the bidirectional cavo-pulmonary anastomosis or Fontan procedure

		PAp (mmHg)	LAp (mmHg)	TPG (mmHg)	Systemic saturation
Elevated PA pressure	High pulmonary vascular resistance:	>15	<5 (normal)	>10	80 %
	Intrinsic/pulmonary				
	Obstruction to PA or PV (thrombosis or stenosis)				
Elevated LA pressure	Single ventricle dysfunction or noncompliance	>10–15	>5	<10	80 %
	Subaortic narrowing				
	AV valve insufficiency				
	Pericardial tamponade				
	AV dissociation				

Normal pulmonary artery pressure is 10–15 mmHg, Normal left atrial pressure <5 mmHg. Normal transpulmonary gradient is less than 10 mmHg. Normal systemic saturation is 80 ± 5 %

Pap pulmonary artery pressure, *Lap* left atrial pressure, *TPG* transpulmonary gradient, *PA* pulmonary artery, *PV* pulmonary vein, *LA* left atrium, *AV* atrioventricular

has been suggested to be performed early in the setting of a failing BCPA circulation [73]. Interstage attrition between in the BCPA and Fontan procedure is reported to be approximately 12 % [114], although early analysis of the SVR trial data suggests this might be an overestimate [30]. Despite the fact that right ventricular dysfunction was not found to be a risk factor for interstage mortality, the significance of moderate or greater tricuspid valve regurgitation may result from, and contribute to volume overload, that could have lasting effects on ventricular function [114].

Total Cavo-Pulmonary Anastomosis

The Fontan operation has several commonly used anatomic variants, all designed to achieve optimum fluid dynamics and minimize the risk of long-term complications. Although one may still encounter older individuals with direct right atrial to pulmonary artery connections, the most common current approaches to the Fontan operation are the creation of either an intracardiac lateral tunnel or extra-cardiac conduit. The lateral tunnel involves placement of a semi-circular tube, usually Gore-Tex (WL Gore & Associates, Flagstaff, AZ), along the lateral wall of the right atrium from the inferior vena cava to the SVC. Patients with a prior bidirectional Glenn then need to have the proximal portion of the SVC reconnected to the pulmonary artery, whereas those who have had a prior hemi-Fontan need only to have the patch between the pulmonary artery and right atrium taken down. The extra-cardiac conduit uses a complete circular tube of Gore-tex or pericardium to connect the inferior vena cava to the pulmonary artery (Fig. 24.4). The conduit is placed along the outer surface of the right atrium and thus creates a connection incapable of dilating over time, unlike the classic Fontan, or even potentially the lateral tunnel. Either variation on the Fontan can be fenestrated by leaving a hole of known size in the baffle. In the case of the extra-cardiac Fontan, fenestration requires connection of the conduit to the atrial wall.

The different approaches to the Fontan connection may have implications for post-operative physiology, although no consensus on which technique is preferable has yet been reached. The arguments in favor of the lateral tunnel are that it is less thrombogenic, can be done at a younger age and retains the possibility for growth without the likelihood of severe dilation. Those who favor the extra-cardiac approach argue that it preserves kinetic energy better, that it can be performed without cardioplegia thereby reducing the incidence of post-operative myocardial dysfunction and that it is less arrhythmogenic since there is no atrial suture line [115, 116]. In the absence of a conclusive study, the differences between Fontan techniques remain largely theoretical.

Fontan physiology is a hybrid of bidirectional Glenn and normal cardiovascular physiology. Like the BCPA, Qp is dependent on systemic venous pressure, and all Qp is effective [100]. If the Fontan baffle is fenestrated, there may still be a right-to-left shunt causing some mild systemic arterial desaturation, but the systemic and pulmonary circulation are largely separated, as with a normal heart. Important issues for the intensive care physician arise when there is elevated pulmonary artery pressure. This can occur in the setting of elevated PVR, mechanical pulmonary artery obstruction, or elevated pressures in the pulmonary venous atrium due to myocardial dysfunction (Table 24.5). Elevated pulmonary artery pressure (>10–15 mmHg) and impaired ventricular function are associated with poor outcome after the Fontan operation [117], that can be secondary to third space losses that occur with elevated central venous pressures. As these fluid losses progress, patients develop pleural effusions, ascites and generalized edema. In the face of a full abdomen, heavy chest wall and smaller effective pleural cavities, it often becomes necessary to increase ventilator pressures to

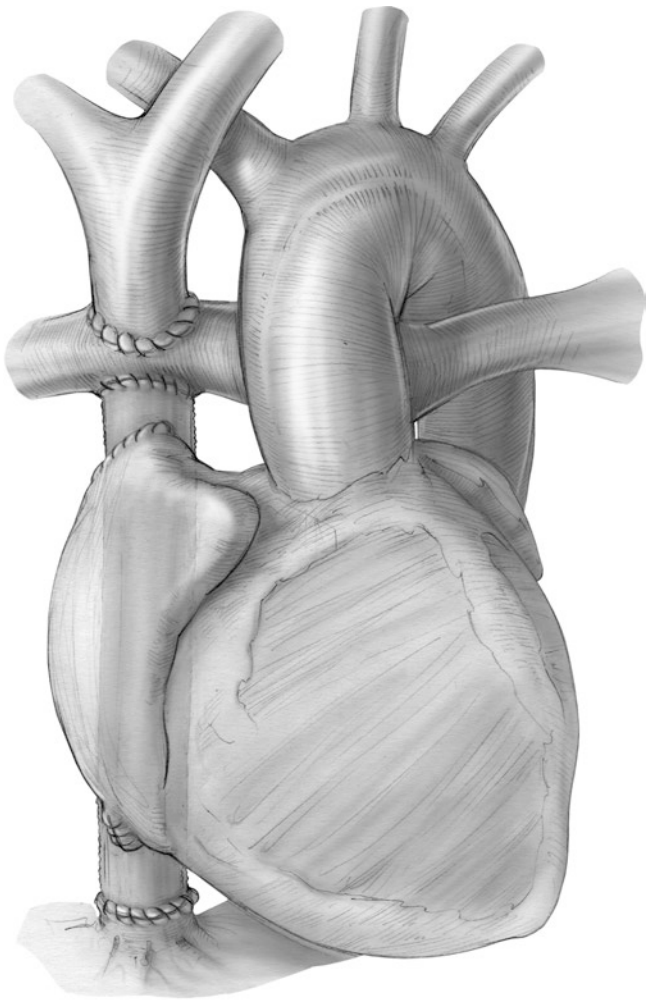


Fig. 24.4 The Fontan procedure (intracardiac lateral tunnel Fontan) – the third and final stage palliation for hypoplastic left heart syndrome (Courtesy of James St. Louis, MD)

maintain adequate functional residual capacity and tidal volume. Increased intrathoracic pressure, particularly in the absence of parenchymal lung disease than effectively raises pulmonary resistance and necessitates even higher venous pressures to maintain cardiac output, creating a vicious circle. Furthermore, as central venous and intra-abdominal pressure rise, renal perfusion pressure decreases, especially in the face of low cardiac output and borderline hypotension. In general, a Fontan fenestration can lower the risk of some of these complications by providing a source of systemic blood flow that is not dependent on passing through the pulmonary circulation [118]. The fenestration can also decrease pulmonary artery pressure enough to reduce third space losses of fluid. Despite the benefits of maintaining cardiac output in the fenestrated Fontan patient with high PVR, there remains the risk associated with systemic embolization, systemic desaturation, and those associated with later catheter closure [119, 120]. In the current era, some centers have adopted the philosophy that Fontan fenestration should be reserved for patients at highest risk, which includes those with a single lung, elevated PVR or transpulmonary gradient, significant atrioventricular valve regurgitation or poor ventricular function and those who have anatomy that is not amenable to an extracardiac conduit [118]. A recent study demonstrated that hospital length of stay and duration of chest drains were not increased with the use of a nonfenestrated extracardiac conduit [118]. Finally, the effects of altitude on the Fontan circulation have been largely unknown. A recent study demonstrated that moderate altitude was not associated with increased PVR or outcomes in patients with a single ventricle after the BCPA or Fontan procedure [121]. Despite the fact that altitude does not seem to affect immediate outcomes following the Fontan procedure, it does appear to impact the exercise capacity in these patients, and can increase risk of adverse events in patients who move from low to moderate altitude [122]. Exercise impairment is due to a reduction in stroke volume, which ultimately leads to inadequate tissue oxygen delivery to the muscles, and early onset of anaerobic metabolism. There appears to be limited increase in passive pulmonary blood flow with exercise and coupled with the increased sympathetic tone at elevation, oxygen delivery, ventilation/perfusion matching and forward flow of blood to the lungs are compromised [123].

When an individual with Fontan physiology is in a low cardiac output state, it is essential to determine and treat the underlying cause. It is not uncommon for post-operative Fontan patients to require large amounts of volume in the first day after surgery. Persistently low central venous and left atrial pressures strongly suggest the need for volume. Pulmonary artery obstruction should be considered as the cause of low output when left atrial pressure is low and central venous pressure is high. If central venous pressure is not monitored, large third-space fluid losses with a low or normal left atrial pressure should raise the suspicion of this diagnosis. Even in the presence of a fenestrated Fontan, the capability of the fenestration to preserve cardiac output in the face of anatomic or physiologic obstruction to pulmonary blood flow is significantly limited compared to the situation after the bidirectional cavo-pulmonary anastomosis. Therefore, limited pulmonary flow can result in low cardiac output and, when a fenestration is present, significant cyanosis. Cyanosis can also result from intrapulmonary arteriovenous malformations or ventilation-perfusion mismatch related to low cardiac output.

If high pulmonary resistance is responsible for the elevation of central venous pressure, institution of the standard therapies of supplemental oxygen, hyperventilation and alkalosis is indicated. As with the bidirectional Glenn patient, the use of high positive pressures to achieve these ends may be counter-productive. Negative pressure ventilation can augment stroke volume and cardiac output and high-frequency jet ventilation may lower $PaCO_2$ at low mean airway pressures [54, 104]. Intravenous vasodilators such as prostacyclin should be used with caution because of the risk of systemic vasodilation with limited cardiac output. Inhaled nitric oxide has been reported to be effective in lowering the transpulmonary pressure gradient [124]. Sildenafil, a selective inhibitor of phosphodiesterase type 5 has been shown to decrease pleural effusions and increase systemic saturations and exercise performance following the Fontan procedure [125, 126]. The effects of the immediate use of sildenafil following the Fontan procedure have not been studied.

Low cardiac output with high left atrial and central venous pressures indicates myocardial dysfunction in the patient with Fontan physiology. Myocardial dysfunction can occur from ischemia-reperfusion injury if aortic cross clamping and cardioplegia are used to create the Fontan baffle. It may also be related to poor pre-operative myocardial function. The only effective long-term therapy for low cardiac output with ventricular dysfunction following a Fontan operation is to improve cardiac output and reduce left atrial pressure. The use of inotropic agents that do not increase ventricular afterload, such as phosphodiesterase inhibitors (milrinone), dobutamine and low dose epinephrine ($\leq$0.05 μg/kg/min) may be helpful. If systemic blood pressure will tolerate it, aggressive afterload reduction with vasodilating agents may also lower left atrial pressure significantly. If there is good reason to believe the insult to ventricular function is reversible, mechanical circulatory support can also be effective therapy. Because persistent aortopulmonary collateral vessels can be associated with hemodynamics similar to those of ventricular dysfunction, aggressive assessment and embolization of these vessels may be useful in this situation, although recent retrospective data was not able to demonstrate an association between pre-operative coiling and shorter postoperative hospital stay or improved late outcomes [124].

In addition to post-operative unexplained hypoxemia (Table 24.4), additional post-operative considerations warrant discussion. Rhythm disturbances following the Fontan operation are generally poorly tolerated. Junctional rhythm can be overcome using atrial pacing, which reduces left atrial pressure and increases atrial kick as a contribution to systemic stroke volume. Tachyarrythmias such as atrial flutter and junctional ectopic tachycardia are associated with an increased risk of hemodynamic instability (low cardiac output and myocardial dysfunction) following the Fontan procedure due to loss of atrioventricular synchrony [63, 127–129]. Early recognition and intervention of arrhythmias is imperative prior to onset of cardiovascular collapse. Thromboembolic complications are not uncommon following the Fontan operation [130]. The etiology is multifactorial, including hypercoagulabilty, endothelial dysfunction, decreased levels of protein C, protein S, antithrombin III, certain coagulation factors and increased platelet reactivity [131]. While it is clear that anticoagulation is necessary, the exact combination of pharmacologic therapies remain to be determined [132, 133]. Other long-term complications from the Fontan operation include but are not limited to protein losing enteropathy, plastic bronchitis, and hepatic cirrhosis [134–140]. The etiology for these complications may be related to elevated venous pressures.

Conclusion

In conclusion, single ventricle congenital cardiac lesions are a complex interplay between maintaining cardiac output and pulmonary blood flow. Patients are living longer following the Fontan procedure, however heart transplantation is often considered to be the fourth stage of palliation in this complex condition.

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Long-Term Outcomes in Congenital Heart Disease

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Abstract

The long-term survival of children with congenital heart disease (CHD) continues to improve due to advancements in cardiac surgery and perioperative care and enhancements in cardiovascular diagnostic and interventional capabilities. As the mortality rate associated with congenital heart defects has continued to decline, the number of adults with CHD has increased exponentially. In fact, it is estimated that there are now more than one million adults living with CHD. While ongoing improvement in short-term results remains important, the clinical focus of medical caregivers has expanded to evaluating late outcomes. Understanding the long-term outcomes of our CHD survivors allows for intervention opportunities to prevent these late complications and treat them if they are present. The late outcomes encompass not only cardiac specific physiologic and anatomic abnormalities, but also important non-cardiac sequelae such as neurodevelopmental and psychosocial morbidity on the individual and their families.

This chapter will describe the long-term outcomes of specific CHD lesions. The specific CHD lesions are grouped into broad categories including left-to-right shunts, right and left-sided obstructive lesions, mixing lesions, and single ventricle anatomies. The evaluation of neurodevelopmental outcomes is discussed as we attempt to better understand brain development in CHD patients and minimize brain injury that may result from the underlying CHD lesion or the therapies required to repair or palliate the defect. Each section begins with an overview of the anatomy and physiology of the lesion followed by a brief description of the surgical intervention. Complications and long-term outcomes are then described for each lesion.

Keywords

Congenital heart disease • Congenital heart surgery • Outcomes • Neurodevelopmental outcome

Introduction

The long-term survival of children with congenital heart disease (CHD) continues to improve due to advancements in cardiac surgery and perioperative care and enhancements in cardiovascular diagnostic and interventional capabilities. As the mortality rate associated with congenital heart defects has continued to decline, the number of adults with CHD has increased exponentially. In fact, it is estimated that there are now more than one million adults living with

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CHD [1]. While ongoing improvement in short-term results remains important, the clinical focus of medical caregivers has expanded to evaluating late outcomes. Understanding the long-term outcomes of our CHD survivors allows for intervention opportunities to prevent these late complications and treat them if they are present. The late outcomes encompass not only cardiac specific physiologic and anatomic abnormalities, but also important non-cardiac sequelae such as neurodevelopmental and psychosocial morbidity on the individual and their families.

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Categories of Lesions

Left-to-Right Shunts

Atrial Septal Defects (ASD)

There are three types of ASDs: ostium secundum, ostium primum, and sinus venosus defects. The most common type is the secundum ASD, accounting for 70 % of all atrial defects [2]. The ostium primum ASD is the second most common ASD type, accounting for 20 % of all ASDs, often a part of a complete atrioventricular canal defect. The least common ASD type is the sinus venosus defect, comprising 10 % of all ASDs, in which anomalous right upper and middle pulmonary venous return is common. The size and diastolic compliance of the ventricles determines the direction and amount of atrial level shunting in these patients. While transcatheter device closure of secundum type defects has become more widespread, surgical intervention remains a mainstay and is the only approach for ostium primum and sinus venosus ASDs. Surgical techniques for ASD closure include primary suture closure of small to moderate ASDs, autologous pericardial patch closure of larger defects, and baffle closure when associated with partial anomalous pulmonary venous connection [3, 4]. Mortality is nearly zero with relatively minor complications. Long-term survival in patients following secundum ASD repair before age 25 years is 97 % at 5 years, 90 % at 10 years, 83 % at 20 years, and 74 % at 30 years [5]. Repair and outcomes of ostium primum defects is discussed below in the section on atrioventricular canal defects.

Residual atrial shunts are rare following surgical repair. Pulmonary venous obstruction can develop when associated with anomalous drainage although the incidence is less than 1 % [6]. In adults, pulmonary vascular obstructive disease may be present in 15 % of the ASD population in whom the ASD is undiagnosed for many decades [7]. Due to this risk, most pediatric cardiologists advocate ASD repair during childhood. Atrial flutter or fibrillation is a late complication evident in unrepaired and repaired patients with some relation to the timing of surgery and pulmonary artery pressure. When repaired in early childhood, atrial arrhythmias and sick sinus syndrome are very rare. If repaired before age 40 years, the incidence is 1 %. After age 40 years, the risk of atrial arrhythmias and sick sinus syndrome increases to 15 % [8].

Ventricular Septal Defects (VSD)

The five types of VSDs are muscular, perimembranous or conoventricular, malalignment, inlet, and supracristal or subpulmonary. Not including those VSDs which are part of more complex CHD, isolated ventricular septal defects are the most common congenital heart defect comprising 15–20 % of all congenital heart lesions. Approximately 50–75 % of small muscular and perimembranous VSDs will close spontaneously within the first 2 years of life [9–12]. Those defects that are considered restrictive measure smaller than the aortic valve, have a pressure gradient between the left and right ventricles, are usually hemodynamically insignificant. These patients do not require surgical closure if there is normal pulmonary artery pressure and no secondary evidence of left sided volume overload. If a hemodynamically significant VSD is not repaired, irreversible pulmonary vascular obstructive disease will occur over time resulting in Eisenmenger physiology.

In children with a VSD, the development of aortic cusp prolapse and associated aortic regurgitation, double chamber right ventricle, and subaortic membrane are indications for VSD closure despite the VSD potentially being restrictive. Larger hemodynamically significant VSDs will require surgical repair. Long-term survival is excellent for most patients following VSD repair, particularly in those individuals with an isolated defect, with 87 % survival at 25 years [9]. Long-term complications after VSD repair include the development of aortic regurgitation (15 %), sinus node dysfunction requiring implantation of a pacemaker (5 %), and residual pulmonary hypertension from pulmonary vascular obstructive disease (5 %) [13].

Atrioventricular Canal Defects (AVCD)

AVCDs may be sub-categorized into complete, transitional, and partial or incomplete defects. A complete AVCD is the most common type of AVCD, which includes an ostium primum ASD, inlet VSD, and common atrioventricular valve. The left ventricular outflow tract is elongated due to the

downward, or apical, displacement of the posterior mitral valve leaflet and superior bridging leaflet. Attachments to the crest of the ventricular septum are often present. The elongated left ventricular outflow tract classically resembles a "goose neck" on echocardiogram and angiography. In most children with this defect, the atrioventricular (AV) valve sits equally over two normal-sized ventricles. This is referred to as a "balanced" AVCD. Less commonly, in a more complex form of AVCD, there may be hypoplasia of one ventricle with the common AV valve directed more toward one ventricle. This is referred to as an "unbalanced" AVCD. Clinical symptoms of congestive heart failure result from the large VSD. Complete AVCD occurs in approximately 40–50 % of children with trisomy 21. Rarely, do children with trisomy 21 have evidence of an unbalanced AV canal defect or left ventricular outflow tract obstruction. Other lesions associated with an AVCD include Tetralogy of Fallot, coarctation of the aorta, patent ductus arteriosus, left superior vena cava to coronary sinus, and heterotaxy syndrome (asplenia type).

Surgical repair of a complete balanced AVCD usually occurs between 3 and 6 months of age. If surgery is not performed during early infancy, these children are at risk for developing pulmonary vascular obstructive disease and Eisenmenger physiology. Surgical repair is performed with either a traditional single patch or a two-patch technique to close the atrial and ventricular septal defects and divide the common AV valve into two separate inflows. The AV valve leaflets are resuspended onto the pericardial patch and the cleft in the left atrioventricular valve is closed. The modified single patch repair (Nunn procedure) consists of suturing the AV valve leaflet to the crest of the ventricular septum to close the inlet VSD while using a patch to close the ostium primum ASD component [14]. In a transitional AVCD, there is a large ostium primum ASD and a small inlet VSD. Surgery for the transitional AVCD includes suture closure of the small inlet VSD, septation of the common AV valve into tricuspid and mitral valve components with closure of the mitral valve cleft, and either a single patch technique or Nunn procedure to close the ostium primum ASD. A patch is generally not utilized to close the small inlet VSD in the transitional AVCD. In a partial or incomplete AVCD, an ostium primum ASD and cleft in the anterior mitral valve leaflet are present. The ostium primum ASD is closed using a single patch technique with closure of the anterior mitral valve cleft.

Hospital mortality following repair of a complete AVCD is 2.5 % [15]. Freedom from reoperation is 96 % at 1 year, 90 % at 5 years, and 84 % at 15 years in patients with a complete AVCD. Similarly, in those with a partial or incomplete AVCD, freedom from reoperation is 96 % at 1 year, 92 % at 5 years, and 85 % at 15 years [16]. Median age at reoperation after complete AVCD repair is 5 years after the initial surgery [16]. The most common indication for reoperation is severe left-sided AV valve regurgitation following surgical repair of complete and partial or incomplete AVCDs. Of the patients requiring reoperation for valve regurgitation, approximately one-third will undergo mitral valve replacement [17, 18]. Survival is 91 % at 10 years and 86 % at 15 years following reoperation for left AV valve regurgitation in patients with a complete AVCD [17]. The presence of severe left AV valve regurgitation preoperatively increases the likelihood of significant residual or recurrent AV valve regurgitation postoperatively [17]. The incidence of left ventricular outflow tract obstruction is 10–15 % and is more common with a partial or incomplete AV canal defect [17]. The development of subaortic obstruction is affected by the abnormally elongated left ventricular outflow tract and the presence of AV valve tissue and attachments to the ventricular septum. Rarely, this may compromise the function of the aortic valve.

Although uncommon, left AV valve stenosis may occur in the setting of mild hypoplasia of the AV valve or a single papillary muscle (parachute mitral valve) [17]. Residual atrial septal defects are rare. Small, hemodynamically insignificant residual ventricular shunts may occur but usually resolve spontaneously [17]. Those children repaired later in infancy or with trisomy 21 may develop pulmonary hypertension and pulmonary vascular occlusive disease [19]. Postoperative complete heart block may occur in up to 6 % of patients, necessitating placement of a pacemaker [20]. In the immediate postoperative period, junctional ectopic tachycardia or atrial arrhythmias may occur.

Right Sided Obstructive Lesions

Tetralogy of Fallot (TOF)

Tetralogy of Fallot is the second most common cyanotic congenital heart defect in the newborn. The four anatomical features of TOF include: subpulmonary/pulmonary valve stenosis, anterior malalignment VSD, "overriding" aorta, and right ventricular hypertrophy (RVH). TOF results from anterior malalignment of the conal or infundibular septum and underdevelopment of the subpulmonary infundibulum. Associated anomalies in children with TOF include coronary artery abnormality in 5 % (left anterior descending coronary artery off the right coronary artery), additional muscular VSDs, right aortic arch in 25–30 %, and discontinuous branch pulmonary arteries in 12 % due to the extension of ductal tissue onto the origin of the left pulmonary artery [21, 22]. The left anterior descending coronary artery arising from the right coronary artery and coursing across the right ventricular (RV) infundibulum may prohibit a transannular patch repair and alter surgical technique [23–26].

Elective surgical repair is usually performed between 4 and 6 months of age in infants who are clinically stable with an acceptable oxygen saturation of greater than 85 % and no history of "hypercyanotic spells". TOF repair consists of patch closure of the VSD, division of RV muscle bundles, and transannular patch repair when necessary for pulmonary

annular hypoplasia. A right ventricular to pulmonary artery conduit may be necessary if the left anterior descending coronary artery arises from the right coronary artery and crosses the infundibulum. For those children with critical pulmonary valve stenosis, severe cyanosis during the neonatal period, or progressive cyanosis during early infancy, some institutions may perform a palliative surgery with placement of an aortopulmonary shunt with subsequent complete repair and shunt takedown later in infancy. The risks of palliation with a shunt include volume overload of the left ventricle from the shunt, branch pulmonary artery distortion or differential growth, and possible shunt thrombosis with severe hypoxemia. In the current era, early correction with VSD closure, RV muscle bundle resection, and pulmonary valvotomy and/or full or limited transannular patch is generally preferred. Potential advantages of early complete repair include resolution of cyanosis, preservation of right ventricular (RV) systolic and diastolic function given reduced need for extensive RV muscle bundle resection, improved late left ventricular function, and decreased incidence of late arrhythmias.

Even if operated on in the neonatal period, survival following TOF repair is excellent. Five-year survival is approximately 93–95 % [27]. The reintervention rate has been low although the long-term effects of chronic pulmonary regurgitation remain an important problem [28, 29]. Specifically, the risk of ventricular arrhythmias, which may be as high as 10 % [30] and myocardial dysfunction, is increased in those individuals with moderate or greater pulmonary regurgitation. Severe pulmonary regurgitation leads to RV dilation and dysfunction. There is data suggesting the development of LV systolic dysfunction is related to RV dilation and dysfunction, indicating potential adverse ventricular-ventricular interaction [31, 32]. There is evidence that decreased longitudinal and circumferential RV strain is associated with interventricular electromechanical dyssynchrony. Timing of pulmonary valve replacement is still debated. Clinical symptoms, including exercise tolerance, progressive right ventricular dilatation and dysfunction, and ventricular arrhythmias are important factors. With advancements in cardiac MRI, which is considered to be the gold standard for RV quantification, a RV end-diastolic volume index of 150–180 mL/m^2 [33–36], RV ejection fraction <47 %, or LV ejection fraction of <55 % are considerations regarding optimal timing of pulmonary valve replacement when severe pulmonary regurgitation is present [36].

Survival in patients with TOF exceeds 90 % 30 years after repair [27]. Patients with TOF must be followed over the long term for recurrent right ventricular outflow tract obstruction, right ventricular dilation secondary to free pulmonary regurgitation, and residual branch pulmonary artery stenosis. The risk of sudden death is 1.2 % 10 years following TOF repair, 2.2 % at 20 years, 4 % at 25 years, and 6 % at 30 years. The cumulative incidence of life-threatening arrhythmias is 10 % [37, 38]. A QRS duration, related to right ventricular size, of greater than or equal to 180 msec is associated with sustained ventricular tachycardia and sudden cardiac death [39]. This may be related to residual RV outflow tract obstruction, RV volume overload, or ventricular scarring. For those individuals with postoperative complete heart block (1–3 %), pacemaker implantation is necessary [40].

Tetralogy of Fallot with Pulmonary Atresia (TOF/ PA)

Outcomes of children born with TOF/PA are variable. Long-term survival is greatly impacted by the size and architecture of the branch pulmonary arteries. Those individuals with confluent, well-developed pulmonary arteries with distribution among the majority of lung segments often do well. However, in many cases, the branch pulmonary arteries are not confluent, diminutive, and many lung segments are supplied primarily by multiple aortopulmonary collateral arteries (MAPCAS) [41, 42]. MAPCAS are abnormal vessels arising directly from the aorta that connect the systemic circulation to the pulmonary circulation. These vessels are often tortuous and become stenotic. The degree of cyanosis in these patients is dependent upon the degree of collateralization.

Cardiac catheterization is usually performed to establish size and continuity of the central pulmonary arteries in addition to the origin and distribution of the MAPCAs. The management strategy is to rehabilitate the branch pulmonary arteries (may be surgical and/or transcatheter approach), establish RV-pulmonary continuity, and close the VSD. Due to hypoplasia and stenosis of the pulmonary arteries, pulmonary artery rehabilitation in the cardiac catheterization laboratory is necessary. RV hypertension is common, therefore, in a subset of patients, the VSD may not be able to be closed. Furthermore, those children who have undergone placement of a right ventricle to pulmonary artery conduit, will require multiple conduit replacements and/or transcatheter valve placement over a lifetime due to progressive conduit stenosis and regurgitation.

A unifocalization procedure where the MAPCAS are disconnected from the aorta to establish continuity with the RV may be done as an initial palliative procedure with the VSD left open or as a single surgery with complete unifocalization and VSD closure. In one large series of 464 patients undergoing unifocalization, immediate VSD closure was possible in only 56 % of patients with 90 % undergoing VSD closure within 5 years [43–45]. Survival following a complete repair (with VSD closure) is 86 % at 10 years and 75 % at 20 years [46]. However, survival without complete intracardiac repair (VSD closure) is 73 % at 10 years and 61 % at 20 years [46]. A significant predictor for late mortality is reopening of the VSD [46].

Tetralogy of Fallot with Absent Pulmonary Valve

Tetralogy of Fallot with absent pulmonary valve occurs in approximately 3–6 % of infants with TOF [21, 47]. In these patients, the pulmonary valve is absent or very rudimentary. Therefore, there is severe pulmonary regurgitation and

associated right ventricular dilatation. Characteristic of this lesion is the massive dilation of the main and branch pulmonary arteries. This results in compression of the bronchi, which are developmentally abnormal, diminutive, and suffer from severe bronchomalacia. The PDA is typically absent. Given the free pulmonary regurgitation and airway disease, ventilation in the newborn may be difficult. Some children fall on the milder end of the spectrum despite the massive pulmonary artery dilation and have minimal bronchial obstruction. Approximately 40–45 % of these babies require mechanical ventilation preoperatively [48, 49].

Surgical repair of tetralogy of Fallot with absent pulmonary valve involves VSD closure and RV outflow tract reconstruction, in addition to plication of the aneurysmal pulmonary arteries. Outcomes in this lesion are primarily dependent on the severity of airway disease and degree of bronchial obstruction. Survival is estimated to be 77 % at 1 year following surgery and 72 % at 10 years [49]. Those babies requiring preoperative intubation had the worst outcomes [49]. In the same series, approximately 42 % of survivors had persistent respiratory findings with relatively few requiring a tracheostomy. In those individuals with persistent respiratory symptoms, reoperation consisting of additional pulmonary artery plication and placement of a valved conduit may result in significant improvement.

Ebstein Anomaly of the Tricuspid Valve

Ebstein anomaly is a disease of the tricuspid valve and right ventricle in which delamination of the septal leaflet of the tricuspid valve fails to occur. The septal and posterior leaflets of the tricuspid valve are apically displaced often with attachments to the right ventricular wall. The anterior tricuspid valve leaflet is very redundant, often described as "sail-like". The abnormal tricuspid valve typically has moderate to severe regurgitation. A portion of the right ventricle above the displaced tricuspid valve is considered to be "atrialized" with the functional right ventricle below the tricuspid valve. Hemodynamic consequences of the tricuspid regurgitation are affected by the size of the right ventricle and the degree of right to left shunting across the ASD. In addition, there is an incidence of Wolff-Parkinson-White syndrome in individuals with Ebstein anomaly of approximately 20 % [50].

Clinically, patients with Ebstein anomaly may be acyanotic and asymptomatic if there is mild apical displacement of the tricuspid valve and relatively normal tricuspid valve function. In contrast, individuals can have profound cyanosis and hemodynamic compromise as a newborn. Cyanosis is the most common presenting symptom in neonates with Ebstein anomaly secondary to the significant tricuspid regurgitation and elevated pulmonary vascular resistance with inadequate pulmonary blood flow [50]. The degree of hypoxemia often improves as the pulmonary vascular resistance decreases with an improvement in the degree of antegrade pulmonary blood flow. In neonates with severe cyanosis and heart failure, the prognosis is poor with survival estimated at 65–70 % [51]. An aortopulmonary shunt may be necessary as a source of additional pulmonary blood flow with Ebstein anomaly that has insufficient pulmonary blood flow.

In a symptomatic individual with significant cyanosis, ventricular dysfunction, or arrhythmias, surgical options include a biventricular approach with tricuspid valve surgery or valve replacement, a single ventricle approach with oversewing of the tricuspid valve with subsequent Fontan operation, or cardiac transplantation. In one study of neonates who underwent a biventricular repair, survival to hospital discharge was nearly 75 % [52]. In neonates who go down the single ventricle pathway, operative survival may be as high as 80 % [53] although complications due to the Fontan circulation will become apparent later in life.

In a natural history series from the Mayo Clinic, the mean age at diagnosis in the non-neonate or infant with Ebstein anomaly was 23.9 ± 10.9 years [54]. These individuals present with fatigue, dyspnea, and mild cyanosis, especially in the setting of RV dysfunction or arrhythmias [54]. Paroxysmal supraventricular tachycardia (SVT) is common in adolescents and adults with Ebstein anomaly. SVT is the most common presenting symptom in adolescents and adults, occurring in 42 % of newly diagnosed patients [50].

Overall survival rates in unoperated patients are 89 % at 1 year, 76 % at 10 years, 53 % at 15 years, and 41 % at 20 years [54]. In the Mayo Clinic experience, survival rates for patients with Ebstein anomaly who have undergone surgical intervention are 94 % at 5 years, 90 % at 10 years, 86 % at 15 years, and 76 % at 20 years [55]. Long-term follow-up is necessary to closely monitor tricuspid valve function with the potential for the development of RV dysfunction, congestive heart failure, or atrial arrhythmias. Sudden death due to ventricular arrhythmia may occur in as many as 5–7 % of patients [54].

Left Sided Obstructive Lesions

Aortic Stenosis

Bicuspid aortic valve is one of the most common congenital heart lesions in the population. It occurs in approximately 1.3 % of the population [56, 57]. Males are more frequently affected. Aortic root dilation can be associated with a bicuspid aortic valve. Approximately 50 % of individuals with a bicuspid aortic valve have aortic root dilation, even in the setting of no significant aortic stenosis or regurgitation [58]. Associated lesions are found in 20 % of individuals with congenital aortic stenosis and may include VSD, coarctation of the aorta, and patent ductus arteriosus [59].

While the bicuspid aortic valve may initially function normally with little aortic stenosis or regurgitation, this malformation is generally progressive with 75 % of individuals eventually requiring surgery for aortic stenosis or

regurgitation. According to the Natural History Study of Congenital Heart Defects, 20 % of individuals with an initial gradient of less than 25 mmHg at initial cardiac catheterization required later intervention [60]. Indications for intervention for aortic valve stenosis include a catheter-derived peak-to-peak gradient of greater than 50 mmHg in an asymptomatic patient or if there is evidence of left ventricular dysfunction [60].

Critical aortic stenosis is the most severe form of aortic valve stenosis in which systemic blood flow is dependent on a patent ductus arteriosus. These children require balloon dilation in the cardiac catheterization laboratory at the time of diagnosis. Survival rates for neonates with critical aortic stenosis is 75 % at 8 years [61]. Approximately 30 % require repeat intervention for residual stenosis with only 11 % having hemodynamically significant residual aortic regurgitation [61]. Hemodynamically significant aortic regurgitation occurs in 38 % of patients with a history of critical aortic stenosis who have undergone balloon aortic valvuloplasty at 4 years follow-up [62]. Depending on the evolution of the aortic valve architecture and left ventricular dysfunction, they may require aortic valve replacement or cardiac transplantation in the future.

Balloon valvuloplasty, surgical valvotomy, Ross or Ross-Konno operation, and prosthetic and homograft valve replacement remain the mainstay of intervention in patients with aortic valve disease. Long-term anticoagulation is required for all mechanical valves although these are the most durable. The incidence of thromboembolic complications in patients with a prosthetic heart valve ranges from 0.6 % to 2.3 % per patient year [63]. The Ross procedure is often preferred in infants and young children. This involves resecting the pulmonary valve from the patients right ventricular outflow tract and placing it in the aortic position, and then placing a pulmonary homograft in the pulmonary valve position. The pulmonary valve, which after the Ross Procedure becomes the neo-aortic valve, is often referred to as the autograft. Importantly, there is the potential for growth of the neo-aortic valve and no indication for anticoagulation. The main disadvantage of the Ross operation is the development of right ventricle-to-pulmonary artery conduit dysfunction. Freedom from conduit reoperation following the Ross operation is between 70 % and 94 % at 5 years [64]. The incidence of complete heart block following the Ross-Konno operation is approximately 5 % [65, 66].

Subaortic Stenosis

Subaortic stenosis commonly results from a discrete thin membrane that is due to a fibromuscular ridge or accessory AV valve tissue in the left ventricular (LV) outflow tract. With significant subaortic obstruction, left ventricular hypertrophy may develop in addition to aortic valve regurgitation. While the degree of associated aortic regurgitation is generally mild, moderate to severe regurgitation may occur, particularly with a Doppler derived peak gradient across the sub-aortic membrane greater than 50 mmHg and increased age at diagnosis [67–69].

Following surgical resection there is a 20 % chance of recurrence [70]. Risk factors for recurrence of subaortic stenosis include a younger age at surgery and preoperative gradient greater than 40 mmHg. The need for aortic valve intervention was less common in patients who underwent early intervention to remove the subaortic stenosis. Many patients require a myomectomy in addition to resection of a subaortic membrane to decrease the risk of recurrence. However, there is a reported incidence of 13 % of complete heart block postoperatively when a more aggressive myomectomy is performed in these patients [71].

Coarctation of the Aorta

Coarctation of the aorta is a discrete narrowing in the distal thoracic aorta typically just distal to the left subclavian artery. Neonates with coarctation of the aorta may present in shock following closure of the ductus arteriosus due to inadequate systemic blood flow. Older children and adults often present with systemic hypertension and a gradient between right upper and lower extremity measured blood pressures. Associated intracardiac lesions include ventricular septal defect (50 % of all infants diagnosed), which may result in left ventricular outflow tract obstruction in malalignment type defects, bicuspid aortic valve (85 % of all infants diagnosed) [72, 73], and aortic valve stenosis (10 %). Coarctation of the aorta can also occur in the presence of multiple left-sided obstructive lesions, such as in Shone-complex [74]. Coarctation can also occur in more complex two-ventricle and single ventricle cardiac defects.

Repair may be surgical or include treatment with percutaneous balloon angioplasty with possible stent placement. Mortality rates are <1 % following surgical repair of an isolated coarctation in infants and children [72, 75, 76]. Resection with end-to-end anastomosis is the primary surgical method for individuals with a discrete coarctation. There is a small risk of late restenosis [72, 75, 77]. Patients with transverse arch hypoplasia may require an extended end-to-end or patch aortoplasty for long segment coarctation. There is an increased incidence of aortic aneurysm development given the use of prosthetic material with an incidence as high as 25 % [78–80]. Subclavian flap is another surgical option; however, a big disadvantage is sacrificing the left subclavian artery.

Long-term complications include recoarctation, systemic hypertension, aortic aneurysm formation, and sudden cardiac death. There is an increased risk of recurrence when repaired at less than 1 year of age, approximately 10 % [81–86]. Recoarctation is less common if repaired after age 2 years and when an extended end-to-end anastomosis in infants is performed [72, 75]. Systemic hypertension is one of the most common long-term complications after coarctation

repair. Children repaired prior to age 1 year are less likely to have systemic hypertension although late hypertension can develop in 10–20 % of patients repaired during infancy [85, 87]. Individuals with recurrent coarctation present with a blood pressure gradient between the right upper and lower extremities or systemic hypertension with confirmation by imaging. A gradient between upper and lower extremities of more than 20 mmHg is an indication for reintervention. Balloon angioplasty for recurrent coarctation following repair is generally preferred [88–91].

Mixing Lesions

D-Transposition of the Great Arteries

D-transposition of the great arteries occurs when the aorta originates from the right ventricle and the pulmonary artery arises from the left ventricle. Systemic and pulmonary circulations are separated and function in parallel. Desaturated systemic venous blood is ejected from the right ventricle to the aorta, whereas the oxygenated pulmonary venous blood is ejected from the left ventricle into the lungs. The degree of hypoxemia is dependent on the amount of intercirculatory mixing [patent ductus arteriosus (PDA), ASD, or VSD]. In individuals with D-TGA, a VSD may be present in 40 %. A posterior malalignment VSD may result in left ventricular outflow tract obstruction (e.g., subpulmonic stenosis, pulmonary stenosis, pulmonary atresia; 10 %); an anterior malalignment VSD may result in right ventricular outflow tract obstruction (e.g., subaortic stenosis, aortic stenosis, coarctation of the aorta or interruption of the aortic arch; 10 %) [92, 93]. Leftward juxtaposition of the atrial appendages (5 %) and straddling of the atrioventricular valves may also be present [92, 93].

Atrial Switch

From the 1950s through the 1980s, palliation for D-transposition of the great arteries included the Senning operation using native atrial tissue and the Mustard procedure using pericardium. The atrial switch resulted in long-term survival. In these operations, there is baffling of the pulmonary venous blood flow to the tricuspid valve and systemic circulation and baffling of the systemic venous blood flow to the mitral valve and the pulmonary circulation. Despite the fact that the right ventricle becomes the systemic ventricle following the atrial switch procedure, there has been good long-term survival in this population. At 25 years, survival is noted to be approximately 75 % [94, 95]. Long-term consequences of the atrial switch operation include:

(1) Arrhythmias – atrial tachyarrhythmias and sinus node dysfunction. Studies have reported that only 20–40 % of patients remain in sinus rhythm at 15–20 years follow-up following atrial switch surgery [96, 97]. Atrial flutter is the most common tachyarrhythmia with a prevalence of 25–35 % [98].
(2) Systemic and pulmonary venous baffle obstruction or leak. Baffle obstruction or leak is a less common complication. Systemic venous obstruction (5–10 %) occurs more often than pulmonary venous baffle obstruction (<2 %) [97]. The superior vena cava (5 %) is more commonly affected than the inferior vena cava (1 %). Residual intra-atrial baffle leaks (20 %) are more common than obstruction and are often small and hemodynamically insignificant. However, there is some risk of a cerebrovascular accident. Larger more hemodynamically significant baffle leaks may be closed with a device in the cardiac catheterization laboratory.
(3) Systemic right ventricular dysfunction and worsening tricuspid regurgitation. Most individuals have mild to moderate tricuspid regurgitation, which is usually well-tolerated. Only 2–7 % develop severe regurgitation [99]. This is often secondary to right ventricular dilatation and stretching of the tricuspid annulus rather than an intrinsic valve abnormality. However, moderate or severe tricuspid regurgitation can impact right ventricular function. In rare cases, tricuspid valve repair or replacement may be necessary. Right ventricular dysfunction occurs in 60 % of the patients following an atrial switch operation. This is due to the workload placed on the right ventricle, which functions as the systemic ventricle. Approximately 40 % will have moderately depressed systolic function and 20 % will have severely depressed ventricular function [100]. Few transplants have been performed in this population. Right ventricular dysfunction should be followed with serial cardiac MRI testing.
(4) Sudden death. Sudden cardiac death is a cause of late mortality in individuals who have undergone an atrial switch procedure. The incidence may be as high as 10 % [101]. Potential risk factors include severe RV (systemic) ventricular dysfunction and atrial arrhythmias although this remains less clear [102].

Arterial Switch

The arterial switch operation (Jatene operation) was originally performed in 1975. Long-term survival following the arterial switch operation (ASO) has been excellent with a late mortality of 1–2 % [103]. This results in anatomic repair of D-transposition of the great arteries with the left ventricle pumping blood to the aorta and the right ventricle pumping blood to the pulmonary artery. After the ASO the native pulmonary valve becomes the neo-aortic valve and the native aortic valve becomes the neo-pulmonic valve. Long term outcomes following the ASO are excellent with an actuarial survival of 96 % at 20 years. Freedom from the operation is approximately 90 % at 7 years [104, 105].

The most common reason for reintervention is supravalvar pulmonary stenosis, which may occur in 5–30 % of survivors [106, 107]. Neo-aortic root dilation occurs in approximately

half of patients following an ASO at 10 years follow-up. However, moderate to severe neo-aortic regurgitation is uncommon [108, 109]. The degree of neo-aortic valve regurgitation progression and the potential need for reintervention remains unclear although it is unlikely in the first two decades of life. ASO survivors are at an increased risk for developing coronary artery disease secondary to coronary artery reimplantation, coronary ectasia or stenosis, or coronary thrombosis. Given the potential for coronary artery disease and myocardial ischemia, there is a risk of sudden death [110]. These children may also be at a higher risk for developing atherosclerosis, hypertension, and diabetes in adulthood.

In neonates with D-TGA, VSD, and severe pulmonary stenosis, the Rastelli operation is often used to redirect blood flow at the ventricular level. In this operation, the proximal main pulmonary artery is divided and oversewn, and the left ventricular blood flow is baffled to the aorta by creating an intraventricular tunnel between the VSD and the aortic valve. A conduit is placed from the right ventricle to the pulmonary artery to redirect the right ventricular blood flow. Complications after the Rastelli operation include left ventricular outflow tract obstruction, conduit obstruction, and complete heart block [111, 112].

Congenitally Corrected Transposition of the Great Arteries (L-TGA)

In L-TGA, there is atrio-ventricular and ventriculo-arterial discordance. When blood enters the right atrium, it goes through the mitral valve into the right-sided morphologic left ventricle, through the pulmonary valve and into the pulmonary arteries. Blood entering the left atrium goes through the tricuspid valve into the left-sided morphologic right ventricle, through the aortic valve and into the aorta. These individuals may have associated ventricular septal defects (65–70 %), Ebstein anomaly of the left-sided tricuspid valve (80–90 %), and pulmonary stenosis (40 %), which may require intervention [113]. From an electrophysiologic standpoint, they are at risk for developing complete heart block (1–2 % each year) and may require pacemaker implantation [114]. Development of complete heart block may be spontaneous or associated with a procedure, such as a cardiac catheterization or surgery. Long-term complications include right (systemic) ventricular dysfunction, which may be worsened by tricuspid regurgitation, and sudden death from arrhythmias [115].

Anatomic repair for L-TGA can be accomplished by performing the double switch, which combines both atrial switch and arterial switch operations. These patients are at risk for both atrial and arterial switch long-term complications. This results in the left ventricle becoming the systemic ventricle. Therefore, one would expect increased preservation of ventricular function. However, according to recent reports, moderate-severe LV dysfunction following the double switch procedure may be greater than 50 % in patients requiring initial retraining of the LV [116]. These individuals were more likely to undergo cardiac transplantation or death.

Truncus Arteriosus

Truncus arteriosus is a conotruncal defect in which a single truncal vessel (great artery) arises from the heart and gives rise to the coronary arteries, pulmonary arteries, and aorta. The single arterial vessel overrides the VSD. Location and separation of the branch pulmonary arteries allows classification of the type of truncus I–IV, with type IV being associated with an interrupted aortic arch in 15–20 % of patients [117]. The truncal valve is often abnormal and myxomatous with some degree of truncal regurgitation present. The presence of moderate or greater truncal regurgitation can negatively impact surgical outcomes. Truncal stenosis is less common and a gradient by echocardiogram across the truncal valve is generally due to the increased cardiac output across the valve. Three truncal leaflets is most common and is present in 50 % of patients, although the valve may have anywhere from two to five cusps. In approximately one-third of patients a right aortic arch with mirror image branching is present. Type IV truncus arteriosus with interruption of the aortic arch will have an obligate patent ductus arteriosus and is often associated with 22q11 microdeletion (DiGeorge syndrome) [117, 118]. Coronary artery abnormalities are common with up to 70 % of children having some coronary anomaly, most commonly high takeoff of the coronary artery although an intramural coronary artery can also be found.

If left untreated, the mortality rate is 90 % by 1 year of age due to the development of pulmonary vascular obstructive disease. There is complete mixing of blood at the ventricular and arterial levels with volume and pressure overload of the ventricles. The degree of truncal regurgitation impacts the ventricles further. As the pulmonary vascular resistance drops within the first few weeks of life, significant left-to-right shunting occurs with pulmonary overcirculation and inadequate systemic blood flow leading to the development of congestive heart failure.

As a result, surgical repair is generally required in the neonatal period. Truncus arteriosus repair consists of baffle closure of the VSD to the aorta, removal of the branch pulmonary arteries from the common trunk, and placement of a conduit from the right ventricle to the pulmonary arteries. Overall outcome is excellent with survival of 90 % at 5 years, 85 % at 10 years, and 83 % at 15 years [119]. The presence of moderate to severe truncal valve regurgitation prior to initial surgery is a risk factor for decreased long-term survival. Freedom from conduit replacement is 57 % at 3 years [120]. Conduits require replacements every few years over a lifetime due to lack of growth and calcification and is the primary long-term complication. Following repair, the integrity of the truncal valve remains a concern and truncal valve dysfunction most often secondary to valve incompetence may

lead to reintervention or replacement [121]. Freedom from truncal valve replacement is 95 % at 10 years in patients with hemodynamically insignificant truncal regurgitation prior to initial repair. If moderate or greater truncal regurgitation is present prior to repair, freedom from truncal valve replacement is significantly lower, 63 % at 10 years [119]. Residual VSD and branch pulmonary artery stenosis with right ventricular dysfunction may also be seen. Pulmonary hypertension is a rare complication.

Total Anomalous Pulmonary Venous Return (TAPVR)

Total anomalous pulmonary venous return is a congenital heart defect in which the pulmonary veins drain anomalously into a systemic venous structure. Four types of TAPVR exist: supracardiac, cardiac, infracardiac, and mixed type. Supracardiac is the most common type. The pulmonary veins drain into a confluence posterior to the left atrium that drains anomalously to a systemic vein in both supracardiac (left innominate vein and right superior vena cava) and infracardiac types (portal venous circulation or ductus venosus into the hepatic vein). Supracardiac type typically becomes obstructed where the vertical vein passes between the left mainstem bronchus and left pulmonary artery. This is known as the "vice". In cardiac type TAPVR, the pulmonary veins drain directly to the coronary sinus and are rarely obstructed. The infradiaphragmatic type almost always becomes obstructed. Obstruction occurs as the vertical vein passes through the diaphragm and connects to the portal venous circulation or the ductus venosus. In addition, the shear length of the infradiaphragmatic vein results in increased resistance.

Surgical repair is performed at the time of presentation in TAPVR. Infracardiac TAPVR is often obstructed at birth and requires emergent surgery. In unobstructed TAPVR, an infant may present within the first couple months of life with congestive heart failure symptoms and mild hypoxemia. In supracardiac and infracardiac TAPVR, the confluence where the pulmonary veins drain is opened and connected to the left atrium. Often the vertical vein is ligated and the associated atrial septal defect is closed. In cardiac TAPVR, the pulmonary veins are baffled to the left atrium. Long-term prognosis is generally excellent and depends upon the presence of recurrent pulmonary venous obstruction at the left atrial anastomotic site or isolated pulmonary vein stenosis and secondary pulmonary hypertension due to changes in the pulmonary vasculature. Three-year survival is 85 % [122]. Residual pulmonary vein stenosis can occur in approximately 15 % of individuals after repair. Despite the availability of transcatheter intervention or reoperation, residual pulmonary vein stenosis is often progressive, which results in only a 41 % survival at 3 years follow-up [122]. Atrial arrhythmias, including supraventricular tachycardia and atrial flutter, can be seen late after repair [123].

Miscellaneous Lesions

Anomalous Left Coronary Artery from the Pulmonary Artery (ALCAPA)

ALCAPA is a rare congenital lesion in which the left coronary artery arises anomalously from the pulmonary artery. This often occurs as an isolated defect. As the newborn transitions with a decrease in pulmonary vascular resistance and pulmonary artery pressure, there is lower left coronary artery perfusion pressure and "coronary steal". This results in myocardial ischemia. Myocardial ischemia is most evident during feeding when a baby has the highest oxygen consumption. These babies are usually described as "fussy" infants. They develop left ventricular dilation and dysfunction and papillary muscle dysfunction with associated mitral regurgitation resulting in congestive heart failure. Typical timing of presentation is at 1–2 months of age. Mortality rate is 90 % by age 1 year secondary to myocardial ischemia or infarction if not repaired [124].

Left coronary artery reimplantation or the Takeuchi operation, which involves creation of an aortopulmonary window and intrapulmonary tunnel baffling the aorta to the left coronary artery, is often performed to establish aortic flow into the left coronary artery. Survival is 91 % at 5 years [124]. For those patients requiring ECMO postoperatively, freedom from cardiac transplantation or reoperation is 0 % at 5 years. However, freedom from transplant or reoperation in patients not requiring mechanical circulatory support is 92 % at 5 years [125]. The need for mechanical circulatory support is primarily due to hemodynamically significant residual mitral regurgitation. The LV systolic function generally normalizes within 1 year following surgical repair with a gradual improvement in the degree of mitral regurgitation.

Vascular Rings and Sling

Three separate vascular anomalies of the great vessels are of particular note regarding their long-term outcomes: pulmonary artery sling, double aortic arch, and right aortic arch with an aberrant left subclavian artery.

Left Pulmonary Artery Sling

Pulmonary artery (PA) sling is a rare congenital vascular anomaly whereby the left PA originates from the posterior aspect of the right PA and passes leftward between the lower trachea and esophagus, compressing the lower trachea with displacement to the left. The anomaly is often referred to as a "ring–sling complex" owing to high prevalence of complete tracheal rings (50–65 %) [126]. External compression and intrinsic stenosis of the trachea lead to respiratory symptoms. The long-term natural history of unrepaired PA sling with airway compression is poor with death resulting from airway obstruction [127]. Current surgical management often involves reimplantation of the left pulmonary artery with concurrent repair of tracheal stenosis and coexisting cardiac

lesions. Tracheal stenosis may be repaired by removal of the complete cartilaginous rings by end-to-end anastomosis or slide tracheoplasty. Long-term mortality in the entire repaired population of individuals with sling anatomy is about 5–10 % [126]. The vast majority of mortality occurs in the peri-operative or immediate post-operative period. However, mortality is primarily determined by the nature of the associated airway compression and the need for concurrent tracheal surgery, as those individuals without airway compression have a long-term mortality of less than 1 % [126, 127]. A variable incidence of PA stenosis at the reimplantation site has been described with rates between 5 % and45 % [126, 128]. There appears to be a surgical era component to the risk of restenosis as the more recent reports suggest the rate of post-operative stenosis is less than 10 % [126]. When present, these areas of stenosis may be subsequently managed percutaneously in the cardiac catheterization laboratory.

Double Aortic Arch

Double aortic arch (DAA) is the most common clinically recognized form of vascular ring [129, 130]. Anterior to the trachea, the ascending aorta divides into left and right arches passing to either side of the trachea. Both arches are usually patent, although one is usually larger than the other. The right arch is dominant in 70 % of cases [131]. Previous studies have shown that associated cardiovascular anomalies are uncommon [131]. DAA manifests earlier than other varieties of vascular rings with symptoms of stridor, dyspnea, cough, and recurrent respiratory infections [132]. In addition to airway symptoms, patients may experience swallowing difficulties related to esophageal compression, which manifests as vomiting and feeding intolerance [132]. Respiratory symptoms are the most common persistent symptoms on early and long-term post-surgical follow-up, occurring in up to 50 % of individuals [132–135]. The cause of these symptoms is residual trachea compression, however this compression is typically mild and does not require re-intervention [133]. The most common post-operative respiratory symptom is stridor, evident in about 50 % of individuals at early follow-up and about a third in long-term follow up. Younger age at repair is associated with the presence of post-operative stridor [133]. The majority of those patients with long-term stridor also had it at initial presentation [133, 134]. Symptoms caused by esophageal compression dramatically improve postoperatively in the majority of cases [132–135].

Right Aortic Arch with Aberrant Left Subclavian Artery

Right aortic arch with aberrant left subclavian artery (SCA) and the Kommerell diverticulum is the most common form of vascular ring [136–138], although as opposed to DAA, it may be clinically asymptomatic and therefore ultimately, unrecognized [136]. This lesion is surgically managed by division of the ligamentum arteriosum, with good post-operative results [136]. However, in some cases, a retained diverticulum and aberrant left SCA can cause the posterior compression of the trachea and esophagus, which may result in residual respiratory symptoms [138]. Additional long-term complications include the development of a diverticulum aneurysm on the descending aorta, with a risk of aneurysm rupture, and subclavian-esophageal fistula, with a risk of severe gastrointestinal bleeding in the long-term [139]. One surgical strategy to minimize these long-term complications has been to remove the Kommerell diverticulum with translocation of left SCA in addition to the division of the ligamentum, thereby relieving the residual symptoms. This approach is believed to prevent future complications of descending aortic aneurysm or aortoesophageal fistula [140]. Studies utilizing this approach have ben promising with 100 % of patients free of residual symptoms at long-term follow up [136–140].

Single Ventricle Physiology

Neonates and infants with functional single ventricle anatomy (e.g., tricuspid atresia or hypoplastic left heart syndrome), face certain early mortality without successful surgical palliation or cardiac transplantation. Staged surgical palliation of single ventricle anatomies is the preferred method of intervention given the limited availability of donor hearts for possible orthotopic heart transplantation. Surgical palliation has undergone a series of revisions over the last several decades, notably the inclusion and success of the Norwood procedure for hypoplastic left heart syndrome and an intervening superior cavopulmonary connection (Bidirectional Glenn and Hemi-Fontan procedure) between the neonatal palliation and the modified Fontan completion procedure. The modified Fontan procedure baffles blood from the inferior vena cava to the superior cavopulmonary connection and is generally performed from 2 to 4 years of age.

Over the last few decades there has been a reduction of early post-operative Fontan mortality from >20 % to less than 2 % [141, 142]. The two current surgical approaches to Fontan completion are the Lateral Tunnel and the Extracardiac Conduit. The Lateral Tunnel Fontan involves creating an intra-atrial baffle that connects the inferior vena cava to the pulmonary arteries through the existing right atrium. The Extracardiac Fontan utilizes a tube graft that lies outside of the heart to connect the inferior vena cava to the pulmonary arteries. The advantages of the Lateral Tunnel approach are a potential for growth over time and low level of power loss by computational fluid dynamic studies [143]. Disadvantages include a higher incidence of sinus node dysfunction [144–148] and increased risk of atrial thrombus formation and systemic embolization as a consequence of intra-atrial prosthetic material. The advantages of the Extracardiac Conduit

approach are ease of operation including flexibility in anatomically difficult cases such as heterotaxy, evidence of less sinus node dysfunction when compared to the Lateral Tunnel Fontan, decreased suture lines and pressure in the right atrium, avoidance of cardioplegic arrest, and decreased systemic embolization risk [144–148]. The principle disadvantage is the lack of growth potential, which necessitates a larger initial conduit (22–22 mm) that may exacerbate issues of power loss.

In the immediate surgical periods, a primary concern is maintaining cardiac output in the setting of elevated central venous pressure. One common Fontan modification to address this issue has been the use of a fenestration to allow right-to-left shunting from the Fontan circuit to the atria. This modification improves the systemic ventricular preload in the setting of elevated central venous pressure at the cost of systemic desaturation. Some studies suggest that the use of a fenestration improves post-operative hemodynamics, reduces the incidence of pleural effusions, and shortens hospital length of stay with excellent survival [149]. However, these advantages are not conclusive, and given the risk of systemic thrombus embolization and stroke in the setting of a right-to-left shunt and the potential need for later fenestration closure, fenestration has not been universally adopted as a Fontan modification.

Overall intermediate and late mortality remains low at 5–23 % at 5 years and 9–28 % at 10 years [142, 150, 151]. Longer term Fontan follow up studies suggest that approximately 10–30 % of Fontan survivors have clinically significant morbidity including progressive ventricular dysfunction and congestive heart failure, hypoxemia, protein-losing enteropathy (PLE), stroke, atrial dysrhythmias, and liver dysfunction [142, 150, 152].

Ventricular Dysfunction

Ideally, ventricular volume unloading over the course of surgical staged palliation resulting in a Fontan circulation reduces ventricular size and wall thickness, which increases ventricular performance. However, in some Fontan cases, ventricular dilation remains as a consequence of early volume overload and the presence of aortopulmonary collaterals (common to patients with chronic cyanosis), which promotes ventricular dysfunction. This is particularly important in the setting of HLHS, as the systemic ventricle is the morphologic right ventricle, which increases the long term risk of ventricular dysfunction. Additionally, any residual obstructive lesions of the systemic output, including intra-ventricular such as a narrowed bulbo-ventricular foramen, and/or atrioventricular valve insufficiency, also promote long-term ventricular dysfunction. This ventricular dysfunction may be systolic or diastolic, or both [153–156]. Ventricular dysfunction should manifest initially as symptoms of congestive heart failure, exercise intolerance, dyspnea, fatigue, and syncope [157, 158].

Hypoxemia

Mild hypoxemia with oxygen saturations in the low 1990s is common after Fontan completion, even without a surgical fenestration [159]. This desaturation is the result of a combination of coronary sinus blood return to the systemic atrium, and the presence of arteriovenous shunts and ventilation/perfusion mismatch in the lung. Some studies suggest that collateral vessels are present in at least one third of all Fontan patients [160]. These collaterals may be arteriovenous or veno-venous.

Protein-Losing Enteropathy

PLE, characterized as severe protein loss from the intestines, occurs in 3–24 % of patients with the Fontan circulation [152]. Importantly, PLE impacts mortality with reports of 30 % mortality at 2 years and near 50 % at 5 years after diagnosis [161–163]. Onset of PLE is variable as it may occur 1 month after Fontan completion or more than two decades after completion. However, most commonly, it occurs 2–3 years after the Fontan [164]. The diagnosis of PLE is made clinically with supporting lab results including hypoalbuminemia, hypoproteinemia, hypocalcemia, lymphocytopenia, and elevated stool alpha-1 antitrypsin [152]. Despite its frequency, the pathogenesis of PLE remains unclear. PLE may be the result of chronically elevated portal vein pressure as a result of elevated central venous pressure, which in turn causes intestinal congestion, lymphatic obstruction, and enteric protein loss [165]. Alternatively, low cardiac output as a consequence of ventricular dysfunction may predispose to mesenteric ischemia and intestinal mucosal injury leading to enteric protein loss [164]. Or PLE may be a byproduct of a gastrointestinal inflammatory condition owing to unknown infections in the absence of hemodynamic derangements [166, 167].

Thromboembolism

Stroke and pulmonary embolism are known risk factors of a Fontan circulation. Large series have demonstrated a prevalence of thrombus formation in the Fontan circuit of near 10 % by transthoracic echocardiography. Thromboembolic events after Fontan occur in a bimodal distribution peaking during the first post-operative year, and again 10 years later [152, 168]. Some smaller series have suggested an even higher thrombus burden of 17–30 % [169], and mortality following thromboembolism is noted to be as high as 25 % in some pediatric series [152]. Risk factors for thrombosis include dehydration, low-flow state, stasis in the Fontan circuit, increased venous pressure, right to left shunting, hepatic dysfunction, PLE, prolonged post-operative immobilization, blind surgical cul-de-sacs (e.g. PA ligation without oversewing of the pulmonary valve), prosthetic material, ventricular dysfunction, and hypercoagulable states [152]. Chronic liver dysfunction and coagulation factor deficiency, especially protein C, may be additional unique risk factors [170]. The overall risk of thrombus formation is further elevated in the presence

of arrhythmias [169, 171, 172]. There is no consensus in the literature as to the optimal type of anticoagulation therapy or if therapy is warranted at all [152]. The largest, prospective, randomized trial comparing heparin/warfarin with aspirin as primary prophylaxis found no significant difference in safety or efficacy in the first 2 years after the Fontan procedure [172].

Arrhythmias

One of the major causes of long-term morbidity and mortality in patients following the Fontan procedure is arrhythmia. In a study of long-term survival of 260 Fontan patients with a median follow up time of 12 years, the majority of deaths outside the perioperative period were classified as sudden and were presumed to be arrhythmic in origin [173]. Patients with a Fontan physiology have a 10–45 % incidence of atrial arrhythmias [150, 174–176]. The etiology of these atrial arrhythmias is thought to be multifactorial and include the presence of sinus node dysfunction, atrial suture lines, and increased atrial wall stress from elevated atrial mean pressure. Some of these risk factors may be minimized by the Extracardiac approach to the Fontan [177]. Pacemaker implantation in Fontan patients is reported to be 23 % by 20 years of follow up [178]. Pacing strategies have progressed significantly from basic ventricular pacing for bradycardia to sophisticated anti-tachycardia pacing algorithms for atrial arrhythmias.

Liver Dysfunction

Chronically elevated systemic venous pressure and ventricular dysfunction increase the risk of progressive hepatic dysfunction, liver fibrosis, and cirrhosis in patients with the Fontan circulation [181]. Biomarkers that may indicate worse cardiac and hepatic function in both Fontan survivors and patients with a structurally normal heart include gamma-glutamyl transpeptidase (GGT), total bilirubin, alanine transaminase (ALT), and liver-specific alkaline phosphatase (Alk Phos). In a large case series of Fontan patients, Camposilvan et al. [181] combined clinical, serum, and hepatic ultrasonographic criteria to produce a "liver disease score" and found that low CI (measured by cardiac catheterization and echocardiography) was associated with hepatic dysfunction (elevated "liver disease score"; abnormal Prothrombin Time (PT)/PTINR; and elevated total bilirubin). In two large Fontan follow-up cohorts greater than 50 % of the patients had elevated GGT [181, 182]. Elevated levels of total bilirubin have also been found in 25–35 % of Fontan survivors [179, 180]. Gentles et al. showed that 96 % of the 97 patients with available transaminase values had elevated levels of ALT [157].

Neurodevelopmental Outcomes

Over the last several decades, new surgical techniques and advances in CPB, intensive care, and interventional cardiac catheterization have significantly lowered mortality rates for children and adolescents with complex CHD [183–185]. Survivors experience physical, neurodevelopmental, and psychosocial morbidity that greatly impact their quality of life (QOL) [186, 187]. Complex CHD survivors are at greater risk for neurodevelopmental (ND) deficits compared to heart-healthy children that result from both biological and environmental risk factors [188, 189]. Biological risk factors include underlying syndromes or genetic disorders [190–197], the circulatory abnormalities specific to the congenital heart defect, the medical and surgical therapies required, and the psychosocial stress of living with a serious chronic disease. Biologic risk factors are modified by environmental risk and resilience factors at home and at school. Developmental concerns among children with CHD may start in infancy but often become more apparent in later childhood and adolescence.

The prevalence and severity of DD and developmental delay increases with the complexity of CHD and the presence of genetic disorders or syndromes [188] (Fig. 25.1). Complex CHD survivors have a distinctive pattern of ND and behavioral impairment characterized by mild cognitive impairment [198–202] and academic achievement [199, 200, 202, 204], deficits in social cognition [205–209] core communication skills and pragmatic language [198, 199, 202, 203, 210, 211], inattention, hyperactivity and impulsivity [199, 203, 204, 211–213], deficits in visual construction and perception [199, 203, 204, 214–217], impaired executive functioning [211, 218], and limitations in gross and fine motor skills [198, 202–204, 210, 211, 214, 219, 220].

In addition, there are often accompanying psychosocial maladjustment with behavioral and emotional issues such as post-traumatic stress symptomatology, anxiety, and depression in both the survivor and the family [221–226]. Many school-age survivors of infant cardiac surgery require supportive services including tutoring, special education, and physical, occupational, and speech therapy. The ND and psychosocial morbidity related to CHD and its treatment often limit ultimate educational achievements, employability, lifelong earnings, insurability, and QOL for many patients. A significant proportion of patients with complex CHD may need specialized services into adulthood. Incorporation of new stratification methods and clinical evaluation and management algorithms may result in increased surveillance, screening, evaluation, diagnosis, and management of developmental disorder and disability (DD) in the complex CHD population and consequent improvement in ND and behavioral outcomes in this high-risk population. With early identification and treatment of DD and developmental delays, children have the best chance to reach their full potential.

Marino et al. recently published the first comprehensive scientific statement formally identifying and stratifying CHD survivors for risk of worse ND outcome, outlined a surveillance, screening, evaluation and management algorithm for CHD survivors, and created recommendations

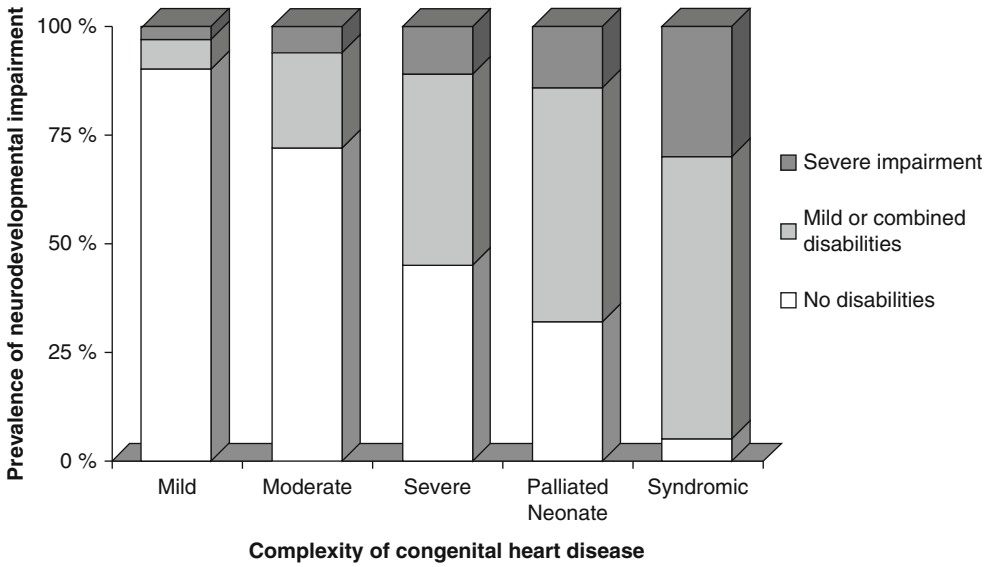


Fig. 25.1 Prevalence of neurodevelopmental impairment in the population with congenital heart disease (CHD) (Adapted from Wernovsky [258]. With permission from Cambridge University Press)

to optimize ND outcome in the pediatric CHD population [188]. A writing group appointed by the American Heart Association (AHA) and American Academy of Pediatrics (AAP) reviewed the available literature addressing DD and developmental delay in the CHD population with specific attention to surveillance, screening, evaluation, and management strategies. A management algorithm was devised that stratified children with CHD for ND outcome based on established risk factors (Table 25.1). For those deemed to be at high-risk for DDs or developmental delay, formal, periodic developmental and medical evaluations are recommended. The CHD Algorithm for surveillance, screening, evaluation, re-evaluation, and management of DD was constructed to serve as a supplement to the 2006 AAP statement on developmental surveillance and screening (Fig. 25.2a, b). The intent is that the algorithm be carried out within the context of the medical home. This scientific statement was meant for medical providers within the medical home who care for patients with CHD. Developmental disorders can be identified and managed through surveillance, screening, early evaluation, periodic re-evaluation, and continuous, comprehensive treatment coordinated through the medical home. The child's primary pediatrician, pediatric cardiologist, psychologist or developmental-behavioral pediatrician may lead care coordination. Children with significant difficulties often benefit from a multi-disciplinary treatment approach, including special education classes, tutoring, behavior management counseling, and physical, occupational and speech/language therapies.

If a child fits the high-risk criteria, it is recommended that the medical home schedule evaluations to assess ND, psychosocial, and behavioral and emotional functioning. The child's cardiologist should continue to handle the cardiovascular issues related to the CHD, but other medical providers and therapists need to join the child's care team. The medical home leader, usually the child's primary care physician, will coordinate care and provide the family with an overall approach to managing their child's ND, psychosocial and physical health needs.

In addition to assessing ND risk level at each medical home visit and referring high-risk patients for formal developmental and medical evaluations, other recommendations in the AHA scientific statement for children deemed high risk for developmental disorders include: (1) Refer high-risk children for early intervention even before a developmental disorder is diagnosed; (2) Re-evaluate for developmental disorders and developmental delays periodically in children with CHD deemed high-risk at 12–24 months, 3–5 years and 11–12 years of age; (3) Consider counseling high-risk children for educational or vocational options when they reach young adulthood. If potential developmental problems can be identified earlier, the hope is to prevent issues from developing in school that will impede children with CHD from reaching their full potential. In the past, treatment goals for children with CHD were focused on survival. Now that survival has improved, the goal is for these children not just to survive but also to thrive.

Research supports the benefit of early evaluation and ongoing treatment of developmental issues. To provide coordinated care leading pediatric cardiovascular centers have established multi-disciplinary cardiac ND follow-up programs to evaluate diagnose and monitor developmental, learning and behavioral problems. Teams often include developmental-behavioral pediatricians, psychologists, educators, occupational therapists, physical therapists, speech pathologists, neurologists, cardiovascular geneticists and pediatric cardiologists. Educators should encourage families to share results of multi-disciplinary evaluations with the child's school system to ensure that recommendations are implemented in the school setting. Those providers who care for a child with CHD are encouraged to talk to the medical home leader about resources in their medical center and/

Table 25.1 Categories of pediatric CHD patients at high risk for developmental disorders or disabilities

1. Neonates or infants requiring open heart surgery (cyanotic and acyanotic types), for example, HLHS, IAA, PA/IVS, TA, TAPVC, TGA, TOF, tricuspid atresia
2. Children with other cyanotic heart lesions not requiring open heart surgery during the neonatal or infant period, for example, TOF with PA and MAPCA(s), TOF with shunt without use of CPB, Ebstein anomaly
3. Any combination of CHD and the following comorbidities:
3.1. Prematurity (_37 week)
3.2. Developmental delay recognized in infancy
3.3. Suspected genetic abnormality or syndrome associated with DD
3.4. History of mechanical support (ECMO or VAD use)
3.5. Heart transplantation
3.6. Cardiopulmonary resuscitation at any point
3.7. Prolonged hospitalization (postoperative LOS _2-week in the hospital)
3.8. Perioperative seizures related to CHD surgery
3.9. Significant abnormalities on neuroimaging or microcephaly[a]
4. Other conditions determined at the discretion of the medical home providers

Reprinted from Marino et al. [188]. With permission from Wolters Kluwer Health
CHD indicates congenital heart disease, *HLHS* hypoplastic left heart syndrome, *IAA* interrupted aortic arch, *PA/IVS* pulmonary atresia with intact ventricular septum, *TA* truncus arteriosus, *TAPVC* total anomalous pulmonary venous connection, *TGA* transposition of the great arteries, *TOF* tetralogy of Fallot, *PA* pulmonary atresia, *MAPCA* major aortopulmonary collateral arteries, *CPB* cardiopulmonary bypass, *DD* developmental disorder or disability, *ECMO* extracorporeal membrane oxygenation, *VAD* ventricular assist device, and *LOS* length of stay
[a]Normative data by sex, including percentiles and *z* scores, are available from the World Health Organization (www.who.int/childgrowth; accessed February 2010)

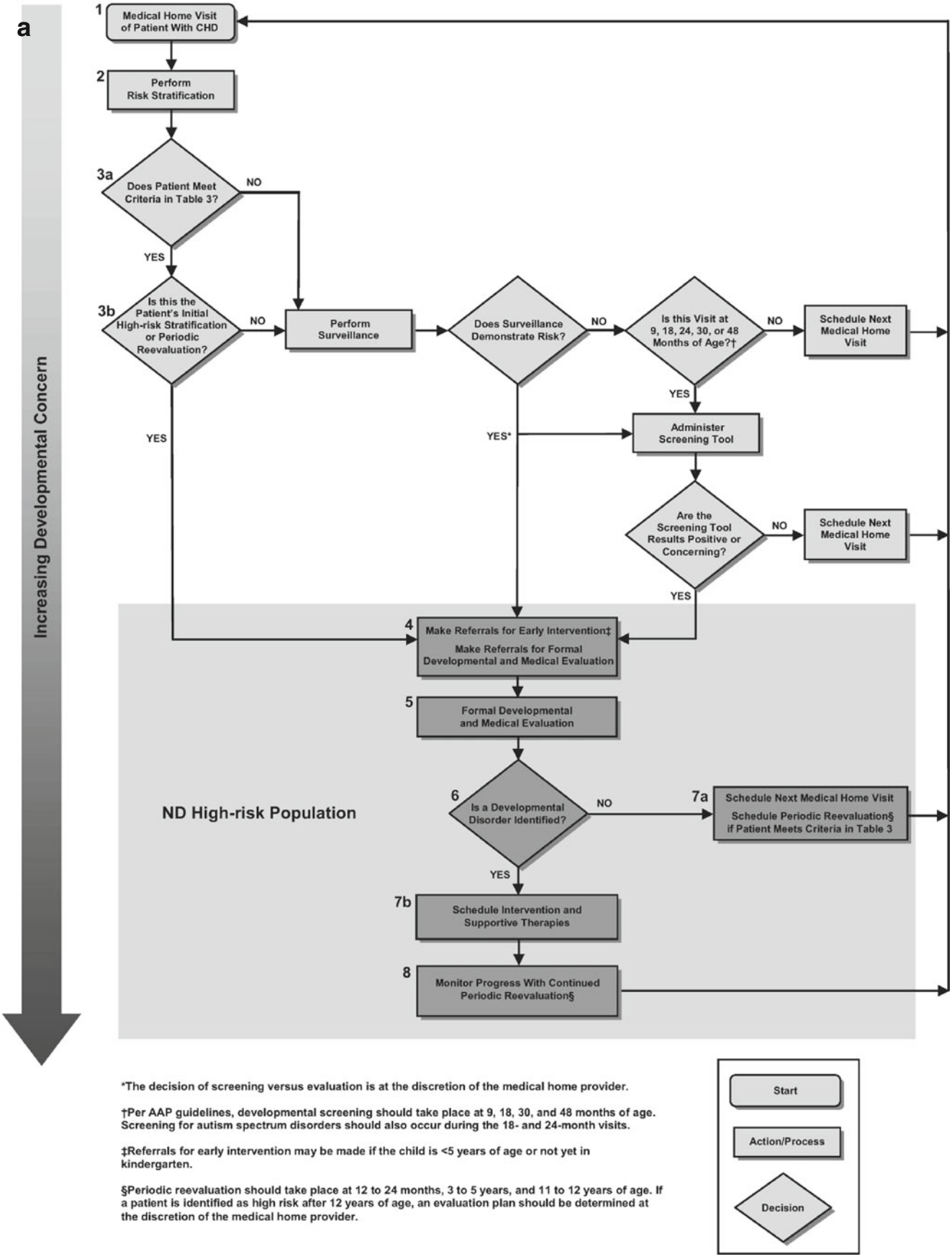
or community to screen, evaluate, periodically re-evaluate throughout childhood to enhance identification of significant deficits, allowing for appropriate therapies and education to enhance later academic, behavioral, psychosocial, and adaptive functioning.

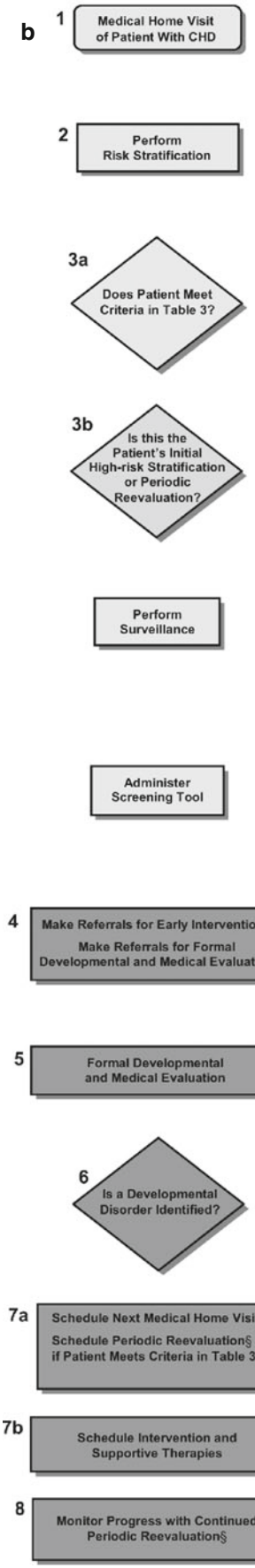
Genetic Anomalies and Associated Congenital Heart Disease

There are more than 700 genetic disorders or syndromes that are associated with CHD. For this reason, a genetic evaluation and counseling are often incorporated into the care of children born with CHD. Typical testing includes amniocentesis and chorionic villus sampling if there is concern during the fetal period, and further chromosome analysis can be performed both pre and postnatally including fluorescence in situ hybridization or multiplex ligation-dependent probe amplification [190]. General recommendations for genetic testing can be found in the 2007 AHA scientific statement endorsed by the AAP [227]. The genetic impact on CHD is complex and rather than following a simple Mendelian pattern of inheritance, factors such as variable penetrance and interactions with the environment play an important role. Therefore, defining the genetic disorders and syndromes that are associated with specific CHDs and subsequently identifying those that meaningfully impact clinical outcome is challenging.

Table 25.2 highlights genetic conditions that are frequently associated with CHD. This abridged list is intended to provide a concise and focused reference and should not be interpreted as an exhaustive list. Table 25.2 features the gene or chromosome associated with each genetic condition, as well as the frequency of association with specific CHD subtypes. In addition, the common extracardiac defects are listed as well. The presence of a genetic syndrome can further affect long-term outcomes in patients with CHD, especially neurodevelopmental outcomes.

Fig. 25.2 (**a**) Congenital heart disease (CHD) algorithm for surveillance, screening, evaluation, and management of developmental disorders and disabilities. *ND* indicates neurodevelopmental, *AAP* American Academy of Pediatrics. (**b**) Description of congenital heart disease algorithm for surveillance, screening, evaluation, and management of developmental disorders and disabilities. *AAP* indicates American Academy of Pediatrics, *CHD* congenital heart disease, *DD* developmental disorder or disability. *The decision of screening versus evaluation is at the discretion of the medical home provider, †Per AAP guidelines, developmental screening should take place at 9, 18, 30 and 48 months of age. Screening for autism spectrum disorders should also occur during the 18- and 24-month visits, ‡Referrals for early intervention may be made if the child is <5 years of age or not yet in kindergarten, §Periodic reevaluation should take place at 12–24 months, 3–5 years, and 11–12 years of age. If a patient is identified as high risk after 12 years of age, an evaluation plan should be determined at the discretion of the medical home provider (Reprinted from Marino et al. [188]. With permission from Wolters Kluwer Health)


a
Increasing Developmental Concern
1
Medical Home Visit of Patient With CHD
2
Perform Risk Stratification
3a
Does Patient Meet Criteria in Table 3?
NO
YES
3b
Is this the Patient's Initial High-risk Stratification or Periodic Reevaluation?
NO
YES
Perform Surveillance
Does Surveillance Demonstrate Risk?
NO
YES*
Is this Visit at 9, 18, 24, 30, or 48 Months of Age?†
NO
YES
Schedule Next Medical Home Visit
Administer Screening Tool
Are the Screening Tool Results Positive or Concerning?
NO
YES
Schedule Next Medical Home Visit
ND High-risk Population
4
Make Referrals for Early Intervention‡
Make Referrals for Formal Developmental and Medical Evaluation
5
Formal Developmental and Medical Evaluation
6
Is a Developmental Disorder Identified?
NO
YES
7a
Schedule Next Medical Home Visit
Schedule Periodic Reevaluation§ if Patient Meets Criteria in Table 3
7b
Schedule Intervention and Supportive Therapies
8
Monitor Progress With Continued Periodic Reevaluation§
*The decision of screening versus evaluation is at the discretion of the medical home provider.
†Per AAP guidelines, developmental screening should take place at 9, 18, 30, and 48 months of age. Screening for autism spectrum disorders should also occur during the 18- and 24-month visits.
‡Referrals for early intervention may be made if the child is <5 years of age or not yet in kindergarten.
§Periodic reevaluation should take place at 12 to 24 months, 3 to 5 years, and 11 to 12 years of age. If a patient is identified as high risk after 12 years of age, an evaluation plan should be determined at the discretion of the medical home provider.
Start
Action/Process
Decision



Through a combination of surveillance, screening, and evaluation, careful developmental monitoring by the medical home can optimize care and allow for prompt recognition and response to DD in a patient with CHD.

This step is a deviation from the original algorithm in the 2006 AAP guidelines on developmental surveillance and screening for the general population and is specific to the CHD population. It is designed to stratify patients with CHD into low-risk and high-risk categories for DD. Although many treatment and patient-specific factors contribute to increased risk for neurodevelopmental impairment, certain categories of pediatric patients with CHD are at higher risk for DDs. More specifically, neonates requiring open heart surgery (cyanotic and acyanotic types), children with other cyanotic heart lesions not requiring open heart surgery in the neonatal or infant period, and children with any combination of CHD and other comorbidities (Table 3) should be considered high risk for DD.

Risk stratification of children and adolescents with CHD into low-risk and high-risk categories for DD, based on the high-risk criteria found in Table 3 can be useful and beneficial. For patients at low risk for DD, heightened surveillance and screening according to the 2006 and 2007 AAP guidelines for general developmental and autism-specific screening can be useful and beneficial. For patients at high risk for DD, direct referral for an initial formal developmental and medical evaluation and periodic reevaluations can be useful and beneficial (proceed to step 3b, CHD algorithm).

For patients stratified as high risk for the first time or at an age for periodic reevaluation (12–24 months, 3–5 years, and 11–12 years of age), direct referral for formal developmental and medical evaluation and early intervention services or early childhood special education services can be useful and beneficial (proceed to step 4, CHD algorithm). For patients who have already had an initial formal developmental and medical evaluation due to high-risk stratification and are not at an age for periodic reevaluation (12–24 months, 3–5 years, and 11–12 years of age), heightened surveillance can be useful and beneficial (proceed to "Perform Surveillance").

Even if a patient with CHD is categorized as low risk for DD or was classified as high risk but was not diagnosed with a DD during formal developmental and medical evaluation, continued developmental surveillance, as proscribed by the 2006 and 2007 AAP guidelines on developmental surveillance and screening, and continued medical record review can be useful and beneficial since the level of risk of a patient with CHD can change over time. AAP guidelines recommend developmental surveillance at every well-child visit.

Even if a patient with CHD is categorized as low risk for DD or was classified as high risk but was not diagnosed with a DD during formal developmental and medical evaluation, periodic developmental screening, as proscribed by the 2006 and 2007 AAP guidelines, and continued medical record review can be useful and beneficial since the level of risk of a CHD patient can change over time. Age-specific screening tools should be used for children and adolescents, to screen for latent DDs (Figure 2A). AAP guidelines recommend standardized developmental screening test at 9, 18, 30, and 48 months of age. Autism-specific screening is recommended at 18 and 24 months of age. For all children with CHD undergoing developmental screening based on age or concerns detected in surveillance, it can be useful and beneficial to perform behavioral screening.

Referrals for formal developmental and medical evaluation and referral to early intervention services or early childhood special education services before confirmation of a specific DD can be useful and beneficial for all high-risk patients with CHD presenting for an initial visit, high-risk patients with CHD at an age for periodic reevaluation, and for low-risk CHD patients who failed heightened developmental surveillance and/or screening. Using the medical home model of care to make referrals can be effective and beneficial.

Because children with CHD can manifest difficulties in multiple areas of neurodevelopment, it can be effective and beneficial for evaluation to use a multidisciplinary team and an individualized evaluation plan. See Table 4 for domains and suggested instruments for developmental evaluation of children and adolescents with CHD.

Information about early identification of DDs and a list of these disorders can be found at www.cdc.gov/actearly. See Table 2 for a list of common genetic syndromes associated with CHD and DDs.

For patients with CHD who are at low risk for DD based on the criteria in Table 3 and who were not identified with a DD, heightened surveillance under the medical home model can be useful and beneficial. For patients at high risk for DD who have not been identified with a DD, periodic re-evaluation, in addition to heightened surveillance, can be useful and beneficial given that signs of DDs, presence of comorbidities, and overall CHD status may change over time. It can be useful and beneficial to perform periodic reevaluation for patients at high risk for DD at 12 to 24 months, 3 to 5 years, and 11 to 12 years of age.

Children 3 to 5 years of age with identified DDs are entitled to early childhood special education through their local school district. Children are also eligible for a wide variety of benefits through the *Individuals With Disabilities Education Act*. More specific information can be found at www.nichy.org.

It is vitally important that patients with CHD and an identified DD are monitored through the medical home and undergo periodic formal medical and developmental reevaluation (12–24 months, 3–5 years, and 11–12 years of age) to ensure optimal interventions, therapies, and outcomes and to detect for the presence of other, potentially latent, DDs.

Fig. 25.2 (continued)

Table 25.2 Chromosomal anomalies/syndromes associated with CHD

Syndrome	References	Gene(s)/ chromosome	Frequency of CHD (%)	CHD types	Extracardiac
Trisomy 13	[228, 229]	13	50–80	Conotruncal (DORV, TOF), VSD, ASD, AVCD, PDA, Polyvalvar dysplasia	Polydactyly Cleft lip/palate CNS anomalies Renal anomalies GU anomalies Scalp cutis aplasia
Trisomy 18	[230]	18	95	Polyvalvar dysplasia VSD, AVCD, TOF, DORV	Overlapping fingers CNS anomalies (posterior fossa) Rocker bottom feet Renal anomalies GU anomalies
Trisomy 21	[231–233]	21	40	AVCD – complete and partial VSD, ASD, PDA, TOF	GI anomalies Endocrine anomalies Leukemoid reaction
Turner syndrome	[234–237]	45X	25	LVOTO (Coarctation, BAV +/− AS, MV anomalies, MVP) Aortic dilation, dissection Hypertension	Horseshoe kidney Neck webbing Lymphedema Infertility Short stature
Williams syndrome	[238]	Deletion 7p13 ELN1	75	Supravalvar AS +/− valvular AS PS, coarctation, coronary artery stenosis	Abnormal calcium Hypodontia Behavior anomalies
Jacobsen syndrome	[239]	Deletion 11q23	55	VSD LVOTO (HLHS)	Thrombocytopenia Renal anomalies Undescended testes
Cat-eye syndrome	[240]	Tetrasomy 22p	50	TAPVC & PAPVC	Coloboma GU anomalies Recto-anal anomalies
DiGeorge syndrome	[241, 242]	Deletion 22q11 TBX1	75–85	Truncus arteriosus, TOF, VSD, aortic arch anomalies including IAA	Cleft palate Hypocalcemia T-cell dysfunction Feeding/speech Psychiatric disorders
Alagille syndrome	[243]	JAG1 NOTCH2	90	Peripheral PS TOF +/− PA ASD, VSD, coarctation	Bile duct paucity Chronic cholestasis Butterfly vertebrae
Char syndrome	[244]	TFAP2beta	20–70	PDA, VSD	Fifth finger anomalies Supernumerary nipple
CHARGE syndrome	[245]	CHD7 SEMA3E	90	Conotruncal (TOF, DORV +/− AVCD), aortic arch anomalies	Coloboma Choanal atresia Genital anomalies Ear Anomalies Cleft Lip/Palate
Cornelia de Lange syndrome	[246]	NIPBL	25	VSD, ASD, PS	Upper limb deficiency
Costello syndrome	[247, 248]	HRAS	75	PS, HCM	Skin/joint laxity Ulnar deviation

(continued)

Table 25.2 (continued)

Syndrome	References	Gene(s)/ chromosome	Frequency of CHD (%)	CHD types	Extracardiac
Holt-Oram syndrome	[249]	TBX5	75	ASD, VSD PAPVC	Upper limb anomalies
LEOPARD syndrome	[250, 251]	PTPN11	70–100	PS, HCM	Café au lait macules Lentigines Deafness
Noonan syndrome	[250, 252–254]	PTPN11 KRAS SOS1	85	PS, ASD, HCM	Short, webbed neck Pectus deformity Cryptorchidism
Rubenstein-Taybi syndrome	[255]	CREBBP	30	PDA, ASD, VSD, coarctation	Broad thumbs and great toes
Smith-Lemli-Opitz syndrome	[256]	DHCR7	45	ASD, VSD, AVCD, TAPVC	Toe syndactyly Cleft palate Lung anomalies Genital anomalies
Townes-Brocks syndrome	[257]	SALL1	25	Truncus arteriosus, TOF, ASD, VSD	Imperforate anus Ear anomalies Thumb anomalies

DORV double outlet right ventricle, *TOF* tetralogy of Fallot, *VSD* ventricular septal defect, *ASD* atrial septal defect, *AVCD* atrioventricular canal defect, *PDA* patent ductus arteriosus, *LVOTO* left ventricular outflow tract obstruction, *BAV* bicuspid aortic valve, *AS* aortic stenosis, *MV* mitral valve, *MVP* mitral valve prolapse, *PS* pulmonary stenosis, *HLHS* hypoplastic left heart syndrome, *TAPVC* total anomalous pulmonary venous connection, *PAPVC* partial anomalous pulmonary venous connection, *IAA* interrupted aortic arch, *PA* pulmonary atresia, *HCM* hypertrophic cardiomyopathy

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Ventricular Assist Device Support in Children

26

Sanjiv K. Gandhi and Deirdre J. Epstein

Abstract

There has been much recent interest in the application of ventricular assist devices in children with end-stage heart failure. Though extracorporeal membrane oxygenation has long been the mainstay for such patients in North America, ventricular assist devices have many potential advantages for these kids. The increasing success of the Berlin Heart ventricular assist device in Europe has spawned significantly increased use of this device in North America over the past decade. Active research is now ongoing to further develop and refine pediatric pumps. This chapter reviews preoperative and postoperative considerations, with respect to the pediatric population undergoing insertion of a ventricular assist device, reviews current and future technology, and briefly presents the recent experience with the Berlin Heart at Saint Louis Children's Hospital.

Keywords

Ventricular assist device • Pediatric heart failure • Berlin Heart

Introduction

Though the treatment of children with acquired and congenital heart disease has advanced significantly in recent years, a subset of patients will experience refractory myocardial failure. In an effort to keep the patient alive until a suitable donor organ becomes available for transplantation or until sufficient myocardial recovery occurs, mechanical circulatory support may be necessary. In adults, many ventricular assist devices (VADs) have been developed to clinical maturity. Options for mechanical support in children include miniaturized intraaortic balloon pumps, extracorporeal membrane oxygenation (ECMO), centrifugal pumps, and, more recently, both pulsatile VADs and axial flow devices [1–6]. ECMO remains the most common form of mechanical support available and is the best option for acute decompensation. ECMO provides total cardiopulmonary support, is relatively rapid, and allows the flexibility of peripheral and central cannulation. ECMO pumps, however, achieve nonpulsatile flow and the circuit is complex. The incidence of medium and long-term bleeding and infectious complications is exceedingly high and neurologic impairment with extended use is also common [7]. ECMO also restricts patient mobility, impairing physical rehabilitation.

Ventricular assist devices have several potential advantages over ECMO as a mechanical bridge to either recovery or transplantation. Pulsatile pumping results in better tissue perfusion and specifically provides better recruitment of the microcirculation of the brain, lungs, and kidneys during extracorporeal circulation. In addition to improving the patient's hemodynamic status and reversing end-organ dysfunction, VADs can be partially or fully implanted and allow for physical

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rehabilitation to improve the patient's overall condition and likelihood for successful transplantation. The first successful pediatric bridge to heart transplantation using a pulsatile paracorporeal LVAD was reported in 1991 in an 8 year-old boy [8]. Despite a substantial worldwide experience with pediatric specific devices, centers in the United States have historically relied on adult-sized devices because of a lack of U.S. Food and Drug Administration (FDA) approved miniaturized VADs [9]. Some pulsatile paracorporeal VADs are implantable in larger sized adolescent patients [10–12]. Studies examining pediatric bridge to transplant experiences have reported bridging success rates between 51 % and 79 % and 1-year survival post-transplant from 62 % to 88 % [11, 13–16]. Recently, there has been renewed interest in the development and application of ventricular assist devices in children.



Fig. 26.1 Thoratec ventricular assist device blood pump

Preoperative Considerations

Timing

As with most things in life, timing is everything. Timing of ventricular assist device implantation is of critical importance. However, classic guidelines for VAD implantation have not always been successful. Though risk factor summation scores systems have been calculated, these models are largely unsubstantiated when applied to children [17]. The indications for pediatric VAD usage are evolving. Our strategy for children with significant ventricular failure is planned VAD implantation. Though implantation of VADs too early exposes the patient to unnecessary surgery and potential device-related morbidity, it is mandatory to attempt to institute mechanical assist device therapy prior to the onset of any end-organ dysfunction. Studies in adult VAD recipients have demonstrated the greatest benefit from mechanical support in those patients who do not exhibit signs of secondary organ malfunction, supporting the strategy of early intervention [18]. The importance of patient selection and timing of device implantation has also been illustrated in the pediatric population [13].

Biventricular Assist Devices (BiVADs) Versus Left Ventricular Assist Device (LVAD)

Isolated LVAD insertion may be sufficient for bridging some patients to transplantation, even in the face of significant preoperative right ventricular dysfunction. Such therapy allows for maximal unloading of the left ventricle, which can appreciably reduce the afterload of the right ventricle. Combined with pharmacologic right heart support, the need for additional mechanical assistance can be more limited. Rather than attempting to pharmacologically support the right ventricle, employment of biventricular assistance in these patients is another option. Other than a slightly prolonged operative time, we have observed few disadvantages to the liberal addition of right ventricular mechanical support. Technical limitations imposed by adult devices are easily overcome by pediatric sized hardware. BiVAD support significantly simplifies postoperative management. Elimination of RV dysfunction completely may aid in postoperative bleeding, secondary to improved liver function, may limit renal dysfunction, and may permit earlier extubation, hence promoting a quicker recovery.

Device Options

Adult Ventricular Assist Devices

Adult FDA approved VADs have been successfully utilized in the older, and consequently larger, pediatric population [15, 19]. These devices include the Thoratec and Heartmate VADs (Thoratec Corp., Pleasanton, CA), the BVS 5000 (ABIOMED, Inc., Danvers, MA), and the NovaCor LVAS (World-Heart Inc., Oakland, CA) [20]. The Thoratec device (Fig. 26.1) has been, by far, the most commonly used VAD in children, with over 200 implants worldwide. As reported by Hill and colleagues [19], through January of 2005, 209 pediatric patients with a mean age of 14.5 years (range 5–18 years) and a mean BSA of 1.6 m^2 (range 0.73–2.3 m^2) had been supported. The mean duration of support was 44 days with 68 % of patients surviving until heart transplantation. However, specific concerns regarding using "oversized" devices have been documented [21]. Pumping large stroke volumes into a small aorta can perpetuate systolic hypertension and subsequent intracranial hemorrhage, stasis in the device can cause thromboembolic complications, and placement of multiple adult size cannulae in a limited pericardial space can be technically challenging.



Fig. 26.2 Berlin Heart EXCOR blood pumps: This is an immediate postoperative picture of a baby who received 10 ml biventricular assist devices (RVAD on *top*, LVAD on *bottom*)



Fig. 26.3 This picture illustrates the RVAD and LVAD cannulae. The order of the cannulae, from *right* to *left*, is right atrial outflow, pulmonary artery inflow, aortic inflow, and left ventricular outflow

Berlin Heart EXCOR Ventricular Assist Device

Within the last decade, the Berlin Heart EXCOR® (Berlin Heart AG Berlin, Germany) device became available for use in North America on a compassionate use basis. The device did not receive formal HDE status, which precluded maintenance of inventory in the United States and also precluded device marketing, which severely limited access. However, a recent FDA supported multicenter IDE clinical trial of the Berlin Heart VAD in North America was completed with results pending. The Berlin Heart consists of a paracorporeal, pneumatically driven polyurethane blood pump with a multilayer flexible membrane that separates the blood and air chambers (Fig. 26.2). Available pump stroke volumes are 10, 25, 30, 50, 60, and 80 mL. Silicon cannulae connect the blood pumps to the patient and triple-leaflet polyurethane valves prevent blood reflux (Fig. 26.3). All blood-contacting surfaces inside the pump, including the polyurethane valves, are coated with heparin by the Carmeda® process. The pump is driven by a pulsatile electropneumatic system. The drive unit (IKUS 2000) has a triple operational control and pneumatic system. The available biventricular operating modes are synchronous, where both blood pumps are filled and emptied in concert, asynchronous, where one ventricle is filled while the other is emptied, and separate, where each pump cycles independently.

A recent retrospective analysis performed by Hetzer and associates [22] in Berlin compared the outcomes of children who were supported by the Berlin Heart EXCOR between 1991 and 1998 (period 1; n = 34), and children supported by this device between 1999 and 2004 (period 2; n = 28). The primary outcomes were survival and hospital discharge. There has been significant era improvement in outcomes. Discharge from the hospital after either weaning from the

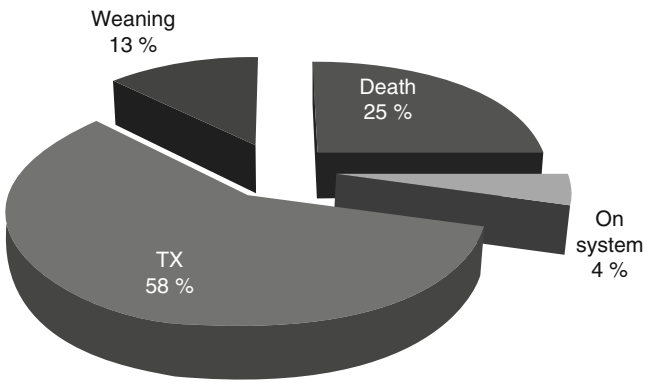


Fig. 26.4 Status of the first 110 North American recipients of the Berlin Heart VAD (Courtesy of Berlin Heart, Inc.)

system or heart transplantation was achieved for 35 % of patients in period 1 and for 68 % of patients in period 2 (p = 0.029). Over 930 children have been supported worldwide with the Berlin Heart.

The North American Berlin Heart experience has increased dramatically in the past 5 years [6, 23, 24]. The first child implanted with the Berlin Heart EXCOR in North America was a 9 year old child with tricuspid insufficiency in 2000. Through December 2010, over 200 children in North America had been supported by this device. The device has been used in over 30 North American medical centers. Contemporary survival rates now approach 75 % (Fig. 26.4), though the morbidity of these devices is not insignificant (Fig. 26.5). The initial multicenter North American experience of the Berlin Heart EXCOR was recently reported and further established the safety and efficacy of this device as a bridge to pediatric cardiac transplantation [25].

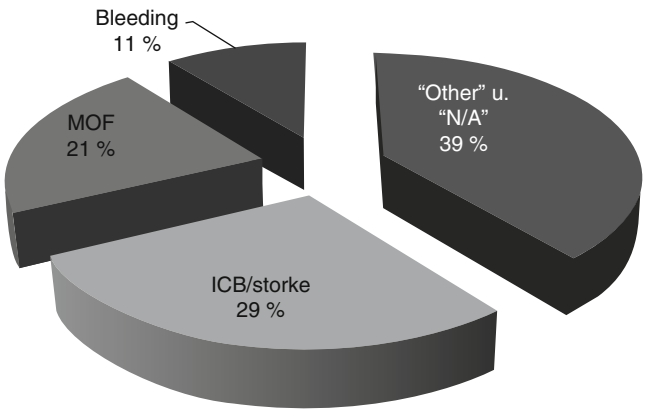


Fig. 26.5 Complications in the first 110 North American recipients of the Berlin Heart VAD (Courtesy of Berlin Heart, Inc.)

The Micromed Heart Assist 5

The Micromed Heart Assist 5 system (formerly DeBakey VAD Child) (Micromed Technology Inc., Houston TX, USA) consists of four subsystems: an implantable pump system, an external controller system, an external Clinical Data Acquisition System, and an external Patient Home Support System. The blood pump, intended to provide mechanical assistance to the failing left ventricle, is a miniaturized, implantable, titanium, electromagnetically actuated axial flow pump. The pump is 30 mm in diameter, 76 mm in length, and weighs 95 g. A titanium inflow cannula connects the pump to the ventricular apex and a Vascutek Gelweave vascular graft (outflow conduit) connects the pump to the aorta. Blood flow from the pump is measured by an ultrasonic flow probe placed around the outflow conduit. The flow probe's wiring is bundled with the pump motor's wiring in a polymer-coated assembly. The cable assembly exits the skin superior to the iliac crest on the right frontal portion of the body and attaches to the device's external controller system. The DeBakey VAD Child is approved for use in providing temporary left side mechanical circulatory support as a bridge to heart transplantation for pediatric patients (5–16 years old, with BSA > 0.7 m^2 and <1.5 m^2), who are in NYHA Class IV heart failure, are refractory to medical therapy, and who are candidates for heart transplantation.

A report by Fraser and colleagues [26] summarized the experience with the DeBakey VAD Child, which consisted of six patients. The average age of the patients was 11 years (range, 6–15 years) with a BSA of 0.8–1.7 m^2. The average duration of support was 39 days, with 84 days being the longest duration of support. Three of the six patients were successfully transplanted.

HeartWare Ventricular Assist System

The HeartWare System (HeartWare Inc, Miami Lakes, FL) consists of a centrifugal blood pump, integrated inflow cannula, an outflow graft, and a percutaneous driveline, which is connected to a controller (Fig. 26.6). The small pump has a displacement volume of 50 cc and weighs 140 g. It has one moving part, which is an impeller that spins blood to generate 1–10 L/min of flow at 1,800–4,000 rpm. A short integrated inflow cannula is inserted into the ventricle, and the outflow graft connects the pump to the aorta. A sewing ring attaches to the myocardium and allows pump orientation adjustments intraoperatively. The device size and short inflow cannula allow pericardial placement, which eliminates the need for device pockets [27]. Investigators from the German Heart Institute recently reported on the use of this device in seven pediatric patients, aged 6–16 years, including one patient with complex congenital heart disease [28]. The outcomes were excellent with low complication rates. This device may be an excellent alternative in children over 20 kg.



Fig. 26.6 The HeartWare System (HeartWare Inc, Miami Lakes, FL) consists of a centrifugal blood pump, integrated inflow cannula, an outflow graft, and a percutaneous driveline, which is connected to a controller

The National Heart, Lung, and Blood Institute (NHLBI) Pediatric Circulatory Support Program

Recognizing a major deficiency in the area of research and development of pediatric mechanical ventricular assistance, the



Fig. 26.7 The University of Pittsburgh PediaFlow® pediatric VAD. Left ventricular placement of PediaFlow system is illustrated. The device is a mixed-flow turbodynamic blood pump for patients up to 2 years old

NHLBI recently supported five pediatric VAD development programs across the United States [5]. These 5-years grants were awarded in March, 2004. The University of Pittsburgh is developing the PediaFlow® pediatric VAD (Fig. 26.7). This system is an implantable, magnetically suspended, mixed flow turbodynamic blood pump for children weighing between 3 and 15 kg. The device is 51 mm in length and 28 mm in diameter and weighs 50 g with a priming volume of 5 mL. The Cleveland Clinic PediPump® is 7 mm in diameter and based on the adult catheter pump. For patients <15 kg the pump may be used in intracorporeal extravascular mode; for older children the device is used as an intravascular pump and implanted into the aorta (LVAD) or the pulmonary artery (RVAD); BiVAD support is also possible. The system developed by Ension Inc. is a paracorporeal centrifugal pump with an integrated oxygenator (Fig. 26.8). The rotor is fabricated from layers of microporous hollow fibers with coating to extend fiber life and minimize anticoagulation. The Jarvik 2000® device has been modified for use in children (Fig. 26.9). The modified version for children of 15–35 kg body weight weighs 35 g and has a priming volume of 10 mL and the device for 3–15 kg children weighs 12 g with a priming volume of 4 mL; both are in the preclinical study stage. Pennsylvania State University is also developing a pediatric pulsatile, pneumatically actuated blood pump that may be used in implantable or paracorporeal mode (Fig. 26.10). The device is available in two sizes, with stroke volumes of 12 and 25 mL, for children weighing up to 35 kg. This NHLBI program has extended into the PumpKIN trial (Pumps for Kids, Infants, and Neonates), with the ultimate goal of commencing

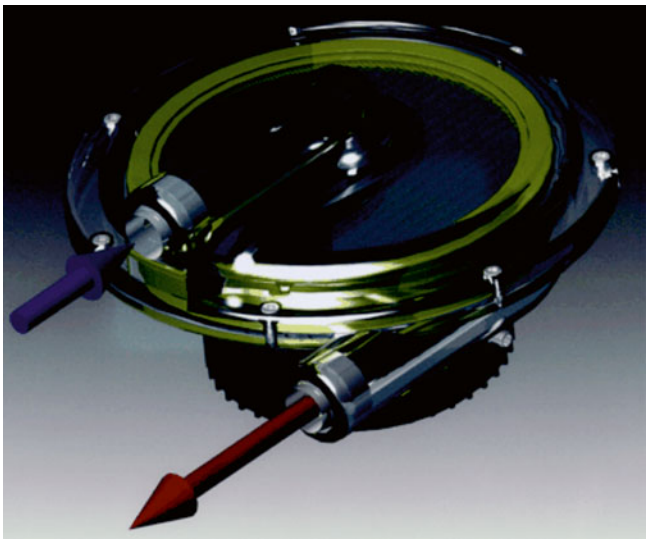


Fig. 26.8 The Ension pCAS system. The *blue* and *red arrows* show the blood inflow and outflow paths, respectively. Gas exchange occurs in the rotor's microporous hollow fibers



Fig. 26.9 The adult, child, and infant Jarvik 2000® devices. The infant model is still at the conceptual prototype stage of development

human trials. Each of these devices has unique features, and the expectation is that the five devices shall play complementary roles in a variety of clinical situations.

Operative and Postoperative Considerations

Surgical Procedure

Insertion of ventricular assist devices requires the use of cardiopulmonary bypass, usually with mild hypothermia on a beating heart. Short periods of fibrillatory or cardioplegic

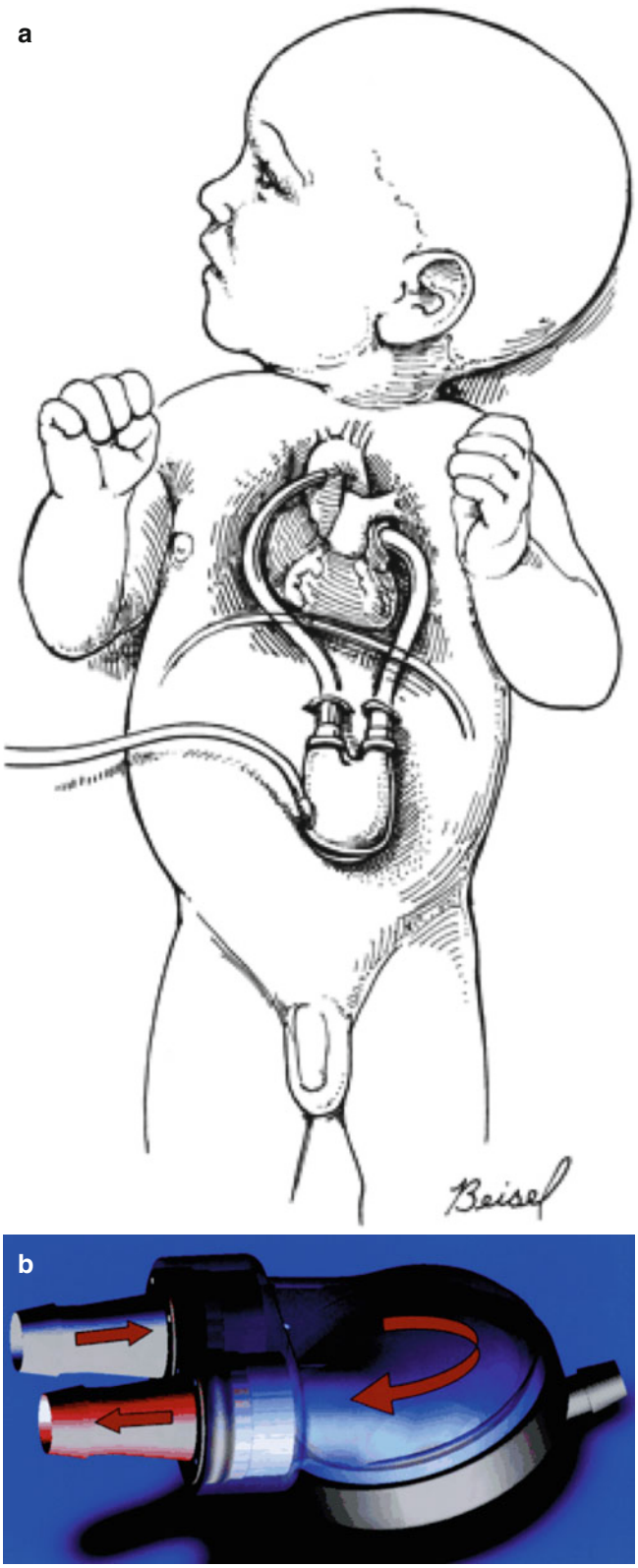


Fig. 26.10 (**a**) The Penn State PVAD, shown in the paracorporeal placement with left atrial-to-aorta cannulation. (**b**) Penn State PVADs are designed to produce rotational blood flow patterns within the pump chambers. The 12-mL infant-size VAD is shown

arrest are employed only to close intracardiac shunts. Inflow cannulation for the LVAD is generally completed via the left ventricular apex or the left atrium. Left-sided outflow cannulation is to the ascending aorta. Right atrial to main pulmonary artery cannulation is preferentially employed for an RVAD, though right ventricle to pulmonary artery cannulation can be utilized for special anatomic circumstances.

Anticoagulation

Postoperative anticoagulation is usually started with intravenous heparin 24 h after admission to the intensive care unit. The goal for the partial thromboplastin time is 40–51 s for the first 72 h and 52–80 s thereafter. The chronic anticoagulation regimen is initiated on approximately postoperative day 3. If using oral warfarin, the goal is to maintain an international normalized ratio between 3 and 3.5. Currently, for our Berlin Heart recipients, a triple drug regimen is utilized, consisting of low molecular weight heparin (initiated at 1 mg/kg/dose subq b.i.d.), aspirin (5 mg/kg/dose p.o. b.i.d.), and dipyridamole (1 mg/kg/dose p.o. q.i.d.). The goal antifactor XA level is maintained between 0.75 and 1.0.

Complications

Adverse postoperative events are not infrequent in this patient population, including postoperative bleeding, neurologic events, infection, and thromboembolism. In the literature, neurologic events vary considerably, from 6 % to 45 %. Some of these problems have been attributed to technical issues, such as left atrial cannulation, which is a known risk factor for stroke [14, 16]. Since the Berlin Heart EXCOR pumps are manufactured in multiple sizes, this obviates large stroke volumes in small children. The employment of polyurethane valves instead of mechanical valves may be less thrombogenic and transparent blood chambers allow for visual control of filling and emptying and transillumination detection of thrombotic deposits. Nevertheless, neurologic event rates using these devices range from 11 % to 45 %, using a combination of left atrial and apical inflow cannulation and varied anticoagulation schemes [4, 14]. Pump exchanges owing to thrombus formation are not infrequent in Berlin Heart recipients.

Sensitization

Perioperative blood transfusions, device-related infections, and the interaction between the device surface and the patient's immune system are recognized mechanisms for high rates of sensitization in VAD patients. The association

Table 26.1 Patient demographics and characteristics

Number of patients	20
Age (median, range)	2 years (12 days to 17 years)
Gender	Male 11, Female 9
Weight (median, range)	11 kg, (3–58 kg)
Etiology of heart failure	Cardiomyopathy: 18 Dilated 13 Restrictive 1 Noncompaction 3 Ischemic 1 Congenital heart disease: 2

of preformed anti-donor antibodies with hyperacute rejection and the persistence of the anti-donor immune response secondary to immunologic memory make allosensitization a relative contraindication to transplantation. Sensitized untreated VAD recipients have been noted to have a prolongation of waiting time to transplantation, an increased risk of acute rejection, and a trend of increased 30-day mortality [29]. However, though many patients show evidence of sensitization by ELISA, this may not be verified by Luminex methodology [24]. Thus, it is important to recognize that surveillance for HLA antibody sensitization during VAD support may be complicated by the development of non-HLA antibodies, which may not reflect true HLA presensitization.

Saint Louis Children's Hospital Berlin Heart Experience

Patients

Patient characteristics and demographics are summarized in Table 26.1. We implanted Berlin Heart BiVADs in 20 patients from April 2005 to June 2010. The patient population included 11 boys and 9 girls. The median age of the patients was 2 years (12 days to 17 years). The median patient weight was 11 kg (3–58 kg). The etiology of heart failure was cardiomyopathy in 18 children and complex congenital heart disease in 2. Of the latter two patients, one patient had congenitally corrected transposition of the great vessels with a small ventricular septal defect, status post epicardial pacemaker placement, and one had a forme fruste variant of hypoplastic left heart syndrome, with no previous intervention.

Preoperative Status

Pre-implantation variables are summarized in Table 26.2. Most children were supported with multiple intravenous inotropes ± mechanical ventilation (13 patients) or ECMO (5 patients) prior to BiVAD implantation. All had severe systemic ventricular dysfunction. At least moderate right ventricular dysfunction, as defined by a 2-dimensional echocardiographic ejection fraction less than 40 %, was present in all patients.

Table 26.2 Pre-implantation variables

Mean length of stay in ICU (days)	9.7 ± 5.2 (1–21)
ECMO	5/20 (25 %)
Mean duration of ECMO support (days)	7.6 ± 1.5 (6–9)
≥2 inotropes support (non-ECMO patients)	13/15 (87 %)
Mechanical ventilation mean duration of ventilator support (days)	15/20 (77 %) 13.1 ± 16.2 (3–30)

Table 26.3 Post-implantation data (days)

Duration of VAD support	Mean 33.6 ± 32.6 (1–137)
	Median 33.5
Post- implant ICU length of stay	Mean 10.2 ± 14.2 (1–65)
	Median 6
Post-implant duration of ventilator support	Mean 4.6 ± 5.6 (1–22)
	Median 3

Management During Support

Time courses for ventilatory support, intensive care unit stay, and duration of VAD support are summarized in Table 26.3. The median ventilatory requirement post VAD insertion was 3 days (1–22 days). Only 3 of 20 patients required mechanical ventilation longer than 1 week. The median length of stay in the intensive care unit was 6 days (1–65 days). Chronic care for all but one patient was managed on a regular cardiac ward. The median duration of VAD support was 34 days (1–137 days).

Outcomes

The primary endpoints included survival to and after heart transplantation. Seventeen of the twenty patients (85 %) who received VADs survived the period of circulatory support. A 3 kg baby died who required immediate ECMO following birth; she had significant pre-VAD renal insufficiency which progressed to anuric renal failure post Berlin Heart insertion. Despite the institution of hemodialysis, the child never thrived and, at the request of the parents, support was withdrawn on postoperative day 10. A 6-year old with myocarditis who was transitioned from ECMO to VADs with an initial smooth postoperative course died from an intracranial bleed 3 weeks postoperatively. A 1-year old with a cardiomyopathy placed on VADs with an uneventful immediate postoperative course had subsequent multiple issues with clots in the blood pumps and died 2 weeks postoperatively; postmortem examination revealed a rare congenital prothrombotic disorder.

Table 26.4 Adverse events during VAD support

Adverse event	Number of patients
Death	3/20 (15 %)
Bleeding requiring re-exploration	1/20 (5 %)
Pump change	13/20 (65 %)
Device malfunction	1/20 (5 %)
Paralyzed diaphragm	1/20 (5 %)
Prolonged ventilator dependence	3/20 (15 %)
Infection:	6/20 (30 %)
	Respiratory: 3/20 (15 %)
	Bloodstream: 1/20 (5 %)
	Driveline: 1/20 (5 %)
	Gastrointestinal: 1/20 (5 %)
Renal insufficiency	2/20 (10 %)
Gastrointestinal bleeding	1/20 (5 %)

Adverse events during VAD support are indicated in Table 26.4. Six patients had infectious complications. One child suffered a blood borne infection while three experienced respiratory infections. One patient suffered a driveline infection, requiring treatment with local wound care and intravenous antibiotics, and one was diagnosed with a *C difficile* infection. There was one episode of postoperative renal insufficiency not requiring dialysis. One patient required mediastinal reexploration in the very early postoperative period related to bleeding. One patient suffered a hemidiaphragm paralysis necessitating plication and one patient had a lower gastrointestinal bleed. There were three patients with neurologic complications. There were 33 total pump changes secondary to fibrin deposition or thrombus in 13 patients; 4 patients required >2 pump changes. There was an acute mechanical failure of the IKUS driver in one instance, necessitating manual pumping until the substitute driver was attached. There has been no significant detectable hemolysis, as measured by serial hemoglobin and plasma free hemoglobin assays. The chest was closed primarily in all patients. Overall, all patients who survived the period of mechanical support were successfully bridged to heart transplant. Post-transplant operative survival was 100 %. The clinical course of each patient is summarized in Table 26.5.

Sensitization

Human leukocyte antigen (HLA) sensitization, defined as a dithiothreitol-treated T-cell panel-reactive antibody (PRA) titer greater than 10 % immediately before transplantation, occurred in three patients in the series. All were supported longer than 30 days and all developed an extremely elevated (>90 %) PRA by ELISA that was not confirmed by Luminex;

Table 26.5 Summary of patient demographics, mechanical support data, complications, and outcome

Age	Weight (kg)	Implant date	Diagnosis	Implant duration (days)	Complications	Pump changes	Outcome
18 months	9.4	4/05	CMP	43	Bloodstream infection	2	Transplant
12 days	3	5/05	CMP	10	Renal failure	1	Death
4 months	5.5	10/05	CMP	1		0	Transplant
2 years	10.3	2/06	CMP	2		0	Transplant
9 years	24.4	2/06	CMP	35		4	Transplant
2 years	12.8	4/06	CHD	39	Driveline infection, IKUS failure	3	Transplant
17 years	38	8/06	CMP	5		0	Transplant
1 year	6.8	1/07	CHD	77	Pneumonia, renal insufficiency	0	Transplant
1 year	7.2	7/07	CMP	65	Pneumonia, diaphragm paralysis	2	Transplant
10 years	45	12/07	CMP	3		0	Transplant
13 years	45	2/08	CMP	33	Pneumonia	2	Transplant
12 years	40	6/08	CMP	42		2	Transplant
18 months	9.9	8/08	CMP	45	Postoperative bleeding, C difficile	2	Transplant
3 years	13.6	12/08	CMP	137	CVA	2	Transplant
6 years	22	3/09	CMP	19	Intracranial bleed	2	Death
17 months	8.4	9/09	CMP	4	GI bleed	0	Transplant
15 years	58	9/09	CMP	34		2	Transplant
29 days	3.5	10/09	CMP	47		6	Transplant
3 years	11.8	12/09	CMP	15		0	Transplant
13 months	7	2/10	CMP	17		3	Death

Key: *CMP* cardiomyopathy, *CHD* congenital heart disease

none had a positive donor-specific T or B cell retrospective crossmatch. There has been one episode of rejection (with hemodynamic compromise) in the transplanted patients.

Conclusion

Since the 1980s, cardiac transplantation has been the most effective long-term therapy for children with intractable heart failure. However, it is not unusual for a child listed as a status 1A heart transplant candidate to wait several months before an organ becomes available. In reality, non-pulsatile devices such as ECMO and centrifugal pumps have historically been the mainstay of pediatric circulatory support technology, particularly when biventricular support is required. These technologies reliably provide immediate cardiopulmonary support, however, their long-term use is associated with significant potential risks. Also, the intricate circuits mandate patient immobilization, which has a detrimental impact on rehabilitation. Although small pulsatile devices suitable for ventricular support in children have been available in Europe for some time, such miniaturized pumps have not been approved for use in North America. Insertion of pulsatile paracorporeal VADs has been validated as an effective strategy to bridge patients with refractory myocardial dysfunction to heart transplantation. Recent experience emphasizes the importance of continued development and refinement of mechanical ventricular assist devices in the pediatric population.

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Arrhythmias

27

David S. Cooper and Timothy K. Knilans

Abstract

The spectrum of cardiac arrhythmias in the pediatric intensive care unit (PICU) range from those which are immediately life threatening to rhythms with little or no hemodynamic consequence. When a cardiac arrhythmia is suspected or diagnosed in the PICU, the first step should not be to specifically diagnose the rhythm mechanism, but rather to determine the effects of the rhythm, some of which may have need for immediate intervention perhaps without a specific diagnosis. At the other end of the spectrum are rhythms which may initially appear to be benign, but may exert sub-clinical effects prior to resulting in hemodynamic collapse. Thus even rhythm abnormalities that do not initially appear to be of hemodynamic significance should be completely investigated. The Electrocardiogram (ECG) remains the primary modality for diagnosis of cardiac rhythm abnormalities. This Chapter will review the interpretation of ECGs, basic mechanisms and treatment of cardiac arrhythmias and special circumstances involving arrhythmias in the PICU.

Keywords

Arrhythmias • ECG interpretation • Pediatric ICU • Bradyarrhythmia • Tachyarrhythmia Antiarrhythmic medications

Introduction

The spectrum of cardiac arrhythmias in the pediatric intensive care unit (PICU) range from those which are immediately life threatening to rhythms with little or no hemodynamic consequence [1]. When a cardiac arrhythmia is suspected or diagnosed in the PICU, the first step should not be to specifically diagnose the rhythm mechanism, but rather to determine the effects of the rhythm, which may require immediate intervention (perhaps even before making a specific diagnosis). At the other end of the spectrum are rhythms which may initially appear to be benign, but may exert sub-clinical effects prior to resulting in hemodynamic collapse [2]. Other arrhythmias may never result in hemodynamic collapse, but their effects may prolong the duration of mechanical ventilation or PICU length of stay [3]. Thus even rhythm abnormalities that do not initially appear to be of hemodynamic significance should be completely investigated.

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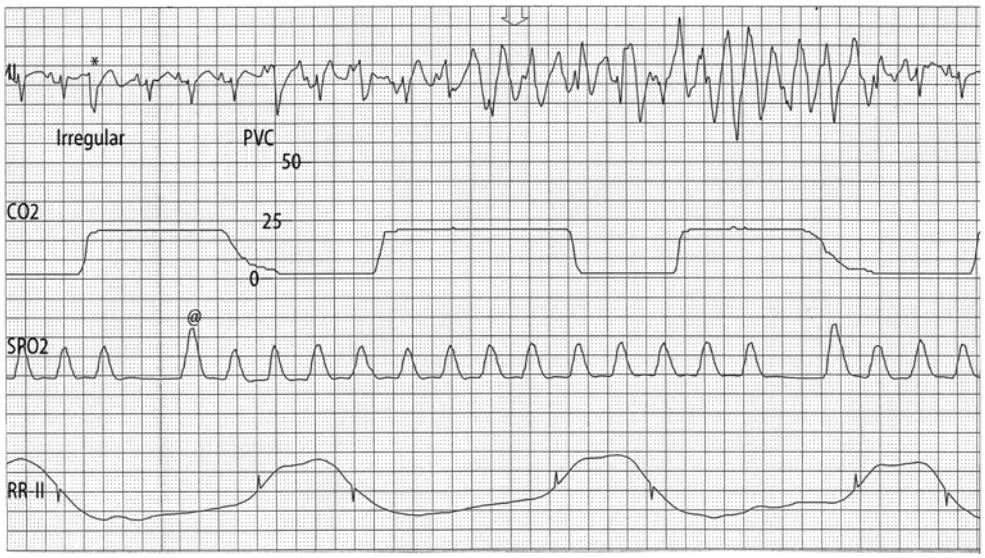


Fig. 27.1 Recording from monitor full disclosure review of an infant. Recorded is ECG lead II, end-tidal CO_2, pulse oximeter waveform and chest impedance respirometer. The rhythm is sinus with the third beat being a premature ventricular contraction (*). The pulse oximeter waveform does not show a waveform from the PVC, but shows an accentuated pulse from the post extra-systolic beat (@). The ECG recording subsequently develops significant artifact, which was initially interpreted as polymorphic ventricular tachycardia. The pulse oximeter shows a regular pattern throughout with another pause, suggesting a second PVC, but confirming artifact in the ECG recording rather than ventricular arrhythmia

Patients in the PICU are often on continuous electrocardiographic (ECG) monitoring with *full-disclosure* review [4] with or without *a telemetry technician* [5]. Ideally, multiple electrocardiographic leads and other monitoring parameters are simultaneously reviewable. *Reconstructed* 12-lead ECGs are available without attachment of the standard 10 electrodes in some current commercial systems [6, 7] and others allow recording of 12-lead ECG with standard lead placement using the bedside monitor. These multi-channel recordings and *full-disclosure* review greatly aid in establishing heart rhythm diagnoses and reduce the need for traditional ECG machines that may delay diagnosis and treatment.

In addition to surface electrocardiographic recordings, other parameters are frequently helpful in rhythm diagnosis and assessment. Atrial electrical activity may be directly recorded in patients with recent cardiac surgery with the use of epicardial temporary atrial *pacing* wires [8]. Atrial activity can also be recorded from the esophagus [9] in patients via a bipolar oro- or naso-esophageal catheter or swallowed *pill electrode*. Central venous or left atrial pressures and pressure waveforms may also be helpful in arrhythmia diagnosis. Monitoring heart rates with the use of arterial line waveform or pulse oximetry deflections may also be important, especially when artifact is present in the ECG recording (Fig. 27.1). In pacemaker dependent patients, the algorithm of a monitoring system may interpret the artifact of an electronic pacing spike as a QRS complex and not trigger an alarm if capture failure occurs. Heart rate monitors based on secondary indicators which require pacemaker capture, such as pulse oximetry or arterial pressure will notify personnel immediately should capture failure occur.

Interpretation of Electrocardiograms

The ECG remains the primary modality for diagnosis of cardiac rhythm abnormalities. In most cases and for most interpreters, printing the ECG on paper aids in the analysis of the heart rhythm. If *full disclosure* review is available, identifying the point of initiation, termination and any spontaneous perturbations of the arrhythmia and reviewing them in as many recorded leads as available should be done. A stepwise approach to interpretation of the ECG is most helpful.

Identification of atrial activity is the most helpful first step in arrhythmia analysis. Marking the location of visible p waves with pen on paper can help in the identification of a pattern of atrial activity. Measuring calipers can also be quite useful. The atrial mechanism is often regular and if it is dissociated from ventricular activity, caliper measurements can identify the probable timing of P waves that are concealed by QRS complexes or T waves. When readily available from post-operative temporary epicardial pacing wires, recording an ECG with augmented atrial activity can easily identify previously concealed atrial activity. Ideally this recording is performed with a separate amplifier channel recording a unipolar or bipolar atrial electrogram separate from, but on the same recording paper as the surface ECG (Fig. 27.2). When such recording equipment is not available, atrial augmentation



Fig. 27.2 Recording of surface ECG lead aVF, V1 and V6 with the simultaneous recording of an atrial electrogram with a separate amplifier. Rapid regular atrial activity identifies an atrial tachycardia with variable AV conduction and confirms atrial activity, which is more difficult to identify on the surface ECG

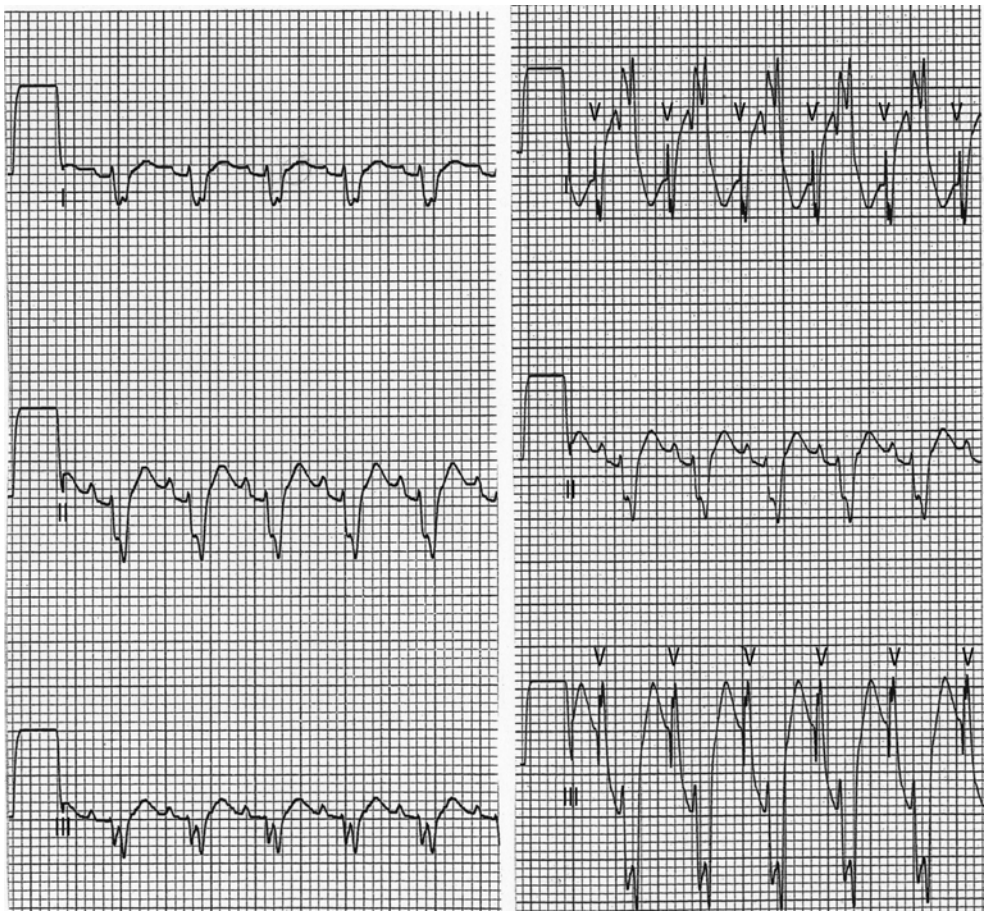


Fig. 27.3 Recording of surface ECG lead I, II and III in the *left panel* and the same recording with placement of an epicardial atrial wire under the left arm electrode. The rhythm in both cases is sinus rhythm conducted with aberration. In the *right panel*, augmentation of atrial activity is evident in leads I and III, but lead II is unaffected

can be achieved by attaching the atrial epicardial wire to the left arm lead. When this is done, recording from leads I and III will show atrial electrogram augmentation, while lead II recorded simultaneously will show a normal non-augmented ECG (Fig. 27.3). Similar atrial electrogram recordings can be performed with a greater degree of difficulty using an esophageal electrode recording. More complex arrhythmias or those where atrial pacing may be useful in termination of a tachycardia or treatment of bradycardia favor this technique when epicardial wires are not available [10].

Once all atrial activity has been identified and marked, the atrial rate can be determined. If the atrial rate is the same as the ventricular rate, there is likely to be either AV conduction, VA conduction or both (AV reentrant rhythm). If the atrial rate exceeds the ventricular rate, there is AV block of higher than first degree (Fig. 27.2) or non-conducted atrial

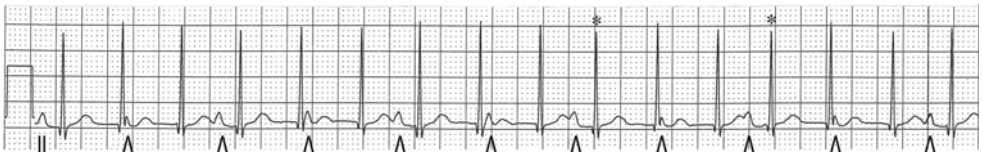


Fig. 27.4 Accelerated junctional rhythm in a child with retrograde block to the atrium. P waves that are dissociated from QRS complexes are labeled with *arrows*. AV conduction is evident by advancement of the QRS complex when atrial activity occurs at an opportune time (*)

ectopy. If the ventricular rate exceeds the atrial rate, there is an abnormal ventricular mechanism, which depending on the ventricular rate itself may be due to an inappropriately slow atrial rate, or an abnormally fast ventricular rate with some degree of ventriculo-atrial block (Fig. 27.4).

The p wave axis and morphology and QRS axis, duration and morphology should be inspected and if possible compared to the p waves during sinus rhythm and QRS complexes conducted from atrial activity from previous ECG recordings on the same patient (if they are available). The performance of a multi-lead ECG on all patients immediately prior to interventions anticipated to result in potential intra-procedural or post-procedural arrhythmia is strongly advised for this purpose. P waves with a morphology and axis identical to sinus rhythm seen during a tachycardia suggest sinus tachycardia or sinus node reentrant tachycardia, but some automatic atrial tachycardias may have very similar P waves and careful review in all leads, especially leads V1 and V2 should be undertaken. P waves that are upright in the inferior leads during a tachycardia are inconsistent with AV nodal reentrant tachycardia and unlikely to be seen in accessory pathway mediated tachycardias like orthodromic AV reentrant tachycardia.

Narrow QRS complexes during a tachycardia most often indicate a supraventricular mechanism, but ventricular tachycardia in children may have QRS complexes that have a duration that is less than the upper limits of normal for age (Fig. 27.5). If the QRS complex during a tachycardia is identical in morphology and duration to that seen during sinus rhythm, the tachycardia is supraventricular in mechanism. Care must be taken to review the QRS morphology in several leads, as it may appear similar or even identical in some leads, but quite different in others.

Supraventricular tachycardia may occur with wide QRS morphology due to aberrant conduction (Fig. 27.6) or ventricular preexcitation. Aberrant conduction may be caused by preexisting conduction system abnormality or block in the conduction system related to a rate faster than the refractory period of a portion of the His-Purkinje system, so called *rate dependent aberrant conduction*. Ventricular preexcitation may be due to conduction over an accessory atrioventricular connection or less commonly a connection between the AV node and a fascicle of the conduction system or the ventricular myocardium [11, 12]. Conduction

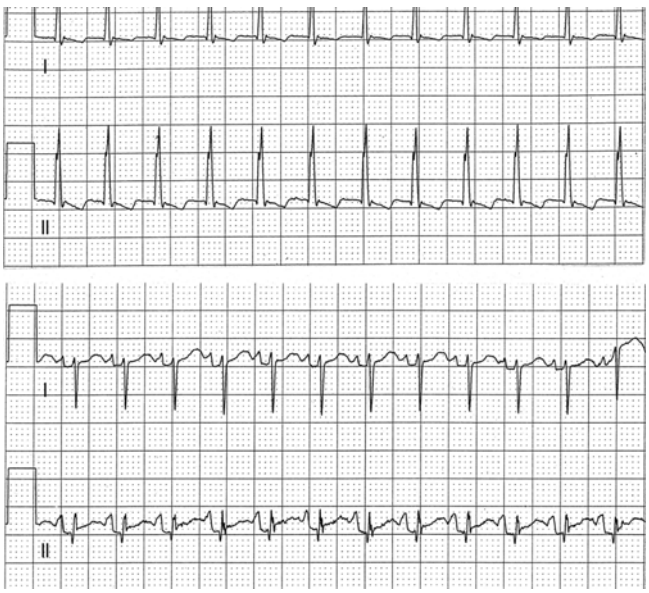


Fig. 27.5 Narrow QRS complex ventricular tachycardia in a child is shown in ECG leads I and II in the *upper panel*. The QRS duration is normal for age, but the QRS morphology is substantially different from that seen during sinus rhythm in the same leads in the *bottom panel*

with aberration can usually be distinguished from preexcited conduction by the presence of a sharp high frequency depolarization during the first 40 ms of the QRS complex (Fig. 27.7a). This represents normal activation of the ventricle over the functional portion of the conduction system, while the terminal portion of the QRS complex is delayed. Preexcited conduction will generally show a low frequency, slurred pattern at the beginning of the QRS complex due to activation of ventricular myocardium by the accessory pathway (Fig. 27.7b). This pattern may not be present if the accessory pathway inserts into a fascicle of the conduction system, thereby resulting in rapid depolarization of ventricular myocardium by specialized conduction fibers. If aberrant conduction or ventricular preexcitation is seen on previous ECG from the same patient during sinus rhythm, the pattern may be extremely helpful in diagnosis of the tachycardia. Again, the availability of multiple leads for comparison may be critical. On rare occasion, ventricular preexcitation and aberrant conduction may be seen in the same patient. This is especially true for patients with Ebstein's anomaly of the tricuspid valve where right sided accessory AV connections are



Fig. 27.6 Atrial tachycardia conducted with aberration is seen in the left side of the panel, resulting in a wide QRS complex tachycardia. The aberrant conduction resolves in the middle of the recording and the tachycardia develops a narrow QRS complex. P waves are more easily seen during the narrow QRS complex tachycardia, but in retrospect can also be seen during the wide QRS complex tachycardia

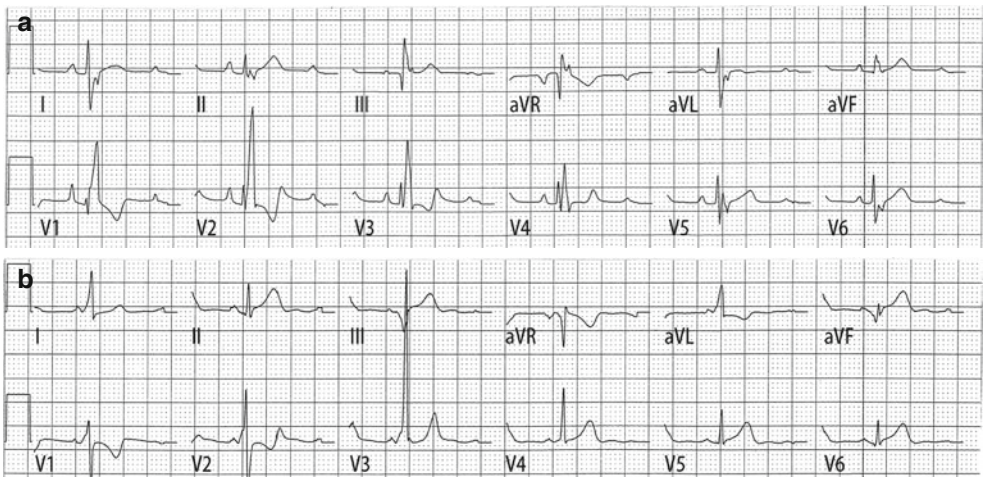


Fig. 27.7 Panel (**a**) shows the appearance of a wide QRS complex related to conduction with aberration. A sharp high frequency depolarization is seen in the first 40 ms of the QRS complex. Panel (**b**) shows the appearance of a wide QRS complex related to ventricular preexcitation. In addition to the shorter P-R interval, the QRS complex shows a low frequency, slurred pattern in the first 40 ms of the QRS complex

common and right bundle branch block is frequently seen. In this scenario, the right sided accessory pathway may function as a surrogate for the right bundle branch and result in normalization of conduction [13].

Basic Mechanisms of Cardiac Arrhythmias

Heart rhythms can be classified as bradycardia, tachycardia or normal based on their rate. Normal heart rates vary by age and physiologic state. Typically when classifying a rhythm by rate, the physiologic state is discounted. As such, it is recognized that *tachycardia* may be normal under conditions of stress and that *bradycardia* may be normal during sleep. Normal resting heart rate ranges can be found in Table 27.1.

Table 27.1 Normal ranges for pediatric heart rhythm intervals

Age	Heart rate (beats/min)	PR interval (ms)	QRS duration (ms)
0–1 day	93–155	79–161	21–76
1–3 days	91–158	81–139	22–67
3–7 days	90–166	73–136	21–68
7–30 days	106–182	72–138	22–79
1–3 months	120–179	72–130	23–75
3–6 months	106–186	73–146	22–79
6–12 months	108–169	72–157	23–76
1–3 years	90–151	81–148	27–75
3–5 years	72–138	83–161	30–72
5–8 years	64–132	90–163	32–79
8–12 years	62–130	88–171	32–85
12–16 years	61–120	92–176	34–88

Bradycardia Mechanisms

Bradycardia results from improper impulse formation in the sinus node or from failure of the impulse to propagate from the sinus node to the atrium (SA exit block) or from the atrium to the ventricle (AV block). Failure of adequate impulse formation in the sinus node may be the result of intrinsic abnormalities of the node. These include congenital abnormality of cardiac ion channels [14] or improper or absent sinus node development and damage to the node from auto-antibodies, inflammation or surgical intervention. It can also occur because of extrinsic factors such as parasympathetic stimulation or metabolic disturbance. The severity of the abnormality may range from a sinus rate that is slightly less than normal to sinus arrest (complete absence of impulse formation). Failure of propagation of the impulse from the sinus node to the atrium clinically can be difficult to differentiate from failure of adequate impulse

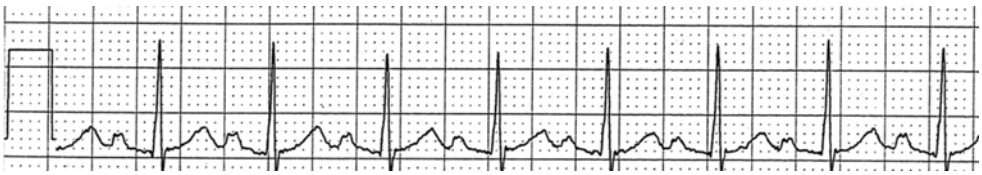


Fig. 27.8 Sinus rhythm with first degree AV block is demonstrated by a P-R interval of 190 ms, above the upper limits of normal for a child

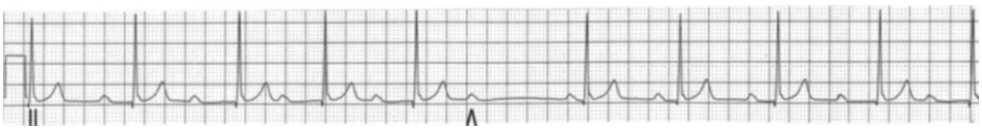


Fig. 27.9 Sinus rhythm with second degree AV block, Mobitz type I (Wenckebach) is demonstrated with progressive PR interval prolongation followed by a non-conducted sinus P wave marked with an *arrow*



Fig. 27.10 The atrial mechanism is sinus at a rate of 125/min as evidenced by large P waves with a regular pattern. There is complete AV block as evidenced by a slower regular ventricular rhythm at a rate of 60/min with narrow QRS complexes marked with *arrows*. The narrow QRS complex suggests a junctional mechanism

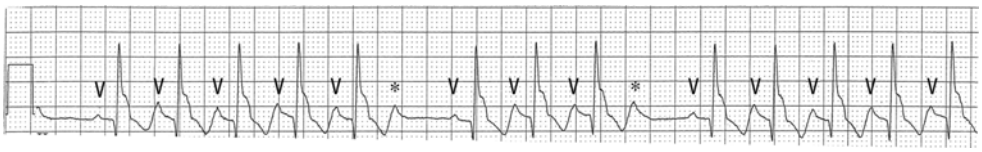


Fig. 27.11 Sinus rhythm with second degree AV block, Mobitz type II is demonstrated with a regular atrial mechanism marked with *arrows* with a constant P-R interval and sudden non-conducted P waves (*)

formation as sinus node activity can not be directly seen on the surface ECG. It may result from congenital or acquired abnormalities and from a practical standpoint differentiation is usually not important as these problems are typically treated in the same way [15].

Abnormalities in propagation of the impulse from the atrium to the ventricle (AV block) are similar to those seen in the sinus node and occur related to intrinsic abnormality of the AV node or extrinsic factors, identical to those that cause sinus node dysfunction. Conduction abnormality may occur at the level of the AV node, the common bundle of His or the right or left bundle branches or their ramifications. In the case of severe prolongation of the QT interval, the impulse conduction may fail due to functional inexcitability of the His-Purkinje system [16] or the ventricle itself. The P-R interval (measuring from the beginning of the p wave to the beginning of the QRS complex) measures the conduction time through the atrium, the AV node, the His bundle, the bundle branches and the Purkinje fibers. When all atrial impulses are conducted, but the P-R interval is longer than normal for age, criteria for first degree AV block are satisfied (Fig. 27.8). The range of normal P-R intervals can be found in Table 27.1. As first degree AV block does not reduce the relative frequency of ventricular activity compared with atrial activity, it will not result in bradycardia. When some but not all atrial impulses are conducted from the atrium to the ventricle, there is second degree AV block (Fig. 27.9). When no atrial impulses are conducted to the ventricle there is third degree or complete AV block (Fig. 27.10).

Second degree AV block occurs in three forms, Mobitz types I and II and 2:1. In Mobitz type I, also referred to as Wenckebach conduction, there is progressive prolongation of the P-R interval before conduction block occurs (Fig. 27.9). This electrocardiographic pattern is most commonly observed when the conduction abnormality is occurring in the AV node [17]. In Mobitz type II there is a constant P-R interval preceding a non-conducted p wave (Fig. 27.11). This pattern is most commonly seen when the His-Purkinje

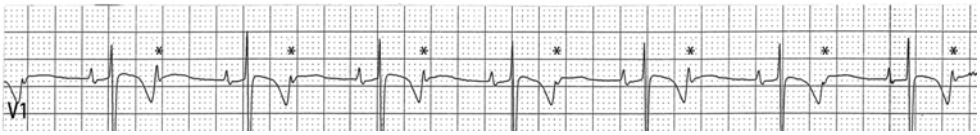


Fig. 27.12 Sinus rhythm with second degree AV block, 2:1 is demonstrated with a regular atrial mechanism with every other P wave not conducting to the ventricle (*). Note that the non-conducted p waves may be somewhat concealed within the previous T wave

Table 27.2 Bradycardic rhythms

	Mechanism	Causes	ECG appearance
Slow atrial rate	Sinus node dysfunction	Mechanical damage to sinus node; Congenital ion channel, metabolic or autonomic abnormality resulting in slow sinus rate or atrial inexcitablity	Slow sinus rate or absence of sinus activity with ectopic atrial escape or atrial standstill
	Sinus node exit block	Congenital or acquired mechanical abnormality; Congenital ion channel abnormality	Same as sinus node dysfunction if first or third degree; Definable pattern of atrial depolarization if second degree
Atrial rate > Ventricular rate	Second degree AV block, Mobitz type I (Wenckebach)	Most commonly AV nodal block: Congenital, mechanical or autoantibody damage; Congenital ion channel abnormality; Autonomic abnormality	Partial AV association: Progressive increase in P-R interval followed by non-conducted P wave
	Second degree AV block, Mobitz type II	Most commonly His Purkinje system block: Mechanical damage to conduction system, myocardial infarction	Partial AV association: Constant P-R interval followed by sudden non-conducted P wave; Usually with wide QRS, often bi-fascicular block pattern
	Second degree AV block, 2:1	Usually associated with Mobitz type I or type II	Partial AV association: Two p waves for every QRS complex, constant P-R interval of conducted P wave
	Complete (Third degree) AV block	Same as causes of second degree AV block types I and II	AV dissociation with faster atrial than ventricular rate; Regular ventricular mechanism: Narrow QRS complex if junctional escape, wide QRS if ventricular escape

conduction system is abnormal [18]. Because of this, there is usually a bundle branch block or intraventricular conduction delay pattern (wide QRS complex) accompanying Mobitz type II AV block. In 2:1 AV conduction there is conduction of every other atrial complex (Fig. 27.12). This eliminates the ability to determine whether or not there is P-R prolongation. Most individuals with 2:1 AV block will have either Mobitz type I or II AV block at other times and thus the expected level of conduction block may be inferred from the associated Mobitz type of block. AV block occurring in the AV node is considered to be better in prognostic significance in pediatric patients [19]. The presence of intact conduction from a subsidiary pacemaker in the AV junction to the ventricle would be expected to protect the patient from sudden asystole in the event of sudden AV nodal block. The presence of adequate subsidiary pacemakers below the level of His-Purkinje conduction block is less likely and thus sudden AV block at this level is more dangerous. From a practical standpoint, in the PICU the anatomic level of AV block is rarely important. These patients are typically on continuous monitoring and if sudden AV block occurs, rapid treatment with chest compressions followed by external, transvenous or epicardial pacing can be instituted. The level of block is far more important for patients no longer in intensive care areas and not on continuous cardiac monitoring. The potential for unsuccessfully resuscitated bradycardic arrest is substantially higher in this setting. Third degree or complete AV block may occur at either of the anatomic levels described for second degree AV block. There may be an escape rhythm from a subsidiary pacemaker in the AV junction or the ventricle, or there may be no escape rhythm. If there is no escape rhythm of acceptable rate, immediate treatment is necessary, usually in the form of cardiac pacing. The causes and electrocardiographic appearance of clinical bradycardic rhythms are summarized in Table 27.2.

Tachycardia Mechanisms

Tachycardia is generally thought to occur due to three basic mechanisms: reentry, automaticity and triggered automaticity. Reentry requires a circular movement of propagated

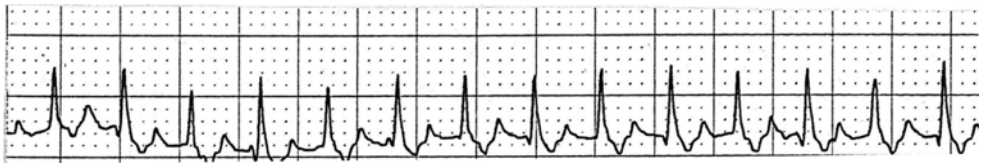


Fig. 27.13 Orthodromic AV reentrant tachycardia is demonstrated by a regular narrow QRS complex tachycardia with 1:1 AV relationship and atrial activity following the QRS with an R-P interval of 100 ms

impulses either over large (macro-reentry) or small (micro-reentry) area of the myocardium. Automaticity occurs when cardiac myocytes have regular spontaneous depolarization to reach threshold and activate surrounding cells. Triggered automaticity is a spontaneous depolarization that occurs in response to a preceding depolarization.

Reentry may take place in the atrium, the ventricle, the normal conduction system, the sinus node or combinations of the above. Reentrant rhythms typically initiate following a premature depolarization and have characteristics of sudden onset and termination. Multiple reentrant circuits, which are active simultaneously, may be responsible for rather disordered rhythms such as polymorphic ventricular tachycardia and atrial and ventricular fibrillation [20].

Automatic rhythms may also originate in any area of the heart. Automatic tachycardia from the sinus node is usually a normal phenomenon, but automatic tachycardias from other cardiac cells result from abnormal automaticity. Automatic rhythms tend to have gradual onset and offset or *warming-up* and *cooling-down* periods. Triggered automatic rhythms are most commonly recognized in ventricular myocardium, but probably also result in tachycardia in atrial tissue as well. They are implicated in tachyarrhythmia related to digitalis toxicity and congenital and acquired QT prolongation.

Clinically tachycardias are usually divided into narrow and wide QRS complex tachycardias. Narrow QRS complex tachycardias are those that activate the ventricle via the normal AV conduction system. They most commonly occur with 1:1 AV relationship, but can have faster atrial than ventricular rates and vice versa. When a 1:1 AV relationship exists, the tachycardias are the result of automatic mechanisms in the atria or AV junction or reentrant mechanisms in the atria, AV node or utilizing the AV node and accessory AV connection (Fig. 27.13). Some patients with complex congenital heart disease will have duplication of the AV conduction system or *twin AV nodes* and have an AV reentrant tachycardia utilizing the two conduction systems [21]. Rare ventricular tachycardias may have QRS duration that is normal for age, generally because the ventricular mechanism activates the conduction system in some way, resulting in more rapid ventricular depolarization (Fig. 27.5). These ventricular tachycardias may have 1:1 conduction to the atrium over the AV node. Regular narrow QRS complex tachycardias with a 1:1 AV relationship, their causes, ECG appearance and responses to adenosine and cardioversion are summarized in Table 27.3.

When a narrow QRS complex tachycardia occurs with a faster atrial rate than ventricular rate, the mechanism is an automatic or reentrant mechanism in the atrium or AV node with variable or no conduction to the ventricle (Fig. 27.14). The ECG appearance and adenosine and cardioversion responses of these clinical tachycardias are summarized in Table 27.4. Rarely, narrow QRS complex tachycardias are seen with a faster ventricular rate than atrial rate. Most commonly this is automatic junctional tachycardia that is seen in a familial congenital form as well as following cardiac surgery. There may be some degree of conduction to the atrium or complete VA block (Fig. 27.4). Narrow QRS complex ventricular tachycardia can also occur with retrograde conduction to the atrium. These rhythms are summarized in Table 27.5.

Wide QRS complex tachycardia represents either supraventricular tachycardia with aberrant [22] or pre-excited conduction [23] or ventricular tachycardia [24]. The causes and response to adenosine and cardioversion for these rhythms are the same as their narrow QRS complex counterparts. Wide QRS complex supraventricular tachycardia may offer important insights into the mechanism of the tachycardia. When a narrow QRS complex tachycardia is seen to progress directly into a wide QRS complex tachycardia or vice-versa, the mechanism of both tachycardias is likely common. If the wide QRS complex tachycardia is occurring due to rate dependent aberrant conduction and the R-P interval is longer during the wide than the narrow QRS complex tachycardia, the mechanism of the tachycardias is likely to be orthodromic AV reentrant tachycardia utilizing an accessory pathway which is ipsilateral to the side of the bundle branch block causing the aberrant conduction.

The pattern of the QRS complexes in a wide QRS complex tachycardia may also be helpful in differentiation of a supraventricular versus ventricular mechanism [25, 26]. A typical right or left bundle branch block pattern favors supraventricular tachycardia, whereas atypical bundle branch block patterns or bundle branch block with an opposite QRS axis (e.g. right bundle branch block with left axis deviation) favor ventricular tachycardia. Likewise, a concordant pattern of QRS complexes in the precordial leads (all leads showing either a positive or negative deflection) favors ventricular tachycardia [27].

Table 27.3 Regular narrow QRS complex tachycardia with atrial rate = ventricular rate

Mechanism	Causes	ECG appearance	Adenosine response	Cardioversion response
Automatic atrial tachycardia	Congenital, myocarditis, metabolic, autonomic	RP > PR, P wave morphology different than sinus, rate may vary slightly	Transient AV nodal block then continuation of tachycardia, Atrial rate may slow, rarely terminates	Usually none, autonomic response may accelerate the tachycardia rate
Reentrant atrial tachycardia	Congenital or post cardiac surgical reentrant circuit	RP > PR, P wave different than sinus, rate usually fixed	Transient AV nodal block then continuation of tachycardia, Atrial rate constant, occasionally terminates	Terminates, may reinitiate
Orthodromic AV reentrant tachycardia	Congenital accessory AV connection	RP < PR, P wave usually negative in inferior leads, may have ventricular preexcitation in sinus rhythm	Slowing of tachycardia with increase in P-R and termination with last event being a P wave	Terminates, may reinitiate
Permanent form of "Junctional" Reciprocating Tachycardia (PJRT)	Congenital accessory AV connection with slow pathway conduction	RP > PR, P wave negative in inferior leads, tachycardia is usually incessant	Slowing of tachycardia with increase in P-R and termination with last event being a P wave	Terminates, usually reinitiates
Typical AV nodal reentrant tachycardia (A-V over slow pathway, V-A over fast pathway)	Congenital or acquired dual AV nodal pathways	Nearly simultaneous P and QRS, P may be visible slightly before or after QRS, always negative in inferior leads	Slowing and termination of tachycardia	Terminates, may reinitiate
Atypical AV nodal reentrant tachycardia (A-V over fast pathway, V-A over slow pathway)	Congenital or acquired dual AV nodal pathways	RP > PR, P waves always negative in inferior leads	Slowing and termination of tachycardia	Terminates, may reinitiate
Junctional automatic tachycardia with conduction to atrium	Congenital, post cardiac surgical	Nearly simultaneous P and QRS	Transient AV dissociation with faster ventricular rate, continuation of tachycardia	Usually none, autonomic response may accelerate the tachycardia rate
Ventricular tachycardia with narrow QRS complex and conduction to atrium	Usually congenital	RP < PR, QRS morphology different than during sinus rhythm	Transient AV dissociation with faster ventricular rate, usually continuation of tachycardia, may terminate tachycardia	Usually terminates

RP R-P interval (time interval from beginning of the QRS complex to the beginning of the next P wave), *PR* P-R interval (time interval from beginning of the P wave to the beginning of the next QRS complex)

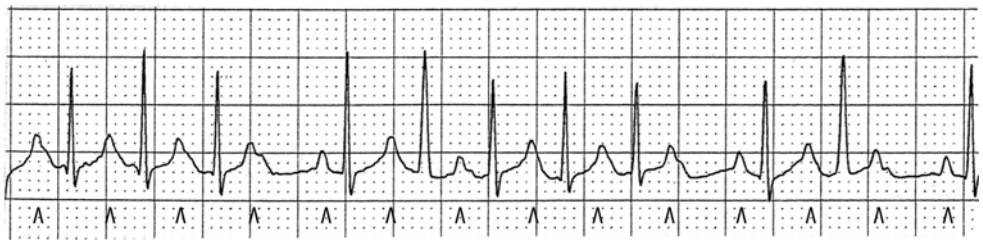


Fig. 27.14 An atrial tachycardia with variable AV conduction is demonstrated by a regular atrial mechanism the rate of which exceeds that of the ventricular mechanism. The QRS complexes are related in a pattern consistent with second degree AV block Mobitz type I (Wenckebach) with prolongation of the PR interval prior to a non-conducted P wave

Mechanisms of Arrhythmia with Normal Heart Rate

Many arrhythmias occur with heart rates that are within the range of normal for the patient's age. First degree AV block is rarely of clinical significance, but in patients with marginal hemodynamic status, providing a normal atrial to ventricular mechanical coupling may reduce the need for other support. In most circumstances the invasive intervention required to provide such support is prohibitive. In patients who have had immediately preceding cardiac surgery and have post-operative atrial and ventricular epicardial pacing wires, ventricular pacing tracking atrial activity is relatively simple. Isolated atrial and ventricular ectopy do not usually result in alteration of the heart rate from normal. Frequent premature atrial complexes that are non-conducted, alternating with

Table 27.4 Regular narrow QRS complex tachycardia with atrial rate > ventricular rate

Mechanism	ECG appearance	Adenosine response	Cardioversion response
Automatic atrial tachycardia with second or third degree AV block	Regular atrial rhythm with P wave morphology different than sinus P wave, Irregular ventricular response with pattern of type I or type II second degree AV block or regular ventricular response if complete AV block with junctional rhythm	Atrial rate may slow transiently and rarely terminate, degree of AV block may increase if second degree; no effect on ventricular rate if complete AV block already present	Usually none, autonomic response may accelerate the atrial rate or enhance AV nodal conduction
Reentrant atrial tachycardia with second or third degree AV block	Regular atrial rhythm with P wave morphology different than sinus P wave, Irregular ventricular response with pattern of type I or type II second degree AV block or regular ventricular response if complete AV block with junctional rhythm	Atrial rate remains constant and occasionally terminates, degree of AV block may increase if second degree; no effect on ventricular rate if complete AV block already present	Terminates, may reinitiate
AV nodal reentrant tachycardia with AV block below AVN or His bundle	Regular atrial rhythm, usually with 2:1 A-V relationship, p waves always negative in inferior leads, one p wave usually nearly simultaneous with QRS complex	Tachycardia usually slows and terminates, rarely AV nodal conduction is affected in such a way that 1:1 AV conduction develops	Terminates, may reinitiate

Table 27.5 Regular narrow QRS complex tachycardia with ventricular rate > atrial rate

Mechanism	ECG appearance	Adenosine response	Cardioversion response
Junctional automatic tachycardia with second or third degree VA block	Narrow QRS complex tachycardia with AV dissociation, p waves may be negative in inferior leads and have relationship to QRS if second degree VA block, sinus P waves if complete VA block	None on ventricular rate, may increase degree of VA block if second degree	Usually none, autonomic response may accelerate the atrial and or ventricular rate
Ventricular tachycardia with narrow QRS complex with second or third degree VA block	QRS morphology different than during sinus rhythm, p waves may be negative in inferior leads and have relationship to QRS if second degree VA block, sinus P waves if complete VA block	May slow or terminate tachycardia, increase degree of VA block if second degree	Usually terminates

sinus complexes that are conducted (atrial bigeminy) may result in a ventricular bradycardia [28]. Frequent premature ventricular complexes in a bigeminal pattern will result in a normal ventricular rate, but may result in an effective bradycardia hemodynamically as the premature contraction is rather ineffective due to a limited ventricular filling time preceding it. Atrial tachyarrhythmias, which are conducted with second or third AV block, may result in a normal ventricular rate. Ectopic atrial rhythm and accelerated junctional and ventricular rhythms also occur within normal heart rate ranges, but have abnormal mechanisms and may potentially be hemodynamically compromising.

Treatment of Bradyarrhythmia

Immediate treatment of hemodynamically significant bradycardia includes chest compressions, administration of supplemental oxygen and mechanical ventilation to mitigate the metabolic effects of the slow heart rate and the administration of epinephrine and atropine. If bradycardia persists, cardiac pacing is indicated. Transcutaneous pacing is often incorporated in devices that are used for defibrillation and cardioversion. Transcutaneous pacing, which occurs above the threshold for stimulation, results in ventricular contraction and may also result in simultaneous atrial contraction [29] or atrial depolarization from retrograde conduction [30]. Without instantaneous blood pressure monitoring, it may be difficult to assess the patient for adequate ventricular capture. The application of transcutaneous pacing is tolerated for only limited periods because of skeletal muscle stimulation and skin irritation. If the patient's bradycardia is secondary to isolated sinus node dysfunction, which is rare, esophageal atrial pacing may be utilized for longer periods, but is still quite uncomfortable in a non-anesthetized patient. If AV node dysfunction is present, transvenous pacing with a balloon tipped catheter introduced from the subclavian or jugular vein can provide safe and stable pacing for a longer period in most pediatric patients. Occasionally placement of a lead from a femoral venous approach with the use of fluoroscopy may be needed. Temporary dual chamber transvenous pacing is rarely performed in pediatric patients. Epicardial atrial and ventricular pacing is common in patients following cardiac surgery where pairs of temporary epicardial wires can be placed [31, 32]. In principle, the patient with exclusively sinus node dysfunction benefits the most from atrial pacing alone,

as normal AV conduction is preferential to ventricular pacing such that there is a normal mechanical activation sequence of the ventricle. The critically ill patient with AV block requires ventricular pacing. If sinus node function is intact, ventricular pacing tracking native atrial activity is preferred. In the patient with right bundle branch block, pacing the right ventricle tracking native atrial activity, or an atrial paced rhythm with an appropriate AV delay may be beneficial in allowing for simultaneous right and left ventricular contraction and providing *resynchronization* with a single pacing lead.

Temporary cardiac pacing, as mentioned, can be performed with either epicardial or transvenous endocardial pacing leads or for shorter periods with esophageal atrial pacing, esophago-gastric ventricular pacing [33] or transcutaneous pacing [34]. Regardless of the specific method, some general principals apply. Pacing capture and sensing thresholds exist for the given patient, pacing arrangement, physiologic circumstance and time. The capture threshold is the amount of energy required to effectively stimulate the heart. In temporary pacing devices, the current is generally adjustable and the pulse width (duration of stimulation) is fixed, but in some instances may be adjustable. A longer pulse width will achieve capture with a lower current than a shorter pulse width and if the pulse width is adjustable, varying the current and pulse width may result in optimal cardiac pacing, and minimize skeletal muscle stimulation. Longer pulse widths are required for esophageal and transcutaneous pacing applications. To determine the capture threshold, the pulse width should be maintained and the current adjusted until a cardiac depolarization is seen following each spike artifact from pacing. As previously mentioned, the wider pulse width and skeletal muscle response to transcutaneous pacing can make assessment of capture with an electrocardiographic recording difficult [34] and secondary indicators such as an arterial pressure waveform may be needed. Once the capture threshold has been determined, the output current should be set at least twice the capture threshold. The sensing threshold is the voltage from a cardiac depolarization that an electrical signal must exceed to be considered by the pacemaker as intrinsic cardiac activity. The sensitivity is programmed in millivolt units. The higher the setting in millivolts, the less sensitive the pacemaker will be to cardiac activity. To determine the sensing threshold, the pacing rate should be programmed to lower than the patient's intrinsic rate and the pacemaker sensitivity should be adjusted to an insensitive or asynchronous mode. The sensitivity setting should then be gradually increased (to a lower millivolt setting) until the device indicates sensing of cardiac activity by an indicator light, or by inhibition of cardiac pacing. The sensitivity should then be set to a millivolt setting of one-half the sensing threshold. In patients with severely inadequate intrinsic rhythms, the ventricular sensing threshold may not be able to be practically determined and sensing can be programmed to a nominal setting (usually 2 mV). Care should be taken to avoid setting the sensitivity to such a highly sensitive setting that extraneous electrical noise or skeletal muscle artifact is sensed as intrinsic cardiac activity and inhibits cardiac pacing. As previously mentioned, if AV nodal conduction is intact and sinus node rate inadequate, atrial pacing is preferred. The rate of pacing can be adjusted to optimize measurable hemodynamic parameters. If sinus node rate is appropriate, but AV block is present, ventricular pacing tracking atrial activity is preferred. The lower rate limit of the pacemaker should be set to a rate slower than the sinus rate and the upper rate set to a value as high as desired. In pediatric pacing the desired upper rate limit is generally greater than 200 beats per minute unless an atrial tachycardia is present. The AV interval (maximal interval from paced or sensed atrial activity to sensed or paced ventricular activity) can also be adjusted to achieve the best hemodynamic benefit. The PVARP (post-ventricular atrial refractory period) is the time after a paced or sensed ventricular event during which the atrial channel of the pacemaker will not sense atrial activity. The primary purpose of this interval in a temporary pacemaker is to prevent the device from sensing the ventricular pacing spike or ventricular electrical activity as intrinsic atrial activity and to prevent *pacemaker-mediated* tachycardia. *Pacemaker-mediated* tachycardia occurs when paced ventricular activity is conducted to the atrium (usually retrograde over the AV node) and is sensed by the atrial channel of the pacemaker, triggering ventricular pacing and resulting in an artificial form of reentrant tachycardia. This form of tachycardia usually initiates with a premature ventricular contraction and can be terminated with brief cessation of ventricular pacing. Programming of the PVARP to a higher value will prevent this form of tachycardia, but will limit the fastest rate which the pacemaker can pace the ventricle tracking atrial activity. In practical application, the PVARP can be programmed to its lowest possible value (usually between 150 and 180 ms) and adjusted to a higher value only if inappropriate sensing on the atrial channel or pacemaker mediated tachycardia occurs.

Patients with permanent cardiac pacemakers and implanted defibrillators require special consideration in the PICU. Electrical noise associated with medical devices, especially electrocautery may be sensed by the device [35] and result in inhibition of output, triggered pacing or an inappropriate shock. Proper management of the device prior to placing the patient in such an environment is critical. Metabolic changes and effects of medications in critically ill patients may result in an increase in the pacing capture threshold and failure of pacing. The defibrillation threshold for defibrillation with an implanted defibrillator may also be elevated by medications or metabolic imbalance. Regular analysis of the device while the patient is in the PICU and appropriate adjustment of the device output and sensitivity is important.

Monitoring should be used which responds to pacing failure with an appropriate alarm. Algorithms for detection of a QRS complex on a monitor may not be adequate to differentiate a pacing spike without capture from a QRS complex. As such a secondary method such as measurement of heart rate from an arterial line tracing or pulse oximeter is helpful as an adjunct.

Treatment of Tachyarrhythmia

Immediate Treatment, Cardioversion, Defibrillation and Pacing

If a tachyarrhythmia is accompanied by poor perfusion and suspected hemodynamic compromise, and demonstrates a wide QRS complex, immediate cardioversion is indicated. If a narrow QRS complex is seen, application of vagal maneuvers or adenosine administration may be applied as long as they do not result in a delay of cardioversion if they are unsuccessful [36]. Rarely, adenosine administration may result in ventricular fibrillation [37]. Availability of a defibrillator should be confirmed prior to its administration. Cardioversion should be performed with paddles, electrical conductive jelly and adequate pressure to the chest wall to maximize skin contact with the paddles and minimize impedance. When available, skin patches are preferred as they allow for more effective application of chest compressions between shocks and as mentioned previously may also allow for transcutaneous pacing in the event of cardioversion or defibrillation to a bradycardic or asystolic rhythm. Placement of the paddles or patches in an anterior/posterior orientation in neonates and infants is frequently preferred to avoid any contact between them. Anterior/posterior orientation may also be preferable in older patients with palliated congenital heart disease, especially when cardioversion of atrial arrhythmias is being performed. In other patients a sternal/apical position is acceptable and does not require raising the patient from the supine position. Synchronization of the shock to the cardiac rhythm is always preferred, if it can be performed. An asynchronous shock delivered during ventricular repolarization, a period of myocardial vulnerability, may convert a stable rhythm to ventricular fibrillation. On the other hand, attempts to deliver a synchronous shock when there is no rhythm for synchronization (ventricular fibrillation) will result in the unnecessary delay of a shock. For this reason, most defibrillators start and reset to an asynchronous mode after each shock. If a synchronous mode is desired, it must be initially activated and reactivated after each shock. Care should be taken to be certain that the device is appropriately synchronizing on a QRS complex each time. The leads may need to be adjusted if synchronization is not appropriate. Shock advisories, an outgrowth of automated external defibrillators, are increasingly available on in-hospital defibrillators in the PICU. These advisories on many devices have been shown to have excellent sensitivity and specificity for identifying "shockable" rhythms in the pediatric population. They may help to guide the novice in delivering an appropriate shock, but should never dissuade an experienced physician from delivering what is felt to be an appropriate shock. When a first shock is not successful, subsequent shocks should be administered as successive shocks reduce chest wall impedance and increase the likelihood for subsequent successful cardioversion or defibrillation.

Tachycardia accompanied by adequate perfusion, good pulses and suspected hemodynamic stability allow for a more considered approach. Diagnostic studies, including multi-lead ECG and atrial electrogram recordings can be performed in an attempt to determine a mechanism for the tachycardia and choose a specific treatment. Rapid adenosine administration during the recording of a multi-lead ECG, preferentially with an atrial electrogram is often diagnostic for the cause of the tachyarrhythmia and may be therapeutic as well [38, 39]. Adenosine is more likely to be diagnostic than vagal maneuvers, which tend to result in patient movement artifact and ECG lead disconnection [40]. If adenosine is diagnostic of an atrial tachycardia showing continuation of the atrial mechanism with AV nodal block, consideration can be given to atrial pacing with an esophageal, transvenous or epicardial lead. As previously mentioned, atrial reentrant mechanisms will be likely to be terminated with a brief period of atrial pacing at a faster rate. Once a tachycardia has been terminated, the subsequent bradycardia and pauses may result in recurrence of tachycardia. Atrial or ventricular pacing may help to prevent this tachycardia recurrence.

Junctional automatic tachycardia is a rhythm that may benefit from atrial pacing at a faster rate. The benefit provided by AV synchrony may offset the negative effects of a somewhat faster heart rate. This rhythm is exacerbated by hemodynamic instability resulting in increased endogenous catecholamines and administration of exogenous catecholamines and as such management with atrial pacing may reduce the need for more aggressive therapies.

Antiarrhythmic Medications

As previously mentioned, adenosine is frequently diagnostic when administered during ECG and atrial electrogram recording. By causing transient AV nodal block it is also therapeutic for AV nodal dependent supraventricular tachycardias such as AV reentrant tachycardia and AV nodal reentrant tachycardia, common in pediatric patients. Intravenous amiodarone has recently assumed a rather wide role in treatment of tachyarrhythmia in the PICU. It is a highly effective medication when given in appropriate dose in appropriate

situations. Amiodarone has effects on cardiac sodium, potassium and calcium channels as well as a beta-adrenergic blocker. It is effective for supraventricular and ventricular tachyarrhythmias of both reentrant and automatic mechanisms. Adverse effects of intravenous amiodarone are common and most frequently include hypotension, bradycardia and AV block [41]. The hypotensive response frequently requires administration of intravenous fluids and supplemental calcium. Bradycardia can be managed by cardiac pacing and unless the use of amiodarone is in a resuscitation setting, plans for cardiac pacing as outlined above should be considered prior to administration of the drug. Nausea and vomiting also occur frequently.

Procainamide and lidocaine are the only currently available sodium channel blocking (Vaughan-Williams class I) drugs available in the US for intravenous administration. Procainamide has potassium channel blocking effects as well and prolongs the action potential duration. It can be effective for supraventricular and ventricular arrhythmias of both automatic and reentrant mechanisms. Although never compared blindly to amiodarone in a study, it seems less effective than amiodarone for most arrhythmias. Procainamide also results in hypotension, depression of cardiac function and bradycardia. Support is frequently needed for these associated problems. Nausea and vomiting are also commonly seen and procainamide administration must be adjusted in the setting of liver or kidney impairment. Additionally, the degradation of procainamide produces the active metabolite N-acetylprocainamide (NAPA), a class III antiarrhythmic agent, which should be monitored. Lidocaine shortens the action potential and ventricular refractory period and is effective for some ventricular arrhythmias. It is ineffective for supraventricular tachycardias and may be detrimental for some atrial tachycardia mechanisms. It has minimal hemodynamic effects and most adverse effects are the result of central nervous system impairment. Compared in adults undergoing cardiac resuscitation for ventricular arrhythmia, intravenous amiodarone has been shown to be more effective than lidocaine. Although the data in children is limited, the 2010 PALS guidelines recommend the administration of amiodarone for refractory ventricular tachycardia. Expert consultation is recommended prior to administration of amiodarone to a patient with a perfusing rhythm.

Beta adrenergic blockade can be extremely helpful in the PICU for control of tachycardia. It can terminate and prevent reinitiation of reentrant tachyarrhythmia. It is also helpful in slowing AV nodal conduction during atrial tachyarrhythmias, thereby reducing the ventricular rate. Hypotension, bradycardia and AV block are also seen with beta blockade. Esmolol, a beta adrenergic blocker with a half-life of approximately 10 min is particularly suited to use in the PICU. However, a significant disadvantage to the use of esmolol is its dilute intravenous solution concentration resulting in significant volume administration, which may not be well tolerated in a critically ill patient. The dose may be titrated to effect or toxicity. If toxic effects predominate, the drug can be discontinued without prolonged effects. If it is effective, a continuous infusion can be given, or the drug can be transitioned to propranolol, which has a longer half-life.

Calcium channel blockade is less commonly used in the PICU. Neonates have limited ability to store calcium in the cardiac sarcoplasmic reticulum and calcium channel blockers can result in hemodynamic collapse. In older children, verapamil and diltiazem can slow AV nodal conduction and terminate and prevent reinitiation of AV nodal dependent tachycardia. They can also be used to control the conducted rate of atrial tachycardias, but should be used with great caution, if at in combination with beta adrenergic blockade.

Digoxin is less commonly used than it has been in the past, but is still a helpful drug in the PICU. It slows the sinus rate as well as slowing AV nodal conduction and increasing the refractory period of the AV node. It can be administered intravenously in small amounts and inappropriate administration has resulted in serious consequences for many pediatric patients. Determination of the correct dose should be performed in milligram amount, microgram amount and milliliters of the drug and checked by another individual prior to administration. Measurement of the drug should be done with an appropriate syringe (usually a properly marked 1 ml syringe). As mentioned previously, overdosage of digoxin when accompanied by arrhythmia should be managed with digoxin specific Fab antibodies. The drug is effective for AV nodal dependent tachycardias and may also be effective for some atrial tachyarrhythmias and slows the rate of conduction of atrial tachycardia. Digoxin use is relatively contraindicated in individuals with ventricular preexcitation as it may enhance rapid accessory pathway conduction during atrial fibrillation and result in life-threatening arrhythmia. This would be unlikely in infants and young children with low likelihood of atrial fibrillation, and some individuals continue to use the drug in this setting.

Special Circumstances Involving Arrhythmia in the PICU

Electrolyte Imbalance

Imbalance of serum electrolytes is common in patients in the PICU for many reasons. Potassium is the electrolyte with the greatest propensity to cause cardiac rhythm abnormality [42]. Hyperkalemia results in electrocardiographic changes at serum potassium levels far lower than those which cause arrhythmia. With modest hyperkalemia, the T wave will become peaked and narrow. Pediatric patients with faster resting heart rates tend to have narrower T waves and depending on the electrocardiographic

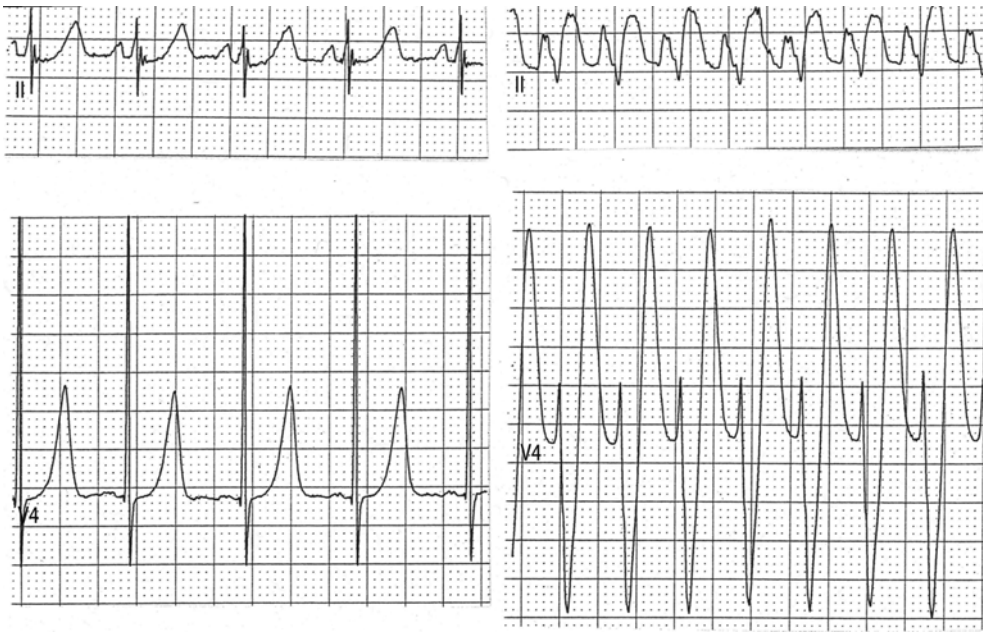


Fig. 27.15 The *left panels* demonstrate ECG leads II and V4 in an infant with hyperkalemia (serum potassium 6.8 mmol/L). The T waves are peaked, but the QRS remains narrow. The *right panels* demonstrate the same lead recordings in the same patient with a serum potassium greater than 9 mmol/L. The QRS complexes are wide and atrial activity can not be clearly seen, but the rhythm likely remains sinus rhythm

leads which are monitored, the peaking of T waves may not be immediately evident. With higher levels of serum potassium, the QRS widens. Sinus tachycardia with wide QRS complexes from hyperkalemia is frequently mistaken for ventricular tachycardia and antiarrhythmic drugs are administered (Fig. 27.15). This frequently will exacerbate the cardiac toxicity of the elevated serum potassium. In situations where hyperkalemia is anticipated, the presence of regular wide QRS complex rhythms should be suspected to be sinus tachycardia. Full disclosure electrocardiographic review when available will show little change in heart rate and gradual increase in the QRS duration in this circumstance and can be very helpful in diagnosing and appropriately treating the electrolyte abnormality. With extreme elevation of serum potassium, ventricular tachycardia and fibrillation will ultimately occur. Hypokalemia results in prominent U waves and prolongation of the QT-U interval. While the arrhythmogenic potential of hypokalemia is typically less than that of hyperkalemia, it may ultimately result in polymorphic ventricular tachycardia and ventricular fibrillation. Imbalance of serum calcium in isolation is rare and even when it occurs does not frequently result in significant arrhythmia. Serum magnesium imbalance in isolation has little effect on the electrocardiogram or heart rhythm. Administration of serum magnesium has been shown to be particularly effective in the treatment of arrhythmia, especially torsades de pointes ventricular tachycardia associated with prolonged QT interval.

Thermal Imbalance

Mild hypothermia slows the rate of sinus rhythm. More significant hypothermia results in the development of a deflection in the terminal portion of the QRS termed an Osborn wave. This is accompanied by QT interval prolongation. Even more profound hypothermia results in AV block and subsequently ventricular arrhythmia and fibrillation [43]. Mild hyperthermia results in sinus tachycardia. In susceptible individuals, fever may increase the likelihood of automatic and reentrant arrhythmias. This is especially true with post-operative automatic junctional tachycardia, which is significantly exacerbated by fever and can be treated with mild hypothermia.

Endocrine Imbalance

Thyroid imbalance is the most significant known endocrine imbalance to affect cardiac rhythm. Relative hypothyroid state is not uncommon in the PICU patient and may result in sinus bradycardia and AV block. Evaluation of thyroid state is important in patients with sinus node or AV node dysfunction prior to intervention with permanent pacing devices [44]. Hyperthyroidism is less common and is associated with sinus tachycardia and more rarely atrial fibrillation.

CNS Injury

Injury to the central nervous system frequently results in significant electrocardiographic changes. These are most characteristically ST segment and T wave changes and QT interval prolongation. These frequently simulate findings of cardiac ischemia. Cardiac rhythm disturbance is less common and includes a gamut of brady- and tachyarrhythmia.

Infection

Systemic infection may result in a reflex sinus tachycardia from an increase in metabolic demand. Endocarditis near the normal conduction system may result in AV block caused by direct mechanical damage to the conduction system. Myocarditis is associated with atrial and ventricular tachyarrhythmia and treatment of suspected or biopsy proven myocarditis with anti-inflammatory medications may treat the associated tachyarrhythmias more successfully than antiarrhythmic agents. Rheumatic heart disease may result in transient or permanent AV block and sinus node dysfunction. Lyme disease is also known to result in AV block and other cardiac conduction abnormalities [45].

Toxins

Many toxic agents are associated with abnormal cardiac rhythm in the PICU. This includes those consumed by patients prior to their admission and those administered in the course of therapy. Those consumed prior to admission include drugs of abuse with cocaine resulting in the most significant arrhythmias. Ventricular arrhythmia is most common and is related to coronary vasoconstriction in combination with sinus tachycardia, increased myocardial oxygen demand and increased afterload. The most common prescribed medications with cardiac arrhythmia risk in the pediatric population include psycho-stimulants for attention deficit and hyperactivity. Less commonly prescribed, but more likely to cause arrhythmia are tricyclic antidepressants and neuroleptic agents [46]. These agents produce cardiac effects similar to sodium channel blocking antiarrhythmic drugs. Newer selective serotonin reuptake inhibitor antidepressants and *atypical* antipsychotic agents have been introduced in the last decade. While these newer agents seem to have a more benign side-effect profile than their predecessors, they have been shown in some individuals to prolong the QT interval and result in significant myocardial depression [47]. Drugs commonly administered in the PICU with significant potential proarrhythmic effects include exogenous catecholamines, digoxin and antiarrhythmic drugs. While the arrhythmic effects of exogenous catecholamines are usually immediately recognized and must be balanced against their beneficial effects, digoxin toxicity may be more insidious. Alteration in renal function in a critically ill patient and administration of medications known to alter digoxin metabolism or excretion are common occurrences. The decreased frequency of administration of digoxin in favor of other more effective agents in the PICU has decreased the likelihood of its toxicity, but has also decreased the recognition of the problem in treated patients. Digitalis toxicity can result in nearly any arrhythmia and frequently results in several types of tachyarrhythmia in short order. Treatment of digitalis toxicity has been simplified with the availability of digoxin-immune Fab antibody therapy. Adverse effects are few and this treatment should be considered for all children with documented arrhythmias associated with digoxin toxicity. When renal failure is present, the bound drug will not be excreted and repeated doses may be necessary. Toxicity with other antiarrhythmic drugs has become less frequent. Quinidine is rarely used and the use of procainamide is also waning. Intravenous amiodarone use has increased substantially in the PICU, both in the cardiac arrest situation as well as the elective treatment of tachyarrhythmia. Immediate adverse effects of intravenous amiodarone are common, but rarely include tachyarrhythmia. Bradycardia and AV block are more common.

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Inflammatory Diseases of the Heart

28

Mary E. McBride and Paul A. Checchia

Abstract

The inflammatory diseases of the heart contribute significantly to the morbidity and mortality of our pediatric patients. This chapter focuses on the disease processes of infective endocarditis, Kawasaki disease and myocarditis as well as their respective management. Endocarditis is a rare diagnosis in pediatrics and those with congenital heart disease particularly with prosthetic material and residual lesions resulting in turbulent blood flow are at particular risk. Management is long-term courses with combination antimicrobials. Complications are not rare and surgical intervention is often employed. Kawasaki disease is prevalent in the pediatric population and while self-limited in nature, can result in life-threatening coronary aneurysms and stenoses. A high-index of suspicion is often necessary to diagnose these children. Intravenous immunoglobulin and aspirin are the mainstays of therapy. Long-term, these patients need to be monitored closely for coronary complications. Myocarditis causes cardiac dysfunction and can result in a cardiogenic shock and circulatory collapse. It can also progress to a dilated cardiomyopathy. Myocarditis is caused most commonly by viruses but also other infectious agents, drugs and systemic illness can be the culprit. Treatment is largely supportive with use of inotropic agents and other heart failure medications. Mechanical circulatory support is often employed. Some of these patients will ultimately require cardiac transplantation.

Keywords

Endocarditis • Kawasaki disease • Myocarditis

Infectious Endocarditis

Infectious Endocarditis (IE) is a rare disease that carries with it significant morbidity and mortality. The diagnosis and management of infective endocarditis has evolved significantly in recent years. Advances in cardiac imaging and microbial testing have improved the ability to diagnose endocarditis. As bacterial antibiotic resistance patterns evolve, the antimicrobials used to treat endocarditis must change as well. In concert with these changes is the need for change in prophylaxis which was last revised in 2007 [1]. The constellation of findings and symptoms make the diagnosis of IE challenging.

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Table 28.1 Definition of infective endocarditis according to the proposed modified Duke criteria, with modifications shown in boldface

Definite infective endocarditis
Pathologic criteria
1. Microorganisms demonstrated by culture or histologic examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or
2. Pathologic lesions; vegetation or intracardiac abscess confirmed by histologic examination showing active endocarditis
Clinical criteria[a]
1. 2 major criteria; or
2. 1 major criterion and 3 minor criteria; or
3. 5 minor criteria
Possible infective endocarditis
1. **1 major criterion and 1 minor criterion; or**
2. **3 minor criteria**
Rejected
1. Firm alternate diagnosis explaining evidence of infective endocarditis; or
2. Resolution of infective endocarditis syndrome with antibiotic therapy for ≤4 days; or
3. No pathologic evidence of infective endocarditis at surgery or autopsy, with antibiotic therapy for ≤4 days; or
4. Does not meet criteria for possible infective endocarditis, as above

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[a]See Table 28.4 for definitions of major and minor criteria

Epidemiology

The incidence of IE has been reported as 0.38 cases/10,000 person-years in adults [2] and accounts for roughly one in 1,280 pediatric admissions per year [3]. The epidemiology of IE has changed dramatically in recent years, as survival for children with congenital heart disease has improved and the incidence of rheumatic heart disease has decreased. Patients with congenital heart disease, particularly those who have had palliative or corrective surgery, now make up the most likely group to acquire IE. The increased use of central venous catheters predisposes patients to catheter-related endocarditis [4]. Native valve endocarditis also occurs, rarely, in patients who are otherwise healthy.

Pathogenesis

The development of IE occurs in a step-wise progression. First, there is the formation of a nonbacterial thrombotic endocarditis (NBTE) [5]. The NBTE develops after the endothelium has been damaged, likely by turbulent blood flow. Transient bacteremia then develops after trauma of endothelium from surfaces with endogenous flora. Bacteria in the bloodstream adhere to the NBTE. Then, the bacteria proliferate within the vegetation [5]. The bacteria are protected from phagocytic cells and other host mechanisms by fibrin and other deposited matter [4].

Diagnosis

When patients present with the classic findings of bacteremia, valvular disease, embolic phenomenon, and immunologic disease, the diagnosis of IE is relatively straightforward. Unfortunately, however, IE can present with variable manifestations. The Duke criteria have been accepted as the diagnostic criteria of choice [6]. The modified Duke criteria were established via analysis of the Duke University database to improve the sensitivity and preserve the specificity of the Duke criteria (Tables 28.1 and 28.2) [7]. The Duke criteria were originally developed to facilitate clinical and epidemiological research, so expanding its use to clinical diagnosis can be a challenge as it is such a heterogeneous disease.

Clinical Findings

Children with IE often present with an indolent course of prolonged fevers and non-specific findings of fatigue, weakness, and rigors. The signs and symptoms that children with IE present with are directly related to bacteremia, valvulitis, immunologic responses, and emboli [4]. Endocarditis can lead to the development of a new or changed murmur as well as the presence of signs and symptoms of congestive heart failure. Vegetations in a systemic to pulmonary shunt can produce hypoxemia as pulmonary blood flow is diminished. Emboli can occur in the abdominal, pulmonary, intracranial, or coronary vessels, as examples. Extracardiac signs of endocarditis, such as Osler nodes or Roth's spots are less common in children than adults. Signs and symptoms most commonly observed in children with IE include fever, petechiae, murmur, dental caries, and hepatosplenomegaly [8]. A child with endocarditis can also present acutely ill with a fulminant presentation.

Risk Factors

Patients with congenital heart disease make up the population with the greatest risk for IE. In general, lesions with high

Table 28.2 Definition of terms used in the proposed modified Duke criteria for the diagnosis of infective endocarditis (IE), with modifications shown in boldface

Major criteria
Blood culture positive for IE
Typical microorganisms consistent with IE from 2 separate blood cultures:
Viridans streptococci, *Streptoccoccus bovis*, **HACEK** group, *Staphylococcus aureus*; or Community-acquired enterococci, in the absence of a primary focus; or
Microorganisms consistent with IE from persistently positive blood cultures, defined as follows:
At least 2 positive cultures of bllod samples drawn >12 h apart; or
All of 3 or a majority of ≥4 separate cultures of blood (with first and last sample drawn at least at least 1 h apart)
Single positive blood culture for *Coxiella burnetii* or antisphase I IgG antibody titer >1:800
Evidence of endocardial involvement
Echocardiogram positive for IE (**TEE recommended in patients with prosthetic valves, rated at least "possible IE" by clinical criteria, or complicated IE [paravalvular abscess]; TTE as first test in other patients**), defined as follows:
Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; or
Abscess; or
New partial dehiscence of prosthetic valve
New valvular regurgitation (worsening or changing of pre-existing murmur not sufficient)
Minor criteria
Predisposition, predisposing heart condition or injection drug use
Fever, temperature >38 °C
Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway's lesions
Immunologic phenomena: golmerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor
Microbiological evidence: positive blood culture but does not meet a major criterion as noted above[a] or serological evidence of active infection with organism consistent with IE
Echocardiographic minor criteria eliminated

Reprinted from Li et al. [7] with permission from Oxford University Press
TEE transesophageal echocardiography, *TTE* transthoracic echocardiography
[a]Excludes single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis

velocity or turbulent blood flow are at the greatest risk. This risk is highest among those who have undergone an operation to relieve obstruction to pulmonary blood flow, such as Blalock-Taussig shunt, and in those with prosthetic aortic valve replacement [4]. The risk is higher when prosthetic material and conduits are used, particularly in those with low cardiac output in the perioperative period [9].

Laboratory Findings

The diagnosis of IE, as discussed above, requires a high index of suspicion. Certainly and at a minimum, blood cultures should be obtained in any child who is at risk for IE (see above) who presents with fever and a new murmur. Three blood cultures should be obtained by separate venipunctures at presentation. If there is no growth by the second day of incubation, two additional blood cultures should be obtained [4]. More cultures may be necessary if the patient has been treated with antibiotics prior to the initial blood draw. In general, gram-positive cocci are the most common causes of IE in children with *Streptococcus viridans* being the most common. *Staphylococcus aureus* and coagulase-negative staphylococcus are implicated in IE resulting from infected vascular access catheters or prosthetic material. In neonates, group B Streptococcus and *Streptococcus pneumoniae* should be considered [4]. Cultures should also be evaluated for fungi such as candida and aspergillus, particularly in those children with indwelling catheters. The mortality associated with fungal endocarditis has been reported to be greater than 50 % [10, 11].

Culture-negative endocarditis is defined by the presence of clinical and/or echocardiographic evidence for endocarditis in the presence of serial negative blood cultures. Failure to produce positive cultures may prove to be the result of inadequate microbiological techniques (particularly in children), infection with highly fastidious bacteria, infection with a non-bacterial pathogen that does not grow in culture media, such as aspergillus, or prior administration of antibiotics [5]. The HACEK group of bacteria is a notorious group of fastidious bacteria that cause endocarditis, defined by the initials of the representative genera in the group – *Haemophilus* (including *H. parainfluenzae*, *H. aphrophilus*, *H. paraphrophilus*), *Actinobacillus* (most notably, *A. actinomycetemcomitans*), *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*. All of these bacteria rep-

resent normal oropharyngeal flora and collectively account for 5–9 % of all cases of IE among individuals who do not use IV drugs [6, 8, 12, 13]. Additional serologic testing for bartonella, chlamydia, coxiella, and brucella is probably justified in those patients with culture-negative IE [14].

Laboratory investigation outside of microbiology may provide useful adjunct, albeit non-specific, information. Anemia is a common finding in children with IE (either due to the so-called anemia of chronic disease or as a consequence of hemolysis). A high white blood cell count is not typical of endocarditis, but a left shift with immature cells can be seen. Elevated acute phase reactants such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are characteristic. Hematuria with red blood cell casts, proteinuria and renal insufficiency are seen in patients who develop immune complex glomerulonephritis [4].

Echocardiography

As indicated by the Duke criteria, echocardiography is a key component in the diagnosis of IE. All patients with suspected IE should have an echocardiogram, which can be to determine the site and extent of infection, as well as the presence or absence of cardiac dysfunction. Additionally, echocardiography provides serial determination of ventricular dimensions, valvular regurgitation, and valvular function. While transesophageal echocardiography (TEE) is more sensitive than transthoracic echocardiography (TTE), initial (first) TTE has been shown to have a sensitivity of 82 % in children [15]. TEE should be considered in patients with poor imaging windows (e.g. obesity), congenital heart disease, left ventricular outlet tract disease, and those with a negative TTE with high clinical suspicion for IE. The presence of large vegetations, severe valvar insufficiency, valvar perforation or dehiscence, and abscess are all associated with a more complicated course of IE, as well as the need for surgical repair [14].

Antimicrobial Management

Antimicrobial therapy should be tailored to the organism discovered by blood culture and whether the infection is of native or prosthetic tissue. (Tables 28.3, 28.4 and 28.5) [4] If cultures are negative, empiric therapy should be started in patients who are acutely ill, to cover common endocarditis organisms. In patients who are not acutely ill, antibiotics should be held for 48 h while additional blood cultures are obtained [4]. While *E. coli*, *Serratia* or *Pseudomonas* can rarely cause endocarditis, a gram-negative infection is more typically an infection from the HACEK group. These patients should generally be treated for 4 weeks with a 3rd generation cephalosporin or ampicillin with gentamicin. It is also important to consider uncommon or rare pathogens, such as bartonella, chlamydia, coxiella, brucella, legionella, tropheryma whippleii, and non-candida fungi. With few exceptions, medical therapy alone for fungal endocarditis is unsuccessful [4]. A surgical procedure in conjunction with antifungal therapy is typically required. Amphotericin B is the first line agent, though it does not penetrate vegetations well. Imidazoles are then used for lifetime suppressive therapy. Some recommend 5-fluorocytosine and amphotericin B for synergy in candidal infections [4].

Surgical Management

Common indications for surgery as adjunct in management of IE include cardiac failure, valvular obstruction, perivalvular extension of infection, fungal infection, persistent bacteremia despite appropriate antibiotics, unstable prosthesis, ruptured sinus of valsava or ventricular septum, and any significant embolic events [16]. Disease of the conduction system from extension of a perivalvular infection, more common with prosthetic valves, can occur and those patients should undergo surgical resection [17]. Cardiac failure is the most common cause of death in patients with IE. While the operative mortality is high in patients with heart failure and endocarditis, the mortality is reduced in those who undergo operative repair [17].

Complications

The complications of endocarditis are varied in their spectrum. The development of heart failure secondary to valvular dysfunction as well as ventricular dysfunction are the most common [17]. Emboli from intracardiac vegetations occur not uncommonly in endocarditis and can affect major arteries of the lungs, central nervous system (CNS), bowel and spleen as well as the coronary arteries. Signs and symptoms for CNS embolic events are variable but care providers should have a low threshold to obtain CNS imaging. Prolonged fever should raise suspicion for a metastatic focus of infection. In one series, 23 % of children with fever longer than 14 days after initiation of antimicrobials were found to have a metastatic focus [8].

Prophylaxis

The American Heart Association revised their recommendations for IE prophylaxis in 2007 [1]. Patients with higher-risk lesions for the development of IE should receive prophylaxis, and include children with prosthetic cardiac valves or material used for valve repair, previous history of endocarditis, unrepaired or palliated cyanotic congenital heart disease (CHD), complete repair of CHD with prosthetic material or device for six months after the procedure, repaired CHD but with residual defects that would prohibit

Table 28.3 Regimens for therapy of native valve IE caused by viridans group streptococci, *Streptococcus bovis* or enterococci[a]

Organism	Antimicrobial agent	Dosage, per kg per 24 h	Frequency of administration	Duration, weeks
Penicillin-susceptible streptococci (MIC ≤0.1 μg/mL)[b]	Penicillin G[c]	200,000 U IV	q 4–6 h	4
	or			
	Ceftriaxone	100 mg IV	q 24 h	4
	Penicillin G[c]	200,000 U IV	q 4–6 h	2
	or			
	Ceftriaxone	100 mg IV	q 24 h	2
	plus			
	Gentamicin	3 mg IM or IV	q 8 h[b]	2
Streptococci relatively resistant to penicillin (MIC >0.1–0.5 μg/mL)	Penicillin G[c]	300,000 IV	q 4–6 h	4
	or			
	Ceftriaxone	100 mg IV	q 24 h	4
	plus			
	Gentamicin	3 mg IM or IV	q 8 h[b]	2
Enterococci[d]	Penicillin G[c]	300,000 U IV	q 4–6 h	4–6[e]
Nutritionally variant viridans streptococci or high-level penicillin-resistant streptococci (MIC >0.5 μg/mL)	Plus gentamicin	3 mg IM or IV	q 8 h[f]	4–6[e]

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For treatment of patients with prosthetic cardiac valves or other prosthetic materials, see text. MIC indicates minimum inhibitory concentration of penicillin

[a]Dosages suggested are for patients with normal renal and hepatic function. Maximum dosages per 24 h: penicillin 18 million units; ampicillin 12 g; ceftriaxone 4 g, gentamicin 240 mg. The 2-week regimens are not recommended for patients with symptoms of infection >3 months in duration, those with extracardiac focus of infection, myocardial abscess, mycotic aneurysm, or infection with nutritionally variant viridians streptococci (*Abiotrophia* sp.)

[b]Studies in adults suggest gentamicin dosage may be administrated in single daily dose. If gentamicin is administered in 3 equally divided dosed per 24 h, adjust dosage to achieve peak and trough concentrations in serum of ≈3.0 and <1.0 μg of gentamicin per mL, respectively

[c]Ampicillin 300 mg/kg per 24 h 4–6 divided dosages may be used as alternative to penicillin

[d]For enterococci resistant to penicillins, vancomycin, or aminoglycosides, treatment should be guided by consultation with specialist in infectious diseases (cephalosporins should not be used to treat enterococcal endocarditis regardless of in vitro susceptibility)

[e]Studies in adults suggest that 4 weeks of therapy is sufficient for patients with enterococcal IE with symptoms of infection of <3 months' duration; 6 weeks of therapy recommended for patients with symptoms of infection of >3 months' duration

[f]Adjust gentamicin dosage to achieve peak and trough concentrations in serum of ≈30 and <1.0 μg of gentamicin per mL, respectively

endothelialization, and cardiac transplant with valvulopathy (Table 28.6) [1]. This group should receive prophylaxis before dental procedures that involve manipulation of the oral mucosa. Prophylaxis should also be administered prior to invasive respiratory procedures, which includes incision or biopsy of respiratory mucosa. No prophylaxis is necessary for gastrointestinal or genitourinary procedures. Health care providers should refer to the American Heart Association guidelines for more specific recommendations about individual procedures and infections [1].

Kawasaki Disease

Kawasaki was first described by Dr. Tomisaku Kawasaki in 1967. Our knowledge of this disease process has evolved significantly since that time. Kawasaki disease is now the most common cause of acquired heart disease in children in industrialized countries and typically affects previously healthy children. While Kawasaki disease is a self-limited vasculitis, these children may develop coronary artery aneurysms, myocardial infarction, and sudden death. Kawasaki disease occurs predominantly in infants and young children between the ages of 6 months and 5 years of age [18]. After decades of intense research, the etiology of this disease is still unknown. The initial phase of therapy is aimed at reducing inflammation in the coronary artery wall, in order to prevent the development of coronary artery aneurysms. Long-term management is directed at minimizing the effects of the sequelae, such as prevention of myocardial infarction and sudden death. In untreated patients, 20–25 % will develop coronary artery aneurysms [19].

Epidemiology

Kawasaki disease is more prevalent in Japan and in children of Japanese descent [20–22]. The incidence in Japan is 216.9

Table 28.4 Treatment regimens for therapy of IE caused by viridans group streptococci, *Streptococcus bovis*, or enterococci in patients unable to tolerate β-lactam[a]

Organism	Antimicrobial agent	Dosage, per kg per 24 h	Frequency of administration	Duration, weeks
Native valve (no prosthetic material)				
Streptococci	Vancomycin	40 mg IV	q 6–12 h	4–6
Enterococci[b] or nutritionally variant viridans streptococci	Vancomycin	40 mg IV	q 6–12 h	6
	plus			
	Gentamicin	3 mg IM or IV	q 8 h[c]	6
Prosthetic devices				
Streptococci	Vancomycin	40 mg IV	q 6–12 h	6
	plus			
	Gentamicin	3 mg IM or IV	q 8 h[c]	2
Enterococci[b] or nutritionally variant viridans streptococci	Vancomycin	40 mg IV	q 6–12 h	6
	plus			
	Gentamicin	3 mg IM or IV	q 8 h[c]	6

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[a]Dosages suggested are for patients with normal renal function. Maximum daily dose per 24 h of gentamicin is 240 mg

[b]For enterococci resistant to vancomycin or aminoglycosides, treatment should be guided by consultation with specialist in infectious diseases

[c]Dosage of gentamicin should be adjusted to achieve peak and trough concentration in serum of ≈ 3.0 and <1.0 μg of gentamicin per mL, respectively

Table 28.5 Treatment regimens for endocarditis caused by staphylococci[a]

Organism	Antimicrobial agent	Dosage, per kg per 24 h	Frequency of administration	Duration
Native valve (no prosthetic materials)				
Methicillin susceptible	Nafcillin or oxacillin	200 mg IV	q 4–6 h	6 weeks
	With or without gentamicin[b]	3 mg IM or IV[c]	q 8 h	3–5 days
β-Lactam allergic	Cefazolin[d] with or without[b]	100 mg IV	q 6–8 h	6 weeks
	Gentamicin[b]	3 mg IM or IV[c]	q 8 h	3–5 days
	or			
	Vancomycin	40 mg IV	q 6–12 h	6 weeks
Methicillin resistant	Vancomycin	40 mg IV	q 6–12 h	6 weeks
Prosthetic device or other prosthetic materials				
Methicillin susceptible	Nafcillin or oxacillin	200 mg IV	q 4–6 h	≥6 weeks
	or			
	Cefazolin[d]	100 mg IV	q 6–8 h	≥6 weeks
	Plus rifampin[e]	20 mg po	q 8 h	≥6 weeks
	Plus gentamicin[b]	3 mg IM or IV[c]	q 8 h	2 weeks
Methicillin resistant	Vancomycin	40 mg IV	q 6–12 h	≥6 weeks
	Plus rifampin[e]	20 mg po	q 8 h	≥6 weeks
	Plus gentamicin[b]	3 mg IM or IV[c]	q 8 h	2 weeks

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[a]Dosages suggested are for patients with normal renal and hepatic function. Maximum daily doses per 24 h: oxacillin or nafcillin 12 g; cefazolin 6 g; gentamicin 240 mg; rifampin 900 mg

[b]Gentamicin therapy should be used only with gentamicin-susceptible strains

[c]Dosage of gentamicin should be adjusted to achieve peak and trough concentrations in serum of ≈3.0 and <1.0 μg of gentamicin per mL, respectively

[d]Cefazolin or other first-generation cephalosporin in equivalent dosages may be used in patients who do not have a history of immediate type hypersensitivity (urticaria, angioedema, anaphylaxis) to penicillin or ampicillin

[e]Dosages suggested for rifampin are based upon results of studies conducted in adults and should be used only with rifampin-susceptible strains

Table 28.6 Cardiac conditions associated with the highest risk of adverse outcome from endocarditis for which prophylaxis with dental procedures is reasonable

Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
Previous IE
Congenital heart disease (CHD)[a]
Unrepaired cyanotic CHD, including palliative shunts and conduits
Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure[b]
Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)
Cardiac transplantation recipients who develop cardiac valvulopathy

Reprinted from Wilson et al. [1]. With permission from Wolter Kluwers Health

[a]Except for the conditions listed above, antibiotic prophylaxis is no longer recommended for any other form of CHD

[b]Prophylaxis is reasonable because endothelialization of prosthetic material occurs within 6 months after the procedure

per 100,000 children aged 0–4 years and this incidence has been steadily increasing each year [22]. In the continental U.S., the incidence is 17.1 per 100,000 children [23]. Children outside of the usual age range tend to present later in the disease course, leading to a delay in treatment and the attendant risk for complications [24, 25].

Etiology

The etiology of Kawasaki Disease remains unknown. There is evidence to suggest an infectious etiology (e.g., seasonality, regional outbreaks, age of occurrence, and laboratory and clinical features) [23]. Another theory suggests that Kawasaki disease is an immunological response to multiple organisms of infection. This is supported by the findings of multiple organisms in patients as a whole with Kawasaki disease and failure to find a single pathogen in multiple years of study, but not supported by the distinct clinical pattern seen in these patients [20]. There is a dramatic immune response with activation of the cytokine cascade, endothelial cells, monocytes, macrophages, and plasma cells. The data indicate a higher rate of disease in twins, siblings and parents suggesting a genetic predisposition [26, 27].

Pathogenesis

While notorious for its coronary involvement, Kawasaki disease is a systemic vasculitis involving medium-sized arteries and, to a lesser extent, other vessels are involved. It also results in a non-vascular systemic inflammatory response affecting most organ systems [19]. Neutrophils followed by lymphocytes and macrophages are found in the vessel wall. These cells secrete cytokines that breakdown collagen and elastin fibers and weaken the wall which results in dilatation and aneurysm formation [28–30]. As the vessel heals, the lesions become fibrotic and stenotic, leading to scar formation [31]. Slow blood flow in aneurysms predisposes to thrombus formation [31].

Table 28.7 Diagnostic criteria for Kawasaki disease[a]

1. Fever ≥5 days
2. Nonpurulent conjunctivitis, bilateral
3. Cervical lymphadenopathy, >1.5 cm
4. Polymorphous skin rashes
5. Abnormalities of lip or oral mucosa: strawberry tongue, fissured lips, diffuse erythema of oropharynx
6. Abnormalities of extremities: edema of palm and soles, desquamation of finger tips

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[a]The diagnosis of Kawasaki disease is considered confirmed by the presence of fever and 4 of the remaining 5 criteria if other known diseases can be excluded[3]

Diagnosis

Clinical

Kawasaki is diagnosed based on the presence of fever for ≥5 days and at least four out of five of the principle clinical features (Table 28.7) [32]. In a child with fever ≥5 days and any principle clinical features, Kawasaki disease should remain in the differential diagnosis [20]. The fever is typically high and persists for an average of 11 days without therapy, typically resolving in 2 days with therapy [20]. Distinct erythema, with or without painful induration occurs in the acute phase with desquamation of the digits, which may include palms and soles 2–3 weeks after the fever. An erythematous rash, in virtually any form, but more commonly maculopapular, manifests within 5 days of the fever onset [20]. It is usually widespread and also can desquamate, particularly in the perineal region [20]. A limbus-sparing, non-purulent, bilateral conjunctivitis develops shortly after onset of the fever and resolves rapidly [20]. Red, dry, cracked lips, strawberry tongue, and diffuse oropharyngeal redness without exudate or ulcerations are also seen [20]. The least common of the principle clinical features is cervical lymphadenopathy which is usually ≥1 lymph node, unilateral, confined to the anterior cervical triangle, and is >1.5 cm in diameter [20]. The pericardium, myocardium, endocardium, valves and coronary arteries are involved in the acute phase of Kawasaki [20]. An astute cardiac exam is essential to evaluate for murmurs or a gallop. Patients can present critically ill with low cardiac output syndrome or shock. Arthritis and arthralgias can occur in the first week involving multiple joints [20]. Irritability is a common finding in Kawaskai.

Abdominal pain, vomiting, and diarrhea occur in 25 % of patients [20]. Hydropic gallbladder, hepatomegaly, and jaundice can occur [20].

Laboratory Manifestations

Approximately 50 % of patients will have leukocytosis with a left shift [20]. Anemia may develop with normal red blood cell indices [20]. Elevated ESR and CRP, not typically seen with viral infections, are seen universally and will likely normalize 6–10 weeks after presentation [20]. In the second to third week of illness, a thrombocytosis occurs, normalizing around 4–8 weeks after presentation [20]. Moderate elevations in transaminases and gammaglutamyl transpeptidase are commonly seen [33]. Hypoalbuminemia is also common and seen with more severe disease [20]. Sterile pyuria is seen in roughly one third of patients [20]. Analysis of cerebrospinal fluid reveals an aseptic meningitis with a predominance of monocytes [34]. ECG can show arrhythmia, prolonged PR interval or nonspecific ST and T wave changes [20].

Incomplete Kawasaki Disease

Incomplete Kawasaki disease refers to those who do not fulfill the criteria for classic Kawasaki disease and should be considered in children with fever ≥5 days and only two or three of the principle clinical features [20]. This is most commonly found in young infants and older children, who unfortunately may also be at higher risk of coronary aneurysms [35, 36]. The laboratory findings described above, although themselves non-diagnostic, may help in diagnosis. Findings on echocardiogram often prove useful in the setting of Incomplete Kawasaki disease. Aneurysms rarely form before 10 days of illness, so evaluating for ectasia, perivascular brightness, a lack of tapering of the coronary, decreased left ventricular contractility, valvular regurgitation or pericardial effusion is prudent [20].

Cardiac Findings

Echocardiography is the ideal imaging modality for children with Kawasaki disease as it is noninvasive and has a high sensitivity and specificity for detecting coronary abnormalities in the proximal right and left coronary artery systems [20]. An echocardiogram should be obtained immediately, but shouldn't delay therapy. This first echocardiogram serves as a baseline to compare future studies regarding coronary aneurysms, thrombi, and perivascular echogenicity as well as left ventricular function, pericardial effusion, and valvular function [20]. The coronary artery size should be measured and adjusted for body surface area [37]. Aneurysms are small if <5 mm, medium when 5–8 mm, and giant if >8 mm. In uncomplicated cases, an echocardiogram should be performed at baseline, 2 weeks, and at 6–8 weeks [20]. Magnetic resonance imaging (MRI) and magnetic resonance angiogram (MRA) may define both aneurysms and flow characteristics in the proximal coronaries [38]. MRI can also be used to assess aneurysms in other arterial systems [20, 38]. Multi-dimensional CT can assess the proximal as well as the length of the coronary which is limited by echocardiography and MRI [39]. Cardiac stress tests of any modality can be used to assess the presence and consequences of coronary abnormalities [20]. Patients with more complex coronary pathology may benefit from cardiac catheterization and coronary angiography after the acute phase [20].

Autopsy studies show that myocarditis is quite common in patients with Kawasaki disease [40]. The severity of myocarditis does not appear to be associated with the risk of coronary aneurysms [41]. Myocardial function improves after intravenous immunoglobulin (IVIG) infusion. Mitral regurgitation may result from transient papillary muscle dysfunction, myocardial infarction (MI), or valvulitis [20]. Aortic regurgitation can also be present but is less common [20]. The conduction system can also be involved with inflammatory cells and manifest with atrioventricular block [42]. Risk factors for developing aneurysms include male gender, age younger than 1 year or older than 5 years, persistent fever refractory to treatment, anemia, hypoalbuminemia and a high CRP [31].

Management

Intravenous immunoglobulin and aspirin are the mainstays of initial therapy for Kawasaki disease. Aspirin alone has been shown to be insufficient at preventing the formation of coronary aneurysms compared to combined therapy with both IVIG and aspirin [43, 44]. In the acute setting, aspirin is administered at a higher dose (80–100 mg/kg/day) before transitioning to a lower, prolonged dose (3–5 mg/kg/day). Some physicians will transition to low-dose aspirin when the patient has been afebrile for 48–72 h, while others transition to low-dose aspirin after 14 days of illness, if the fever has subsided for ≥48–72 h. The duration of therapy with low-dose aspirin will depend on the presence or absence of coronary pathology.

As mentioned above, IVIG combined with aspirin is the mainstay of therapy. Higher dose IVIG (2 g/Kg) in a single infusion has been shown to be more protective than lower-dose or high-dose in multiple infusions [43]. In patients treated with the appropriate dose and timing of IVIG, 5 % will develop, at minimum, transient coronary artery dilation and 1 % will develop giant aneurysms [20]. Newburger et. al. studied corticosteroid administration prior to IVIG administration [45]. There were no significant differences in

outcomes compared to IVIG and aspirin alone, in terms of coronary artery changes, duration of fever, length of hospitalization, and rates of repeat IVIG infusion [45].

About 15–20 % of patients with Kawasaki will fail to defervesce with initial IVIG therapy [46, 47]. This is defined as a persistent fever ≥36 h after completion of IVIG infusion [20]. One study showed that those with a higher band count, lower albumin levels and abnormal echocardiograms were more likely to be resistant to their IVIG infusion [48]. It is standard practice, currently, to administer a second dose of IVIG to these patients which has been shown to achieve defervescence in an additional 67 % [49]. Steroids are often used for recalcitrant Kawasaki disease although the data available in the literature is conflicting. Therefore, those who have received ≥2 IVIG infusions should receive 30 mg/kg of methylprednisolone over 2–3 h for 1–3 days [20].

Thrombosis

Thrombosis of coronary arteries resulting in ischemia, infarction and sudden death is the most significant consequence of Kawasaki disease. Peak mortality occurs 15–45 days after onset of fever as coronary vasculitis is present at the same time as marked thrombocytosis and a hypercoaguable state [20]. Sudden death can also occur many months to years later from MI with development of coronary stenosis [20]. Myocardial infarction occurs in ~2 % of those with a history of Kawasaki disease and about 7 % in those with coronary artery lesions [50].

Prevention of Coronary Thrombosis

Recommendations for the prevention of thrombosis comes from small case series and adult data from coronary artery disease, as no prospective data exists for children with Kawasaki disease [20]. Regimens to prevent thrombus include antiplatelet therapy with aspirin as well as dipyridamole or clopidogrel and anticoagulant therapy with warfarin, low-molecular-weight heparin or some combination of these drugs. Platelet activation is a well-recognized aspect of Kawasaki and therefore, antiplatelet drugs are a mainstay of therapy. Patients with mild disease can be maintained on low-dose aspirin alone. In a patient with more moderate disease, the addition of clopidogrel to aspirin may be more effective in preventing vascular events [20]. Patients with giant coronary aneurysms are at highest risk of thrombosis and generally, these patients are treated with aspirin and warfarin with a goal international normalized ratio (INR) of 2.0–2.5 [20].

Treatment of Coronary Thrombosis

Although the pathogenesis of an atherosclerotic clot is altogether different than that of the evolving clot in a child with Kawasaki disease, again the only data to support therapy of thrombosis is from this population. The goals of therapy are to reestablish patent coronary flow, to perfuse the myocardium, and improve survival [20]. The strategy to achieve these goals targets multiple steps in the coagulation cascade with the use of thrombolytic therapy, aspirin, heparin and platelet glycoprotein IIb/IIIa receptor inhibitors [20]. There is no protocol in children with MI as in adults, but in addition to anticoagulation, the provider should be prepared to treat these patients like any other patient with cardiogenic shock with afterload reduction, inotropy and mechanical support. Mechanical restoration of blood flow has also been in used in children, with both surgical and interventional procedures [20]. Coronary artery bypass grafting has been successful from a surgical standpoint [51]. No specific criteria have been developed regarding timing of surgical intervention. Caregivers should be aware that even when severe, localized stenosis is present by coronary angiography, symptoms are rare and evidence of ischemia is unusual until an actual infarction occurs [52]. With regard to catheterization interventions, a small series showed limited success to percutaneous transluminal coronary angioplasty (PTCA) due to calcifications of older, more organized thrombus while percutaneous transluminal coronary rotational ablation proved more successful [53]. Stent placement is another option and can prevent the occurrence of restenosis [54]. Cardiac transplantation should also be considered for patients with severe irreversible myocardial dysfunction and coronary lesions not amenable to surgical or catheter procedures [20].

Long-Term Management

Lesions in the coronary arteries that develop from Kawasaki disease are a dynamic process [20]. The size of the lesion itself predicts whether an aneurysm will resolve or progress and those with giant aneurysms are at highest risk for poor prognosis with complications of thrombosis and stenosis [55]. About 50–75 % of coronary artery aneurysms resolve spontaneously 1–2 years after the onset of Kawaskai disease [31]. Factors associated with regression include <1 year of age at onset of disease, fusiform rather than saccular morphology, and distal location [56]. Those that do not resolve are at risk of persistence, stenosis, occlusion, abnormal tortuosity, and rarely, rupture [20]. By angiography areas of regression appear normal; however, areas of regional stenosis have occurred at regions of regression in a small number of cases and coronary reactivity to nitroglycerin was significantly lower at areas of regressed aneurysms than in normal segments [57]. Patients with coronary artery lesions have been shown to have abnormal carotid artery walls that are less distensible and thicker than controls [58]. Another study showed an adverse lipid profile in patients with a history of Kawasaki disease compared to normal controls [59].

Myocardial infarction has been shown to occur at a younger age than the usual acute coronary syndrome in adults with other risk factors [60]. Patients with a history of Kawasaki disease need lifelong follow-up [61].

Myocarditis

Acute viral myocarditis is a non-ischemic inflammation of the myocardium with myocellular necrosis, associated with impaired ventricular function. The presentation can be quite variable, and cardiac findings can be subtle, requiring a high index of suspicion. The diagnosis is made by histology via endomyocardial biopsy or clinically, supported by polymerase chain reaction (PCR) [62]. Myocarditis is an important contributor to childhood morbidity and mortality.

Epidemiology

The true incidence of myocarditis is unknown. The incidence is difficult to measure because there are mild cases that do not present to medical care, as well as more severe cases resulting in sudden death that may be missed or misclassified. The incidence has been estimated at 1 per 100,000 children [63]. Autopsy studies looking at causes of sudden unexpected death in previously healthy children have found the incidence of myocarditis to be 5–20 % [64, 65]. Dettmeyer et. al. studied babies with sudden death and found that nearly half had PCR or immunohistochemical evidence of myocarditis [66]. Studies from those with dilated cardiomyopathy show an incidence of 1.1–1.2 per 100,000 children and myocarditis is present in roughly 10 % [67, 68].

Etiology

Myocarditis can result from various infections as well as systemic diseases, drugs and toxins. Drugs that can cause a hypersensitivity myocarditis include anticonvulsants, antibiotics, and antipsychotics [69]. Eosinophilic myocarditis, with a predominant eosinophilic infiltrate in the myocardium, can be seen with systemic diseases such as hypereosinophilic syndrome, Churg-Strauss syndrome, Loffler's endomyocardial fibrosis, cancer, and parasitic, helminthic or protozoal infections [69]. Giant cell myocarditis is rare and often fatal, even when treated aggressively. It is characterized by widespread necrosis, fibrosis, and the presence of giant cells. It is associated with various systemic autoimmune diseases and as such, may respond to aggressive immunosuppressive therapy [70, 71]. Non-viral myocarditis results from bacterial, rickettsial, fungal, and parasitic infections. This chapter will focus on viral myocarditis. Coxsackievirus, parvovirus B19, human herpes virus 6 (HHV-6) type B, and adenovirus are the most frequent pathogens in infants and children [72]. Adenovirus has been shown to be the most common viral cause of myocarditis when enterovirus was thought to be more common [73].

Pathogenesis

First the virus enters the myocyte through specific receptors and co-receptors [74]. Infection of the myocyte results in necrosis and an immune response via toll-like receptors with infiltration of macrophages, natural killer cells, and T-cells [75]. This is followed by macrophage activation with release of cytokines which has a potent negative inotropic effect [62]. These cytokines cause myocyte destruction as well as viral clearance, which can correspond to an asymptomatic myocarditis [72]. The second phase is characterized by a shift to a specific immune response where T-lymphocytes are signaled and destroy infected myocytes [72]. In the third phase, the destroyed myocytes are replaced by fibrosis [72]. Viral persistence in the myocardium is seen with continued ventricular dysfunction and viral clearance is related to improvement [76].

Diagnosis

Clinical

The diagnosis of myocarditis was originally made by endomyocardial biopsy, interpreted with the Dallas criteria, which is the presence of an inflammatory infiltrate associated with necrosis under light microscopy. This process is limited, however, in that the disease process is patchy and specimens are subjected to variability in interpretation. Diagnosis of myocarditis has been advanced by the use of immunohistochemical and PCR analyses [71, 72]. Combination of these modalities, history, physical exam, and the detection of viruses in peripheral blood samples and also at the entry and excretion sites (throat, urine, and stool) as well as in cardiac tissue from endomyocardial biopsy, leads to the diagnosis [72]. Tracheal aspirate PCR has been shown to predict endomyocardial biopsy PCR results in 100 % of a small cohort of patients [77].

Myocarditis frequently has an insidious onset and patients have a recent history of viral symptoms, similar to upper respiratory or gastrointestinal viral illnesses (Table 28.8) [67, 70]. These illnesses are more common in children, cardiac findings can be subtle, and children can compensate well, which can erroneously lead (at least in these cases) a care provider to those more common diagnoses. In fact, one study showed that 84 % of their patients ultimately diagnosed with myocarditis were seen at least once by a provider before the diagnosis of myocarditis was made [78]. Patients can, however, initially present in fulminant circulatory collapse. Cardiac

Table 28.8 Symptoms and physical examination findings

Specific symptoms and physical examination findings	No. of patients (n = 62)
Most common presenting symptoms	
Shortness of breath	43 (69 %)
Vomiting	30 (48 %)
Poor feeding	25 (40 %)
Upper respiratory symptoms	24 (39 %)
Fever	22 (36 %)
Lethargy	22 (36 %)
Most common physical examination findings	
Tachypnea	37 (60 %)
Hepatomegaly	31 (50 %)
Respiratory distress	29 (47 %)
Fever	22 (36 %)
Abnormal lung exam	21 (34 %)
Heart rate findings	
Normal heart rate	41 (66 %)
Tachycardia	20 (32 %)
Febrile and tachycardie	9 (45 %)
Afebrile and tachycardie	11 (55 %)
Bradycardia	1 (2 %)

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findings to evaluate for include tachycardia, mild hypotension, unexplained metabolic acidosis, syncope (arrhythmia), chest pain, and signs and symptoms of congestive heart failure [62]. There are two groups of patients who present with myocarditis – those with acute fulminant myocarditis who present critically ill and requiring significant support and those who have a more indolent course and are more likely to progress to dilated cardiomyopathy [79]. Fulminant myocarditis is characterized by sudden onset of severe congestive heart failure or cardiogenic shock, usually following a flu-like illness. In those with a more indolent course, 10–20 % of cases will evolve to a chronic phase and then 9 % will evolve to a dilated cardiomyopathy [72].

Biomarkers

Several studies have shown that troponin and myocardial creatine kinase isoenzyme (CK-MB) levels are increased in the setting of myocarditis [80]. One study showed that troponin I was more likely to be elevated than CK-MB in the setting of myocarditis [81]. Moreover, children with fulminant myocarditis have higher Troponin I and T levels than those with the less fulminant presentation, suggesting that the level of troponin correlates with the severity of myocarditis [82]. However, the prevalence of an increased troponin T in biopsy-proven myocarditis is only 35–45 % [81, 83].

Imaging and Testing

Electrocardiographic findings in myocarditis are quite variable but include sinus tachycardia, low-voltage QRS, abnormal Q-waves, flattening or inversion of T-waves, dysrhythmias and ST-segment elevation [84]. Sensitivity of the electrocardiogram for myocarditis varies in the literature from 47 to 93 % [85, 86]. An abnormal QRS pattern or left bundle branch block is associated with higher rates of death or transplant [85]. Chest radiograph can be normal but should be obtained to evaluate for cardiac silhouette size, pulmonary edema, and pleural effusion. One series showed that 63 % of those with myocarditis had cardiomegaly on chest radiograph [78].

Echocardiography should be obtained at presentation or once the patient is clinically stable, to evaluate for biventricular size and function, valvar insufficiency, thrombi and pericardial effusion. Regional wall motion abnormalities have been described in the setting of myocarditis [87]. Right ventricular systolic dysfunction has been shown to be a predictor of death or need for transplantation [88]. Felker et. al. showed that those with fulminant myocarditis had near normal LV diastolic dimensions and increased septal thickness and those with acute myocarditis had enlarged LV diastolic dimensions with normal septal thickness; both had systolic dysfunction with decreased shortening fraction [89]. If evaluated early, this could predict a more critical course in those with fulminant disease.

Cardiac magnetic resonance imaging (CMR) has evolved as an important diagnostic tool in the setting of myocarditis. CMR with early and late enhancement after gadolinium contrast injection is becoming an important tool in suspected acute myocarditis [90]. CMR has been shown to enhance biopsy guidance and improve clinical utility of endomyocardial biopsy results [91].

Endomyocardial Biopsy

Endomyocardial biopsy can assess the degree of inflammation and fibrosis and has been viewed as a gold standard for diagnosis [92]. This, however, is fraught with difficulty due to sampling error, sample interpretation, and procedural complications [93]. Biopsy specimens should be analyzed to assess for fibrosis, inflammation and T-cells, viral capsids, viral antigens, and PCR [72]. Virus can exist in the myocardium without inflammation making the histology negative but the PCR positive [71]. In 34 children with clinical presentations compatible with myocarditis, 70 % of the biopsy samples were positive for viral pathogens, and only 50 % had evidence of myocarditis by histopathological examination [94]. Six percent of patients will experience a minor or major complication from biopsy, most of which are transient and without sequelae [95]. Pophal et al. identified risks from endomyocardial biopsy in children, which included death in 0.1 %, perforation in 0.9 %, as well as arrhythmia, pneumothorax, hemothorax, and tricuspid valve damage [96]. Multivariate analysis showed greater risk in those undergoing evaluation for myocarditis and those on inotropic support.

Treatment

There is very little literature in pediatrics regarding medical management in myocarditis. Care should be focused on supportive measures and efforts to lower elevated filling pressures [97]. The use of inotropic support is frequently described as is the use of vasodilators when appropriate. Anti-coagulation is often recommended as well. Oral heart failure regimens are used in patients who are more stable. Mechanical ventilation is often employed to ameliorate respiratory distress as well as to decrease afterload by decreasing transmural left ventricular pressure.

Intravenous immunoglobulin, theoretically, could enhance viral clearance with antibody presentation and decrease inflammation promoted by host cytokine release [98]. There are no prospective, randomized controlled trials in pediatrics regarding the use of IVIG. One pediatric study showed improvement in left ventricular diastolic dimension and shortening fraction in those treated with IVIG, but this study is limited in its design [99]. A Cochrane review for IVIG found only one randomized controlled trial in 62 adults et al. that showed no difference in IVIG group versus control group [100]. A prospective randomized controlled trial is needed.

Animal studies investigating immunosuppressive regimens have been promising [101], but clinical trials have failed to show efficacy [102, 103]. Hia et al. performed a meta-analysis of the literature regarding immunosuppression in myocarditis and found that immunosuppression does not improve outcomes but current studies are made up of small sample sizes and further study is warranted [104]. Immunosuppression has been used with success in patients with giant cell myocarditis [69].

Mechanical support using extracorporeal membrane oxygenation (ECMO) and ventricular assist devices (VAD) have been used to bridge patients to recovery as well as to cardiac transplantation [105]. In one series of pediatric patients with acute fulminant myocarditis 50 % of the patients required ECMO support [106]. Cardiogenic shock with dysrhythmias was documented as the indication for cannulation in 80 % [106]. Survival without transplantation was 80 % [106]. The Extracorporeal Life Support Organization (ELSO) registry demonstrates that the use of ECMO in myocarditis is quite common with 1.3 % of pediatric runs. Survival to hospital discharge in this cohort is 61 % with 3 % ultimately undergoing cardiac transplantation. Multivariate analysis revealed that female sex, arrhythmia on ECMO and renal failure requiring dialysis were associated with increased risk of in-hospital mortality [107].

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Cardiomyopathies in Children

29

Angela Lorts, Thomas D. Ryan,
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Abstract

Pediatric cardiomyopathies are a heterogeneous group of disorders affecting the myocardium. They are associated with abnormal chamber size or wall thickness and systolic and/or diastolic dysfunction in the absence of valve disease, coronary artery disease, hypertension, congenital heart disease, or abnormal loading conditions. While previous classification schema focused primarily on functional and morphologic phenotypes, more recent proposals incorporate causative mechanisms and divide the cardiomyopathies into primary and secondary causes.

Keywords

Cardiomyopathy • Hypertrophic • Dilated • Restrictive • Left ventricular non-compaction

Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM) is the most common cardiomyopathy in children, and is the leading cause for cardiac transplantation in this group of patients [1, 2]. It is a complex disease with a multitude of potential causes and often results in death or transplantation [2]. A thorough understanding of the pathophysiology and etiology of DCM is essential in developing an appropriate treatment strategy.

Clinical Features, Epidemiology, and Diagnosis

Definition and Incidence

DCM is a collection of familial, non-familial, infectious, systemic, and toxic cardiomyopathies that share the final common pathway of a dilated left ventricular (LV) chamber dimension, relatively decreased LV wall thickness, and systolic and diastolic dysfunction [3–5]. While the right ventricle may be affected, this is not necessary for diagnosis. Considering the Law of LaPlace, where wall stress is directly proportional to (LV chamber diameter)(LV intraventricular pressure)/2(LV wall thickness), the spherical and dilated LV in the face of a relatively thin LV wall leads to significantly increased wall stress and decreased function. Chamber dilation can also negatively affect atrioventricular valve function and act as stimulus for ventricular arrhythmias [4]. Incidence of CM in children has been described in two large registries, the National Australian Childhood Cardiomyopathy Study (NACCS) [6] and the North American Pediatric Cardiomyopathy Registry (PCMR) [1]. The incidence of CM is similar between the groups, with NACCS describing 1.24 cases per 100,000 children, and the PCMR 1.13 cases per 10,000 children. Both studies also describe a higher occurrence of cases in the first year of life as well as differences between genders and ethnic groups [1, 6, 7]. DCM makes up more than half of the total cases in each study [1, 8].

Clinical Signs and Symptoms

Diagnosis of DCM is based on clinical phenotype, with 30–80 % of pediatric patients presenting in congestive heart failure (CHF) dependent on etiology [2]. Patient history,

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including symptoms of CHF vary based on age of the patient, and may be quite different between an infant and an adult. Pediatric patients are more likely to exhibit irritability, difficulty feeding, and poor weight gain. Physical exam signs are comprised of tachycardia, gallop rhythm, jugular venous distension, pallor, hepatomegaly, and a murmur consistent with mitral regurgitation. Findings on chest radiography include an enlarged cardiac silhouette and possibly pulmonary edema depending on presence of CHF. Electrocardiography can demonstrate sinus tachycardia, conduction disease, bundle branch block, ST segment changes, and rhythm irregularities. Echocardiography is the standard imaging tool for diagnosis in DCM, showing a dilated and poorly functioning LV (Fig. 29.1), and it may be supplemented in certain cases by cardiac magnetic resonance imaging with delayed enhancement although in young patients this modality may require sedation.

Classification of Heart Failure

Based on clinical findings, patients with DCM can be further stratified by their degree of heart failure. Widely used adult classification schemes, such as that from the New York Heart Failure Association, fail to take into account key factors such as risk for developing disease, and assessing exercise tolerance in young children can be difficult. As such, use of the American Heart Association/American College of Cardiology guidelines is now generally accepted in pediatric cardiology (Table 29.1) [9]. Staging of the patient's disease is important not only in predicting outcome, but also in determining appropriate treatments including medical, surgical, and assistive device [5].



Fig. 29.1 Representative echocardiogram in DCM

Biomarkers

A number of biomarkers are available for diagnosis, management, and prognosis of the patient with cardiomyopathy and heat failure. Many of these markers are validated in adult patients and applied empirically to pediatric patients. These include markers of inflammation (C-reactive protein, tumor necrosis factor alpha), oxidative stress (oxidized low-density lipoprotein), extracellular matrix proteins (matrix metalloproteinases), neurohormones (angiotensin II, renin, aldosterone), myocyte injury (creatine kinase, troponins), and myocyte stress [brain natriuretic protein (BNP), N-terminal pro-BNP (NT-BNP)] [10]. The most commonly used biomarkers include BNP and NT-BNP, which are released during hemodynamic stress and have particular use in distinguishing between dyspnea from heart failure vs. that from lung disease [11]. Studies in pediatric patients with LV dysfunction show that BNP is elevated in patients with LV dysfunction, and patients with BNP plasma values greater than 300 pg/mL are at higher risk for death, hospitalization, or listing for cardiac transplant [12]. Amongst pediatric patients with congenital heart disease, those with DCM have the highest levels of BNP, up to 100-fold higher than values in healthy children [13]. Following trends in BNP and NT-BNP may help guide clinical care, but it should not be considered a standalone test and must be interpreted within the entire clinical context of the patient [14].

Histology

While plasma biomarkers offer a picture of the environment in which a failing myocardium exists, endomyocardial biopsy allows direct visualization and testing of the affected tissue itself. Histologic evaluation can show myocyte hypertrophy and necrosis, enlarged and irregular nuclei, interstitial

Table 29.1 American Heart Association staging of heart failure

Stage	Criteria
A	Infants and children with increased risk of developing congestive heart failure, but who have normal cardiac function and no evidence of cardiac chamber volume overload (*e.g.*, history of exposure to cardiotoxic agents, family history of inherited cardiomyopathy, single ventricle physiology, *etc.*)
B	Infants and children with abnormal cardiac morphology or cardiac function, with no signs and symptoms of congestive heart failure, past or present
C	Infants and children with underlying structural or functional heart disease and past or current signs and symptoms of congestive heart failure
D	Infants and children with end-stage congestive heart failure requiring continuous infusion of inotropic agents, mechanical cardiac support, cardiac transplantation, or hospice care

Adapted from Jessup et al. [9]. With permission from Wolter Kluwers Health

Table 29.2 Partial list of causes of DCM

Idiopathic	Beriberi
Post-myocarditis	Kwashiorkor
Alcoholic	Selenium deficiency
Peripartum	Toxins
Neuromuscular	Anthracyclines
Muscular dystrophy	Cobalt
Myotonic dystrophy	Lead
Metabolic	Arsenic
Carnitine deficiency	Infiltrative
Thyroid dysfunction	Amyloid
Hypocalcemia	Hemochromatosis
Uremia	Sarcoid
Catecholamine cardiomyopathy	Inherited
Connective tissue disorder	Fabry's disease
Systemic lupus erythematosus	Gaucher's disease
Rheumatoid disease	X-linked familial
Polyarteritis	Tachycardia induced
Glycogen storage disease	Anomalous coronary artery anatomy
Nutritional	

edema, replacement fibrosis, inflammation, or evidence of storage disease [15]. Polymerase chain reaction is used to determine presence of viral infection as a cause of DCM [16]. The distinction of disease etiology is critical in determining treatment strategies as divergent as enzyme replacement, immunosuppression, or heart transplantation [4, 5]. However, even with endomyocardial biopsy available, 50 % of all CM cases remain idiopathic [17].

Etiology

DCM may be due to primary or secondary causes (Table 29.2). Primary causes include various genetic and acquired mechanisms, while secondary causes are systemic maladies. However, only about two-thirds of cases have a known cause, leaving a large number to be classified as idiopathic [1, 7]. It is of crucial importance to first exclude potentially reversible causes of injury such as tachyarrhythmias [18], anomalous left coronary artery connections [19], and nutritional deficiencies such as selenium or carnitine [20–22]. A suggested approach to the patient with DCM includes history, physical examination, diagnostic testing, laboratory data, and cardiac catheterization (Table 29.3). This work up may take place as an outpatient or inpatient, dependent on patient condition.

Familial and Genetic Causes of DCM

Approximately 30–40 % of patients with DCM have a positive family history for the disease. Inheritance occurs predominately as autosomal dominant transmission but X-linked, autosomal recessive, and mitochondrial inheritance patterns are also recognized [23]. A number of genes and gene products have been identified as important in the etiology of DCM; for recent reviews see Jefferies and Towbin [4] and Hsu and Canter [7]. Those responsible for causing disease tend to be of two major subgroups, cytoskeletal and

Table 29.3 Initial approach to the patient with DCM

History and physical examination (with attention to recent viral illnesses)
Chest X-ray
Echocardiogram
Electrocardiogram
Laboratory evaluation
Brain natriuretic peptide/N-terminal pro-brain natriuretic peptide
CBC/white blood cell differential, platelet count
Complete metabolic panel
Erythrocyte sedimentation rate
Urinalysis
Serum carnitine level and acylcarnitine profile
Urine carnitine level
Urine organic acid profile
Serology (generally, acute and convalescent serum obtained at least 2 weeks apart)
Epstein-Barr virus
Cytomegalovirus
Herpes simplex virus
Toxoplasma gondii
Coxsackie A, B1-B6
Influenza A & B
Mumps
Polio 1–3
Adenovirus
Thyroid function studies
Serum cholesterol and triglycerides
Viral Cultures (nasopharyngeal, rectal swabs for enterovirus)
24 h Holter (heart rate variability)
Cardiac catheterization with endomyocardial biopsy procedure

sarcomeric proteins. Many of the genes involved are also causative of hypertrophic CM. While these gene alterations may cause DCM in isolation, it may also be the case that DCM occurs in the context of a broader systemic condition. One such example is the dystrophin gene which, when mutated, is cause of a number of muscular dystrophies including Becker and Duchenne. As medical management for these patients has improved cardiovascular disease has been unmasked as the leading cause of death [24–29]. Genetic testing is becoming more common for cardiovascular disease, and can help to identify those patients with a positive genotype for the disease causing mutation even if they have a normal echocardiogram and

Infectious Causes of DCM

An in depth review of myocarditis can be found elsewhere in this text. Infectious etiologies of DCM include bacterial, fungal, parasitic, rickettsial, and spirotricheal infections [4]. However, by far the most common pathogens are viral, primarily parvovirus B19, adenovirus, coxsackievirus B, influenza A, human herpes virus 6, cytomegalovirus, Epstein-Barr virus, herpes simplex virus type 1, and hepatitis C [16, 30]. The predominant virus involved changes by decade, with the current era being that of parvovirus B19 [4].

Peripartum DCM

Development of heart failure symptoms and a DCM phenotype during the last months of pregnancy through 5 months after delivery with no other identified cause is considered peripartum cardiomyopathy [31]. The exact cause of this disorder is unknown, and incidence is highly geographic worldwide [32]. Approximately 23–41 % of women return to normal cardiac function [31], however in those who do not there is a higher incidence of poor maternal outcome with subsequent pregnancies [33].

Toxicity-Related DCM

In adult patients a significant portion of toxicity-related cases of DCM are related to abuse of cocaine and alcohol. For the most part, this is not pertinent in pediatric patients, in whom most cases are a result of chemotherapeutic agents. Use of anthracyclines, *e.g.* doxorubicin and daunorubicin, is known to cause DCM and heart failure in certain patients [34]. The insult involves oxygen free radicals, and use of free radical scavenger agents such as dexrazoxane has shown benefit [35].

Other Causes of DCM

A number of other mechanisms, although rare, may be responsible for DCM in pediatric patients and must be considered as part of a complete differential diagnosis. Inborn errors of metabolism involving amino and organic acids, fatty acids, lysosomal storage disorders, and mitochondrial disorders are most commonly associated with a hypertrophic cardiomyopathy but may also cause DCM [1, 7]. Certain endocrine disorders, Kawasaki disease and autoimmune vasculitis (*e.g.* Churg Strauss syndrome), and nutritional deficiencies (*e.g.* thiamine, selenium, carnitine, hypocalcemia, hypophosphatemia) may each be at the root of a DCM phenotype [3].

Management

Treatment of DCM can be divided into treatment of the symptoms associated with the disease and treatment of the underlying cause of the disease. Traditionally the focus has been on the former but recent advances have allowed more use of the latter. Regardless, is it of crucial import to know the cause of DCM as well as disease severity when deciding how to proceed with therapy of these patients.

Pharmacologic Therapy

Many of the guidelines for treatment of heart failure are based on studies in adult patients which are applied empirically to children, and studies in pediatrics often focus on safety and short-term efficacy. Severity of disease plays an important role in deciding which pharmacologic agents to employ in DCM [5]. Patients who are at risk and classified as Stage A (Table 29.1) generally require no treatment, although evidence exists showing patients with a genetic predisposition for developing CM [36] or known toxic exposure [37] benefit from prophylactic treatment. Patients classified as Stage B, *i.e.* structural disease without symptoms or signs of failure, have been shown to have improved function and symptomatology and favorable remodeling with use of angiotensin converting enzyme inhibitors and beta blockers [7]. Once symptomatic and considered Stage C, addition of diuretics for fluid retention as well as aldosterone antagonists for diuresis and remodeling are recommended. Other drugs such as digitalis, angiotensin receptor blockers, and nitrates have specific applications but are not considered first line [4, 5, 7]. When ill enough to require intravenous inotropic support it is best to avoid those which increase myocardial demand, such as epinephrine and dobutamine, and preferentially use milrinone which improves relaxation and contractility of the myocardium while also achieving afterload reduction. Afterload reduction is key in allowing maximal contribution from a failing heart, and agents such as nitrates work toward this end [38].

Risk of thrombus formation with subsequent embolization leads most clinicians to recommend anticoagulation for patients with DCM, particularly those with decreased systolic function. The agent used is practitioner dependent and a recent adult study showed that between aspirin, warfarin, and clopidogrel, no one agent was superior at preventing a composite endpoint [39].

Certain classes of medication are to be avoided in patients with heart failure as they may exacerbate symptoms. Antiarrhythmic agents exert cardiac depressant and proarrhythmic affects, calcium channel blockers are associated with an increased rate of adverse events, and nonsteroidal anti-inflammatory drugs can cause fluid retention, vasoconstriction, and enhance the toxicity of angiotensin converting enzyme inhibitors [9].

Cardiac Resynchronization and Implantable Cardiac Defibrillators

The goal of cardiac resynchronization therapy, or biventricular pacing, is to eliminate the delay in activation of the LV free wall and improve mechanical synchrony and ultimately relaxation and systolic function [4, 5]. In adult patients this therapy is recommended for those patients with Stage C failure, a prolonged QRS duration on EKG, and depressed ejection fraction despite optimal medical therapy [9]. Results after biventricular pacing have been mixed in pediatric patients [5, 40].

Studies in adults have shown survival benefit after placement of implantable cardiac defibrillators in patients with both ischemic and non-ischemic heart disease. However, in pediatric patients with cardiomyopathy the incidence of sudden cardiac death is quite low, with a 5-year cumulative risk of 2.4–3 %, requiring placement of 26 implantable cardiac defibrillators to prevent one sudden cardiac death [41, 42]. Risk stratification is possible and factors associated with sudden cardiac death include a greater eccentric LV remodeling (*i.e.* thinner wall and more dilated chamber), antiarrhythmic therapy within 1 month of diagnosis, and diagnosis before 13 years of age [41].

Mechanical Circulatory Support

When patients become refractory to medical management, *i.e.* Stage D heart failure (Table 29.1), then mechanical support is an option as either a bridge to recovery or a bridge to transplantation. The decision to use extracorporeal membrane oxygenation (ECMO) or a ventricular assist device (VAD) depends on the clinical scenario and duration of support required. When both circulatory and respiratory support is needed, ECMO is the option of choice; in most situations, ECMO is considered a short-term option only. When long-term solutions are required VAD support should be considered, and indeed survival after transplant is higher in patients receiving VAD support prior to transplant as opposed to those on ECMO [43]. For most adult-sized patients there are multiple options, several of which are portable and could allow discharge to home with the device. In smaller children (body surface area <1.3 m [2]) the only current option is a Berlin Heart EXCOR [44]. While patients are on ECMO or VAD support they may have native cardiac output, and often may be able to come off pharmacologic inotropic support altogether allowing the heart to recover. However, moving to mechanical support early rather than when the patient is *in extremis* is the best way to optimize potential for return of function [44]. Currently, a significant amount of research effort is directed at developing other VAD options for children, as well as VAD as destination therapy, *e.g.* a complete artificial heart.

Intra-aortic balloon pumps, which are a commonly used support modality in adult patients with LV failure after ischemic heart disease, are not generally used in children. Due to technical issues related to small patient and blood vessel size they are more difficult to insert, and they may not be able to achieve effective counterpulsation in the highly elastic pediatric aorta [45].

Surgical Intervention

An exciting prospect on the horizon for DCM is use of surgical techniques, often as bridge to transplant, which reduce the LV dilation or restore the normal elliptical shape of the LV. The Batista procedure is a partial left ventriculotomy thus far used primarily in patients with ischemic heart disease [46]. Other procedures include restoration of the elliptical shape of the LV by volume reduction [47]. In both cases the goal is to improve wall stress and reverse remodeling.

Mitral regurgitation is commonly associated with LV dilation and may contribute to morbidity and mortality. Two recent, small pediatric studies have shown improvement in LV geometry and function with mitral valve annuloplasty [48, 49], although these studies need to be expanded to make inferences about the larger population of DCM patients.

Heart Transplantation

Heart transplantation remains the therapy of choice for end-stage heart failure in children, however given the limited supply of donor organs it is reserved for patients with the most severe disease including those requiring inotropes, mechanical ventilation, and mechanical device support [4, 7]. DCM is the most common reason for transplantation in patients over 1 year of age [2, 50], and has the best survival of all diagnostic groups [7]. Risk among patients with DCM is not uniform between various etiologies, and this must be considered when determining timing of listing for transplantation [2].

Special Considerations: Anesthesia

Patients with DCM will undergo a number of noninvasive and invasive procedures requiring adequate sedation, including imaging studies, line placement, cardiac catheterization, surgery, VAD placement, and transplantation to name a few. Careful consideration of how a patient is managed during these procedures is necessary especially since rapid decompensation is possible. Intravenous induction agents

such as propofol and ketamine decrease preload and systemic vascular resistance as well as depressing myocardial function, and can lead to hypotension. Etomidate is a reasonable substitute in this case given that it has less myocardial depressant effect than the other agents. Use of high dose opioids, particularly in conjunction with benzodiazepines, may cause circulatory depression when not used with caution [51]. Consultation with an anesthesiologist with specialized training in cardiovascular management may be warranted.

Outcomes

Outcomes for children with DCM vary based on several factors, including etiology, age at diagnosis, and presence of heart failure symptoms at presentation. The 1- and 5-year rates of death or heart transplantation in patients with DCM of all causes are 31 % and 46 %, respectively [1]. Once listed, 75 % of patients undergo heart transplantation within 2 years, and 11 % die before receiving a new heart [52]. Survival 10 years after transplantation is currently near 70 %, although improvements in medical management are constantly evolving and will have a positive impact on this figure. An increased risk of death is associated with arrhythmias, mechanical ventilation, and ECMO.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiac disorders. The prevalence of HCM in the general population is at least 0.2 % (1 in 500) [53, 54]. The disease is inherited in an autosomal dominant fashion with over 600 mutations of a variety of genes mostly encoding proteins in the cardiac sarcomere [55, 56]. This disease has great phenotypic diversity due to the many genetic mutations that are causative and the environment that they are expressed in. Children with HCM have differing degrees of hypertrophy and receive individualized treatment depending on their phenotype and risk stratification predicting sudden death. There are many scenarios where a child with HCM may need disease- specific critical care management, for example postoperative recovery following a non-cardiac or cardiac procedure, after resuscitation from a cardiac arrest, or if the child develops severe diastolic and/or systolic dysfunction and requires management of their low cardiac output state.

Clinical Features and Diagnosis

Clinical Signs and Symptoms

There are many different ways that pediatric and adult patients with HCM present to health care. HCM can be detected in asymptomatic individuals with a family history, at the time of a sudden death event (SCD), or in patients with signs of heart failure. Most commonly patients are diagnosed in the first 2 decades of life. Unfortunately, the diagnosis is sometimes made at the time of an autopsy after SCD. If the patient presents with signs and symptoms of heart failure they may be secondary to many different physiologic disturbances including dynamic left ventricular outflow tract (LVOT) obstruction, LV dysfunction, and/or arrhythmias. Exertional dyspnea, exercise intolerance, syncope, fatigue and chest pain may be presenting symptoms. The physical exam may be normal unless there is outflow tract obstruction, leading to a systolic ejection murmur or the ventricular stiffness leads to a S4 gallop [57]. There are times when making the diagnosis is difficult. If there is question of HCM verses hypertrophy from a systemic pathology, such as hypertension, the other condition must be controlled to determine if the hypertrophy will resolve. Physiologic hypertrophy, as seen in the athlete's heart, may make subtle changes on echocardiography difficult to sort out.

Echocardiography/MRI

The primary modality for diagnosis of myocardial hypertrophy is transthoracic echocardiography with Doppler, although MRI is being used increasingly in this population to further quantify the degree and location of hypertrophy. In general, hypertrophy has been defined as a wall thickness of >15 mm in adults and >2 Z scores in pediatrics (Fig. 29.2). These findings will trigger the need to further evaluate the etiology of the hypertrophy. Classically the pattern of hypertrophy is asymmetric, preferentially affecting the anterior interventricular septum [53]. However, the phenotype of HCM may vary dramatically from patient to patient even if

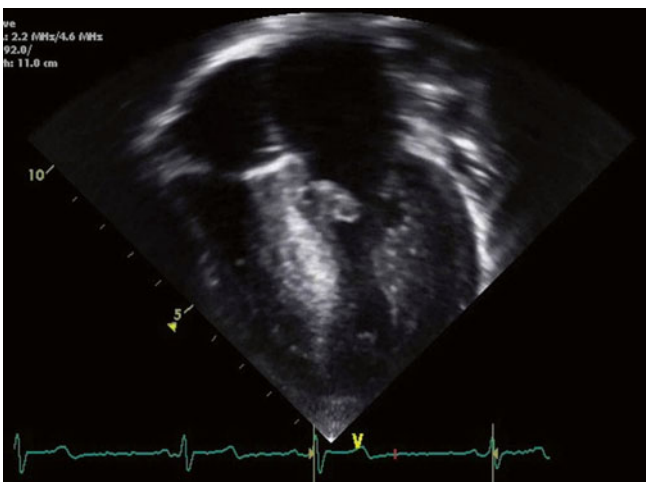


Fig. 29.2 Representative echocardiogram in HCM. In most cases there is asymmetrical septal hypertrophy

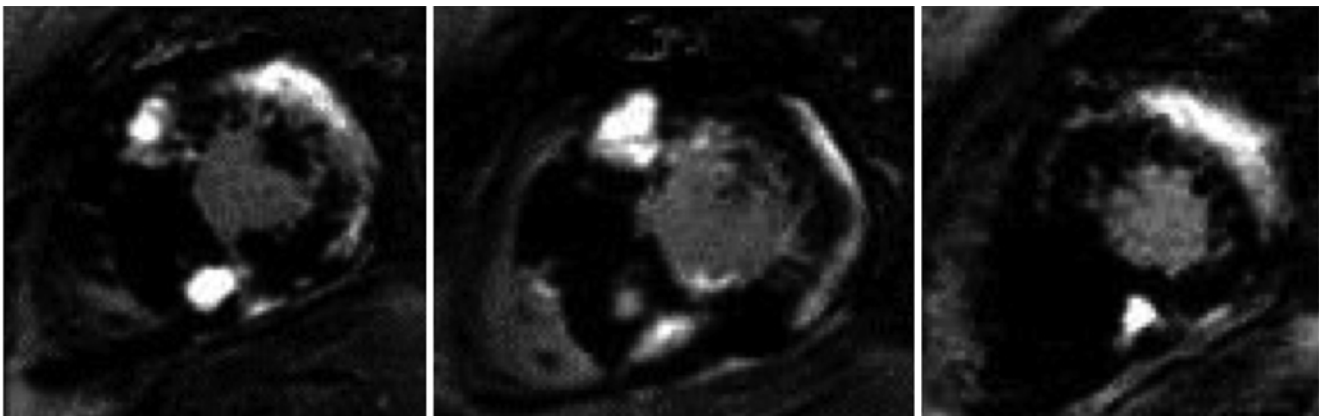


Fig. 29.3 MRI with late gadolinium enhancement indicative of fibrosis in HCM

Table 29.4 Genetics of hypertrophic cardiomyopathy

Gene symbol	Gene name	Frequency in patients with HCM (%)
MYH7	β Myosin heavy chain	25–25
MYBPC3	Cardiac myosin-binding protein C	20–30
TNNT2	Cardiac troponin T	5–15
TNNI3	Cardiac Troponin I	<5
TPM1	Tropomyosin 1 α	<5

they are within the same family with the same genetic mutation. There is no absolute wall thickness that excludes the diagnosis of HCM. With the advancement of genetics, it is now known that a patient may have the genetic mutation but not have findings by echocardiogram.

Magnetic resonance has an increasing role in the management of patients with HCM. When ordering this study it must be determined if the information obtained will be worth the risk of sedation. The MRI will more effectively image the LV apex and LV free wall [58, 59]. It will also allow for the quantification of fibrosis through the identification of late gadolinium enhancement (LGE) (Fig. 29.3). It adults there is a link between fibrosis and ventricular ectopy although this has not been studied in children [60, 61].

Electrocardiography/Holter

The electrocardiogram (ECG) may be normal or more commonly there may be increased voltage consistent with ventricular hypertrophy. In some cases LVH on ECG may signal impending hypertrophy that is not yet evident by echocardiogram [62, 63]. The diagnosis of Pompe disease should be suspected if there are extreme voltages. Once diagnosed, patients have routine Holter testing since they are at increased risk of supra-and ventricular arrhythmias. If the patients genetic testing is positive, knowledge of the mutation may help to risk stratify patients and determine who is at greatest risk for arrhythmias. Family history is also used to determine the subset of patients that are at the greatest risk for arrhythmias and helps to direct management.

Exercise Testing

Risk stratification has been reported with the use of exercise testing with blunting or reduction of blood pressure and/or blunting of heart rate response to exercise being associated with increased risk [64, 65]. Other associated risk factors include syncope, nonsustained ventricular tachycardia, severe LVH on echocardiogram and family history of premature death.

Histology

The histological features found on biopsy include myofibrillar disarray, myocyte hypertrophy, small vessel disease and resultant interstitial fibrosis [53, 54]. Together these pathologic features form the nidus for the ventricular arrhythmias that can lead to sudden death.

Etiology

Familial and Genetic Causes of HCM

HCM is transmitted in an autosomal dominant pattern of inheritance. If a parent has the disease there is a 50 % chance that the child also has the disease. The genetic mutations that have been discovered all link the disease to the sarcomere, the contractile component of the cardiomyocyte. To date, 18 disease causing genes (Table 29.4) have been identified with hundreds of various mutations. At this time 40–60 % of patients with HCM cases will have an identifiable genetic mutation [53, 55, 66]. Mutations in B-myosin heavy chain (MYH7) and myosin-building protein C (MYBPC 3)

account for a majority of the identified mutations. The ability to do genetic testing has dramatically changed the management of first degree relatives. If the index case has a positive mutation, all first degree family members can be tested for that specific mutation [67]. The result of the family members testing will guide the follow up of these potentially affected individuals. Family members who test positive for the familial mutation are considered to be at risk and should receive regular echocardiographic surveillance. If the asymptomatic relative is negative for a mutation that was found in the proband they are felt to be negative for the disease and further clinical monitoring is not necessary. It is important to note, currently only 50–60 % of patients have the HCM phenotype are mutation positive, highlighting the importance of ongoing research efforts.

Other Causes of HCM

A variety of disorders that have apparent LVH and features of hypertrophic cardiomyopathy occur due to infiltrative disorders. The classic form of an infiltrative disease is Pompe disease. Pompe's disease presents in the first few weeks of life with hypotonia and severe cardiomyopathy. The diagnosis can be made by the pathognomonic ECG, showing extremely large voltages. The disease is caused by a genetic deficiency of acid alpha-1.4 glucosidase, leading to massive glycogen accumulation [68]. Other forms of infiltrative diseases have been identified, such as Fabry's disease and Danon's disease [69].

Management

Due the heterogeneity of this disease there are a variety of management strategies that are available to these patients. Medications, beta-blockers, and calcium channel blockers are the mainstay medical therapy [70]. Beta-blockers decrease myocardial oxygen demand, slow the heart rate and inhibit sympathetic stimulation especially during exercise. Calcium channel blockers may be added as a second agent in some cases and are of benefit because they decrease systolic function and improve diastolic relaxation and filling [71]. Unlike dilated cardiomyopathy patients, diuretics are rarely used since optimal physiology in these patients is dependent on adequate preload. Although rare in children, septal hypertrophy may lead to symptoms refractory to medical therapy necessitating a surgical myomectomy or in older patients an alternative would be alcohol ablation. There is limited data in children but one review of 25 children demonstrated an improvement in symptoms and outflow tract obstruction long term follow up [72].

It is well accepted that patients with HCM that have sustained ventricular tachyarrhythmias and or aborted sudden cardiac death should receive an implantable defibrillator (ICD). Risk factors for SCD have been extensively studied in adults and form the basis of the guidelines of when to place a device. Risk factors include prior SCD, family history of SCD, unexplained syncope, abnormal exercise blood pressure, LV thickness >30 mm, and ventricular tachycardia. Although this model describes risk factors for SCD the risk/benefit ratio of placement of an ICD in a child should be based on each individual patient, their family history and family preferences.

Special Considerations: Sudden Cardiac Death

Patients with HCM are at risk of death, in the form of sudden cardiac death due to an arrhythmia or progressive heart failure. HCM is the most common cause of death in young athletes. Risk factors for SCD have been identified in the adult population but very little data exists regarding the pediatric population. Unfortunately, in the pediatric population a sudden death event is often the presenting symptom of HCM. Previously diagnosed patients that are compliant with their exercise restriction and medical therapy have an extremely low risk of SCD. The risk of death related to progressive heart failure is at least as common as SCD in the pediatric population and it has been found that extreme left ventricular hypertrophy and abnormal blood pressure response to exercise is predictive of cardiac death [73].

Restrictive Cardiomyopathy

Restrictive cardiomyopathy (RCM) is characterized primarily by diastolic dysfunction of the myocardium usually with preserved systolic function. This type of cardiomyopathy is the rarest type of all pediatric cardiomyopathies accounting for only 2–5 % of all cardiomyopathy cases in children [6, 74].

Clinical Features, Epidemiology, and Diagnosis

The signs and symptoms of this disease are variable. Children may present with respiratory symptoms that are misdiagnosed as recurrent infections or reactive airways disease. Unfortunately, the first presentation may be with a life threatening arrhythmia. The clinical manifestations in advanced disease are secondary to diastolic dysfunction and include pulmonary edema, pulmonary hypertension and decreased myocardial reserve. On physical exam the most consistent finding is an S3 or S4 gallop due to myocardial wall stiffness [75]. Classical the hemodynamic tracings in the cardiac catheterization laboratory are the gold standard for diagnosis of restrictive cardiomyopathy but MRI is now used frequently

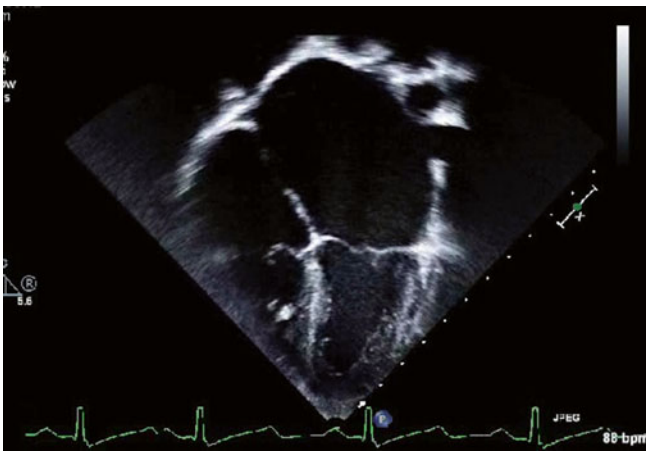


Fig. 29.4 Representative echocardiogram in RCM. The classic finding by echocardiogram is large atria and normal ventricular size

to discern between restrictive cardiomyopathy and constrictive pericarditis. Both cardiac diagnoses present with similar signs and symptoms. Direct measurements of hemodynamics are also important to follow to determine if the disease is having irreversible effects on the pulmonary vasculature, which may increase the postoperative risk after transplantation. Echocardiogram and MRI are also used to monitor disease progression and detect changes in pulmonary vascular resistance (Fig. 29.4).

Etiology

The etiology of restrictive cardiomyopathy in children is much different than that of adults. Many adults with RCM have amyloidosis or a type of endocardial fibroelastosis, but a large number still have an idiopathic and/or presumptively familial disease [76]. The most common acquired cause in pediatrics is exposure to radiation or an underlying storage disease such as Gaucher's or Hurler syndrome. The majority of cases are idiopathic with up to a third being familial. Familial phenotypes may include associated skeletal myopathy with or without conduction system abnormalities. It is extremely important to take a thorough family history and to do genetic screening when appropriate, especially because of the ominous natural history of undiagnosed disease

Management

Restrictive cardiomyopathy is a progressive disease in children with a high mortality rate. At 2 years from diagnosis the mortality rate is 50 % [77, 78]. Although we have made progress in making the diagnosis earlier in these children we have not made progress in treating diastolic dysfunction. Diuretics may be used sparingly to control symptoms of pulmonary edema but other heart failure medications have little utility and may be detrimental. To prevent sudden death by arrhythmia, implantable defibrillators may be useful although the criteria for implantation have yet to be defined. Several studies have shown that transplantation is the best option for these children as long as they do not have irreversible pulmonary hypertension or severe end organ dysfunction [79, 80].

Left Ventricular Noncompaction

Left ventricular noncompaction (LVNC), also known as fetal myocardium, spongioform myocardium, or left ventricular hypertrabeculation, is a genetically and clinically heterogeneous myocardial disorder that was classified as a distinct form of cardiomyopathy in 2006 [81]. LVNC is characterized by the presence of prominent trabeculae, intertrabecular recesses, and thickening of the myocardium in two distinct layers composed of compacted and noncompacted myocardium [82]. A disease primarily of the left ventricle, hypertrabeculation of both ventricles has been reported [83]. Although thought to be a rare disease previously, LVNC is increasingly being diagnosed in both children and adults most likely secondary to increased awareness of the disease. However, many aspects of the disease remain controversial regarding etiology and pathogenesis as well as accepted diagnostic criteria.

Clinical Features, Epidemiology, and Diagnosis

The clinical presentation of LVNC is quite variable based on the age of the patient, recognition of early and late stage heart failure symptoms in children, comorbidities, and awareness of LVNC. The majority of patients over the age of 1 year are completely asymptomatic. However, based on concomitant systolic or diastolic dysfunction, may present with a range of symptoms of heart failure. These may include fatigue, poor weight gain, failure to thrive, edema, shortness of breath, chest pain, abdominal distention, or delayed milestones. In addition, presenting symptoms may be related to arrhythmias which manifest clinically as palpitations, presyncope, or syncope. Infants presenting with LVNC are typically symptomatic and have associated comorbidities that may be life-threatening and impact other organ systems such as inborn errors of metabolism or mitochondrial disease.

There is significant variability in the reported prevalence of LVNC. However, the diagnosis is increasing in frequency given heightened awareness of the disease. Adult echocardiographic laboratories have reported the prevalence of isolated LVNC to be between 0.014 % and 1.3 % [84, 85]. True prevalence remains unknown in pediatric populations.

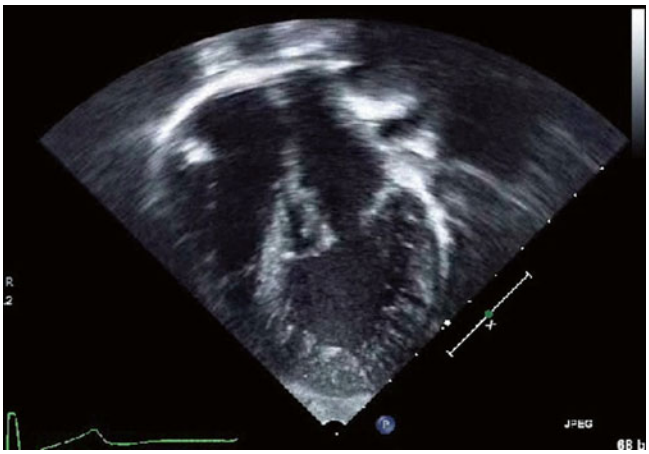


Fig. 29.5 Representative echocardiogram in LVNC. Deep recesses and trabeculations are seen in the apex of this heart

However, LVNC is not an uncommon form of pediatric cardiomyopathy being identified in ~5 % of patients in the Pediatric Cardiomyopathy Registry (PCMR) [86].

The diagnosis of LVNC is typically made by noninvasive imaging studies such as echocardiography (Fig. 29.5) or cardiac magnetic resonance imaging (CMR). Although proposed criteria have been published based largely on comparing the ratio of noncompacted to compacted segments of the LV layers, no consensus currently exists on these criteria for diagnosis [87, 88]. Although abnormalities are typically seen on electrocardiography such as T wave, ST segment abnormalities, and left ventricular hypertrophy, all are nonspecific and not diagnostic of LVNC. Recently published data have suggested that LVNC be classified not only by findings of abnormal LV myocardial compaction but also by coexisting echocardiographic and electrocardiographic findings [89]. Seven distinct subtypes have been proposed that better define LVNC and add to current diagnostic approaches by more completely describing the phenotype. The first subtype is isolated LVNC. In this subtype, LVNC is present but the size, thickness, and systolic function of the LV are normal. The second subtype is isolated LVNC with arrhythmias. In this subtype, the findings are the same as the first subtype but there is evidence of atrial or ventricular arrhythmias which may be life-threatening and increase mortality. The third subtype is a dilated form of LVNC. In this subtype, the phenotype mimics dilated cardiomyopathy (DCM) with a dilated LV and systolic dysfunction. The fourth subtype is a hypertrophic form of LVNC. In this subtype, the phenotype mimics hypertrophic cardiomyopathy (HCM) with a thickened LV, impaired LV relaxation (diastolic dysfunction), and typically hyperdynamic systolic function. The fifth subtype is a restrictive form of LVNC. In this subtype, the phenotype mimics restrictive cardiomyopathy (RCM) with diastolic dysfunction and dilated atria. The sixth subtype is a mixed phenotype that has forms of both DCM and HCM phenotypes which may include thickened LV walls in conjunction with a dilated LV with depressed ejection fraction. The final subtype is LVNC associated with congenital heart disease. In this subtype, LVNC can be seen in conjunction with any structural heart lesion. A unique aspect of LVNC is the reported finding that the phenotype can change over time going from a dilated subtype to a hypertrophic subtype and back again to a dilated phenotype. This has been termed an "undulating phenotype" [90]. This of extreme importance to clinicians as the management strategy is significantly different for those patients with the dilated LVNC subtype compared to those with hypertrophic or restrictive subtypes.

Etiology

During embryogenesis between gestational weeks 5 through 8, the parallel processes of coronary development and loss of LV trabeculations, the process known as compaction, are occurring from the base of the heart moving to the apex [91]. LVNC is speculated to be secondary to a disruption of this normal myocardial compaction during embryogenesis; however, the exact mechanism remains unclear [92, 93]. The result of this disruption leads to two distinct layers of myocardium which are a thin layer of compact epicardium and an overlying layer of noncompacted myocardium. The noncompacted myocardium is characterized by prominent trabeculations along with blind-ending recesses that communicate with LV cavity [94]. These trabeculations and intertrabecular recesses form the morphologic basis used to diagnose LVNC currently in clinical practice.

A greater understanding of the genetics of LVNC has been realized over recent years. The typical mode of inheritance is either autosomal dominant or X-linked recessive [95]. However, the genetics of LVNC are quite heterogeneous with many of the patients having negative genetic testing. Most cases of isolated LVNC are transmitted in an AD fashion and involve sarcomeric genes such as beta-myosin heavy chain (MYH7), alpha-cardiac actin (ACTC), or myosin binding protein C (MYBPC3) [96]. Clinically, mutations in these genes may also lead to hypertrophic or dilated cardiomyopathy phenotypes underscoring the broad phenotypic variations that may be seen in a single family harboring the same genetic mutation [97].

LVNC has been reported in association with all types of congenital heart disease (CHD) such as septal defects (ASD, VSD), valvular disease (pulmonic stenosis), Ebstein's anomaly, tetralogy of Fallot, and hypoplastic left heart (HLHS) [98, 99]. In addition, LVNC has been seen in the setting of numerous genetic syndromes as well as neuromuscular disease [100–102]. LVNC is commonly seen in boys with Barth syndrome (BTS), an X-linked disorder caused by mutations the gene tafazzin (TAZ) that has the additional clinical

associations of neutropenia, skeletal muscle dysfunction, growth retardation, and cholesterol abnormalities [103].

Management

The clinical management of LVNC first is dependent on adequate characterization of the disease and associated myocardial dysfunction which is typically done by noninvasive testing such as echocardiography or cardiac MRI. As outlined above, associated phenotypes are commonly seen with LVNC and treatment is associated around the comorbid phenotype. Those patients with LVNC and dilated cardiomyopathy are managed similarly to those with primary DCM. A similar strategy is employed for those with HCM. The medical and surgical management of these conditions are described elsewhere in this chapter. LVNC may also be seen in association with restrictive cardiomyopathy which is managed aggressively with consideration of possible ICD or cardiac transplant based on recent reports [104, 105]. Care must be taken by providers to conduct ongoing surveillance for arrhythmias both in the inpatient and outpatients settings. Those patients with LVNC admitted to the ICU for any cause should be monitored closely for atrial and ventricular brady- and tachyarrhythmias with appropriate medical and pacing interventions. Typical approach to therapy in those patients with isolated LVNC in pediatric patients has been no standard medical therapy with the understanding that changes in the myocardium may lead to the addition of medical therapies. Some centers will prescribe aspirin therapy as prophylaxis for thromboembolic disease but no benefit to this approach has been documented in children with preserved systolic function. We recommend annual evaluation to monitor for possible changes in myocardial function and thickness in patients with isolated LVNC. Advanced therapies such as mechanical circulatory support are as described in this chapter and previous reports [9, 44]. As with all types of heritable cardiomyopathy, treatment is not just centered on the index patient. Screening is recommended for all at risk first degree family members and appropriate medical treatment should be delivered to those individuals as well based on cardiac phenotype.

Outcomes

Outcome data on patients with LVNC is appear to be dependent on the associated phenotype. In pediatric patients with isolated LVNC that have normal LV size, thickness, and systolic function without evidence of arrhythmia, the outcome is very good with very few patients needing cardiac transplant or experiencing sudden death [86]. However, for those with associated myocardial dysfunction and/or arrhythmias, outcome appears to be predicted by their associated phenotype as described above. However, this is dependent on appropriate management of the associated phenotype such as use of ACEi and beta blockers for LVNC with a dilated cardiomyopathy phenotype. These pediatric data are consistent with previously reported adult data that reported deaths only in patients with LVNC and depressed LV systolic function [85]. However, other comorbidities such as cardioembolism have been reported in adults that have not been previously described in children which may influence outcomes as well [106]. Larger prospective pediatric studies are required to better define risk factors and outcomes in children with LVNC.

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Acute Decompensated Heart Failure

30

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Abstract

The main underlying diagnoses of children with end-stage heart failure are congenital heart disease and cardiomyopathy. These children require close clinical monitoring by a cardiac failure specialist, initially as outpatients treated with oral anti congestive heart failure medication, and eventually as inpatients treated with inotropes. In fact, the majority of patients followed by the Pediatric Heart Transplant Study Group are United Network of Organ Sharing (UNOS) status 1 (heart failure requiring intravenous inotropes). Because of the limited availability of organs, waiting time for heart transplantation is long and as a result, cardiac function continues to deteriorate prior to transplantation, eventually leading to inadequate systemic oxygen delivery and end-organ failure. If the latter develops, the patient is no longer a candidate for heart transplantation. In order to avoid end organ failure, close monitoring of oxygen delivery or surrogate measures of oxygen delivery and step-wise escalation of cardiopulmonary support are required. Other than standard monitoring measures, advanced techniques should be utilized to increase the safety margin and allow timely escalation of support. These advanced monitoring techniques include pulmonary and transpulmonary thermodilution, pulse contour analysis, tissue and regional near infrared spectroscopy, and biochemical markers of perfusion and myocardial strain. Inadequate oxygen delivery in a patient treated with one inotrope warrants admission to the intensive care unit and initiation of a second vasoactive medication. The next step is intubation and mechanical ventilation. Since peritransplantation morbidity and mortality are higher in mechanically ventilated children in comparison to children supported with long-term mechanical assist devices, serious consideration should be given to implantation of a ventricular assist device shortly after intubation.

Keywords

Heart failure • Heart transplantation • Hemodynamic monitoring • Inotropic support • Mechanical ventilation • Oxygen delivery • Ventricular assist device

Introduction

Children with end stage heart failure (ESHF) are at risk of developing acute decompensation, leading to multi-organ failure and death. Since acute decompensated heart failure (ADHF) is expected, measures should be taken to avoid it. Based on the International Society of Heart and Lung Transplantation (ISHLT) database [1], a child listed for heart transplantation (HT) is likely to have ESHF caused by cardiomyopathy or con-

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genital heart disease (CHD). A cardiology follow-up allows early detection of signs of heart failure in children with CHD. However, children with cardiomyopathy may not present until they develop overt signs of heart failure and sometimes not until they develop ADHF. Management of children with ESHF is based on their clinical presentation, underlying diagnosis, and end organ function. Interpretation of diagnostic studies and laboratory tests depends on the clinical presentation and not vice-versa. This is an important concept since the treatment of a child with minimal clinical signs of heart failure and severely depressed ventricular systolic function by echocardiogram is entirely different than the treatment of a child with ADHF and the same echocardiographic findings. In the second case, without escalation of support, end-organ injury will occur and may render the patient ineligible for HT. The only way to avoid this outcome is by anticipation of deterioration and timely escalation of support in a step-wise fashion. Early listing for HT is important because of the limited supply of organs. The first treatment step is long-term inotropic support. The second step includes an addition of a second inotrope, and the third step includes tracheal intubation, mechanical ventilation and long-term mechanical circulatory support. The decision making process related to escalation of support and a detailed discussion of the clinical and technical aspects of each treatment in the pediatric cardiac intensive care unit (PCICU) will be outlined below.

Heart Diseases Leading to ADHF

ADHF is commonly defined as a persistent low cardiac output state manifest by anaerobic metabolism in a child with ESHF. The two major diagnoses in pediatric heart transplant recipients are CHD and cardiomyopathy. CHD is the main diagnosis in infants whereas cardiomyopathy becomes the major diagnosis in all other age groups (1–10 years and 11–17 years).

Congenital Heart Disease

According to the 2010 ISHLT database [1], 62 % of infant (age: <1 year) HT recipients have CHD, 33 % of children between 1 and 10 years of age, and 25 % of children between 11 and 17 years of age. The indications for HT in neonates are ESHF or anatomical configurations that are not amenable for surgical palliation. These configurations include some variants of pulmonary atresia and intact septum with right ventricular (RV) dependent coronary circulation and hypoplastic left heart syndrome (HLHS) with aortic atresia and mitral stenosis and left ventricular (LV) dependent coronary circulation. The main causes of heart failure in children with CHD are: (1) excessive pulmonary blood flow and excessive left ventricular volume load, (2) critical aortic stenosis (ductal dependent systemic circulation), (3) myocardial ischemia related to anomalous left coronary artery arising from the pulmonary artery (ALCAPA), and (4) arrhythmias. Less commonly, delayed recognition and treatment of right, left or biventricular outflow tract obstruction might lead to severe and at times irreversible myocardial dysfunction.

Excessive Pulmonary Blood Flow

The physiology of children with excessive pulmonary blood flow can be biventricular, or univentricular with no restriction to either pulmonary or systemic blood flow. Acute decompensation of these children might be related to the natural progression of the disease, or to exacerbation related to an intercurrent illness. Children with excessive pulmonary blood flow tend to have a reactive pulmonary vascular bed. Pulmonary vascular resistance (PVR) may be elevated in these patients because of excessive pulmonary blood flow, worsening ventricular function leading to elevated left-ventricular end-diastolic pressure (LVEDP), pneumonia leading to hypoxic vasoconstriction, or a combination of the three.

Critical Aortic Stenosis

These patients have critical CHD with ductal dependent systemic circulation. Other left sided structures may be affected including the mitral valve, left ventricle, and aortic arch. Severe left ventricular dysfunction either at baseline or following a corrective or palliative operation may lead to ADHF. Elevated LVEDP may prevent physiological normalization of PVR as well.

Anomalous Left Coronary Artery Arising from the Pulmonary Artery (ALCAPA)

Heart failure in infancy in these children suggests inadequate collateral right coronary blood flow to the left ventricle. Unfortunately, the CPB corrective operation may lead to further worsening LV failure and ADHF.

Arrhythmias

Children with CHD may develop incessant supraventricular tachycardia (SVT) leading to HF. The most common underlying SVT mechanisms are reentry pathways and ectopic automatic foci. Available antiarrhythmic medications carry negative inotropic properties and can be proarrhythmogenic. Initiation of these medications can lead to ADHF in these children.

Dilated Cardiomyopathy

Cardiomyopathy was the second most common diagnosis leading to pediatric HT in the 2010 ISHLT database [1]. Moreover, dilated cardiomyopathy was the most common type of cardiomyopathy reported in this database and is also

the most common diagnosis that leads to HT in children and adolescents [2–4]. Many possible factors can lead to cardiac dilation and decreased systolic function including infectious, metabolic, ischemic, toxic, and hereditary factors [2]. A wide spectrum of clinical presentations is possible, ranging from fatigue and decreased exercise tolerance to cardiogenic shock. However, the clinical presentation is not reflective of outcome because even asymptomatic patients diagnosed incidentally can have a poor prognosis [5]. Underlying diagnosis of myocarditis on the other hand, is probably a positive prognostic factor for recovery, even in patients with ADHF [6]. According to the Pediatric Cardiomyopathy Registry [4] independent risk factors for death or the need for transplantation include age greater than 6 years at presentation, congestive heart failure at presentation, and lower LV shortening fraction. Underlying diagnosis of myocarditis was associated with a decreased risk of death and transplantation compared with idiopathic cardiomyopathy.

Pathophysiology of ADHF

Heart failure (HF) is a clinical syndrome that develops gradually in patients with underlying cardiomyopathy or acutely in response to an insult resulting in a decline in the pumping capacity of the heart. Severe global (systolic and diastolic) systemic ventricle dysfunction is the main cause of low cardiac output and pulmonary edema, setting up a vicious cycle due to the fact that pulmonary edema significantly increases the work of breathing. Moreover, in the context of ADHF, oxygen consumption (VO_2) by the respiratory muscles is supply dependent, such that the overall oxygen debt increases, leading to worsening lactic acidosis (Fig. 30.1).

Most patients with HF are in a compensated state. Their systemic ventricle end-diastolic pressure is chronically elevated, leading to increased PVR. The increased PVR is initially reactive. However, with time, the pulmonary vasculature undergoes pathological remodeling that may lead to a "fixed" elevation of PVR. This pathological remodeling is exacerbated in children with single ventricle physiology following completion of their palliative pathway, since the abnormal pulmonary blood flow pattern in these patients by itself may cause pulmonary vascular damage [7]. Myocardial dysfunction also leads to activation of compensatory neurohormonal mechanisms. These include the autonomic nervous system (ANS), the renin-angiotensin-aldosterone axis, and the cytokine system [8]. The ANS dysfunction is manifest by sympathetic nervous system activation (Fig. 30.2). This activation has implications for both disease progression and survival [10, 11]. In HF, the sympathoinhibitory cardiovascular reflexes such as the arterial baroreceptor reflex are significantly suppressed, whereas the sympathoexcitatory reflex, including the cardiac sympathetic afferent reflex and the arterial chemoreceptor reflex are augmented [12] (Fig. 30.3).

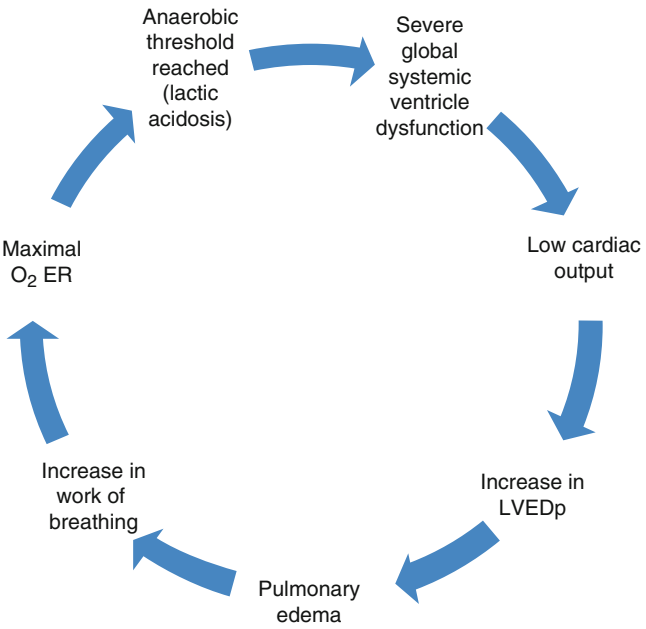


Fig. 30.1 Cyclic Pathophysiology of Acute Decompensated Heart Failure (ADHF). Severe global systolic and diastolic systemic ventricle dysfunction leads to an increase in left ventricle end diastolic pressure (LVEDp) and subsequent pulmonary edema. The decreased lung compliance causes increase in work of breathing. Normally, to meet the increased oxygen uptake by the respiratory muscles, cardiac output increases, however, in the context of ADHF, cardiac output is fixed and therefore, to maintain adequate oxygen uptake as oxygen delivery decreases, oxygen extraction ratio (O_2ER) increases. Once the O_2ER is maximal it becomes fixed, and further decreases in oxygen delivery will result in equivalent decreases in oxygen uptake. As aerobic metabolism begins to decrease, the oxidative production of high-energy phosphates declines, resulting in impaired cell function and eventual cell death

Assessment of ANS function in the context of HF requires utilization of two major measures: heart rate variability (HRV) and autonomic baroreceptor reflex (ABR). HRV is the name for a group of measures that are calculated from the intervals between normal heartbeats that are measured using a continuous ECG. Because the instantaneous magnitude of each interval is continuously regulated by the ANS, changes in HRV provide a surrogate for changing autonomic functioning. HRV has been validated in multiple adult post-myocardial infarction (MI) studies as an independent risk factor for sudden death [13–18]. The ABR regulates blood pressure through reflex changes in autonomic activity to maintain cardiac output and peripheral vascular resistance. The ABR relies on alterations of the combined influence of sympathetic and parasympathetic (vagal) nervous system activity on the heart, as well as modulation of sympathetic tone to peripheral vascular beds such as the heart, kidneys, and brain [19–21]. Therefore, study of the arterial baroreflex is ideally suited for characterizing cardiovascular autonomic reflex function.

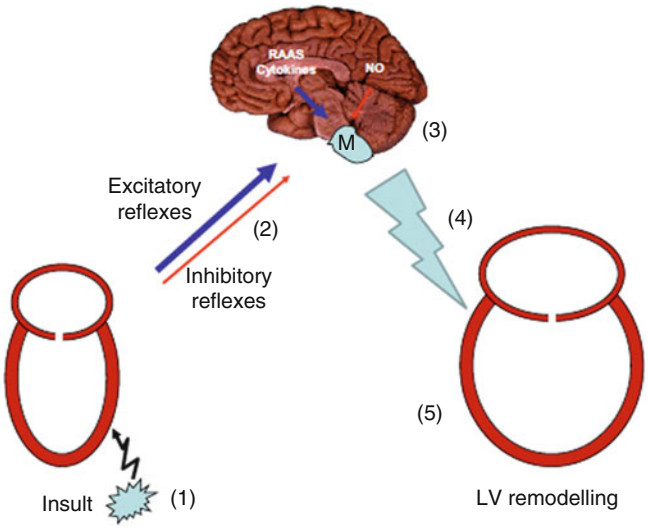


Fig. 30.2 Sympathetic Activation in Systolic Heart Failure. (*1*) An insult causes cardiac dysfunction and decreases cardiac output. (*2*) Attenuation of inhibitory sympathetic cardiovascular reflexes and augmentation of excitatory sympathetic cardiovascular reflexes is associated with increased sympathetic input in the central nervous system. (*3* and *4*) Central facilitation of the augmented cardiovascular sympathetic afferent reflex mediated by an increase in angiotensin II and cytokines and a decrease in nitric oxide (*NO*) contributes to tonic increases in sympathetic output. (*5*) The chronic increase in sympathetic output is associated with structural and functional changes in the cardiomyocytes and the interstitium leading to left ventricular (*LV*) dilation and systolic dysfunction (LV remodeling). *M* medulla, *RAAS* renin-angiotensin-aldosterone system (Reprinted from Triposkiadis et al. [9]. With permission from Elsevier)

Cardiac reflexes are important in the pathogenesis of cardiovascular disease. Early studies suggested that ABR dysfunction might contribute to the pathogenesis of hypertension [22]. Also, in animal models of heart disease, a reduced ABR gain is associated with an increased risk of ventricular fibrillation during a brief ischemic episode [23, 24], and coronary artery occlusion has been shown to attenuate the ABR control of heart rate both in anesthetized dogs and in humans [25, 26]. Reduced ABR sensitivity has also been shown to differentiate high-risk from low-risk patients recovering from myocardial infarction and heart failure [27]. A reduction in the gain of the ABR can therefore contribute to cardiovascular morbidity and mortality via a reduction in parasympathetic activity, an increase in sympathetic activity, or both.

Clinical Approach to ADHF

The clinical presentation differs somewhat in different age groups and different underlying diagnoses; however, the main features remain the same. Patients frequently present with irritability, inadequate enteral intake, emesis, decreased urine output, tachypnea and diaphoresis with exercise. Physical examination findings include various degrees of increased work of breathing, a gallop rhythm, hepatomegaly, and infrequently diminished pulses.

History and physical examination alone are suboptimal tools to assess compromised oxygen delivery before cardiogenic shock develops [28, 29]. The clinical signs of shock are usually obvious if the patient is allowed to progress to this state and consist of altered mental status, tachycardia, tachypnea, prolonged capillary refill, diminished peripheral pulses and oliguria. Unfortunately, irreversible end-organ dysfunction is likely to develop if the patient progresses to shock, and if that occurs, heart transplantation will no longer be possible.

Evaluation of children who present with ADHF should take into account their baseline cardiovascular status. The clinical approach would be different for newly diagnosed patients, patients with a known diagnosis of HF treated with oral anti congestive heart failure (CHF) medications, and patients treated with long-term inotropic support listed for HT. The most common etiologies for ADHF in newly diagnosed patients are unrecognized CHD, acute myocarditis, unrecognized cardiomyopathy, and protracted arrhythmias. Following initial resuscitation and stabilization, a 12-lead ECG and echocardiogram should be obtained. The need for more advanced diagnostic studies, such as a cardiac catheterization, electrophysiological study (EPS), computerized tomography (CT), and cardiovascular magnetic resonance imaging (MRI) will be determined by a multidisciplinary team comprising a heart failure specialist, cardiothoracic surgeon, and cardiac critical care physician. The underlying etiology for ADHF is a better predictor of prognosis than the severity of the clinical presentation. For example, a child with fulminant myocarditis who presents in cardiogenic shock and requires extracorporeal membranous oxygenation (ECMO) carries a better prognosis than a child with dilated cardiomyopathy of unknown etiology who requires inotropic support [30, 31], or a child with end-stage CHD.

Children with a known diagnosis of HF that present with ADHF requiring intravenous inotropic support require escalation of their United Network of Organ Sharing (UNOS) status (assuming that they are already listed for HT), as well as re-evaluation of end-organ function and transpulmonary gradient. Indeed, 72 % of patients followed by the Pediatric Heart Transplant Study Group (PHTS) between 1993 and 2005 were UNOS status 1 (heart failure requiring intravenous inotropes) [32].

Advanced Hemodynamic Monitoring of Patients with ADHF

Hemodynamic and oxygen transport balance monitoring serve as an early warning system for pending shock. Multiple invasive and noninvasive hemodynamic monitoring devices are commercially available. A Pediatric Cardiac Intensive

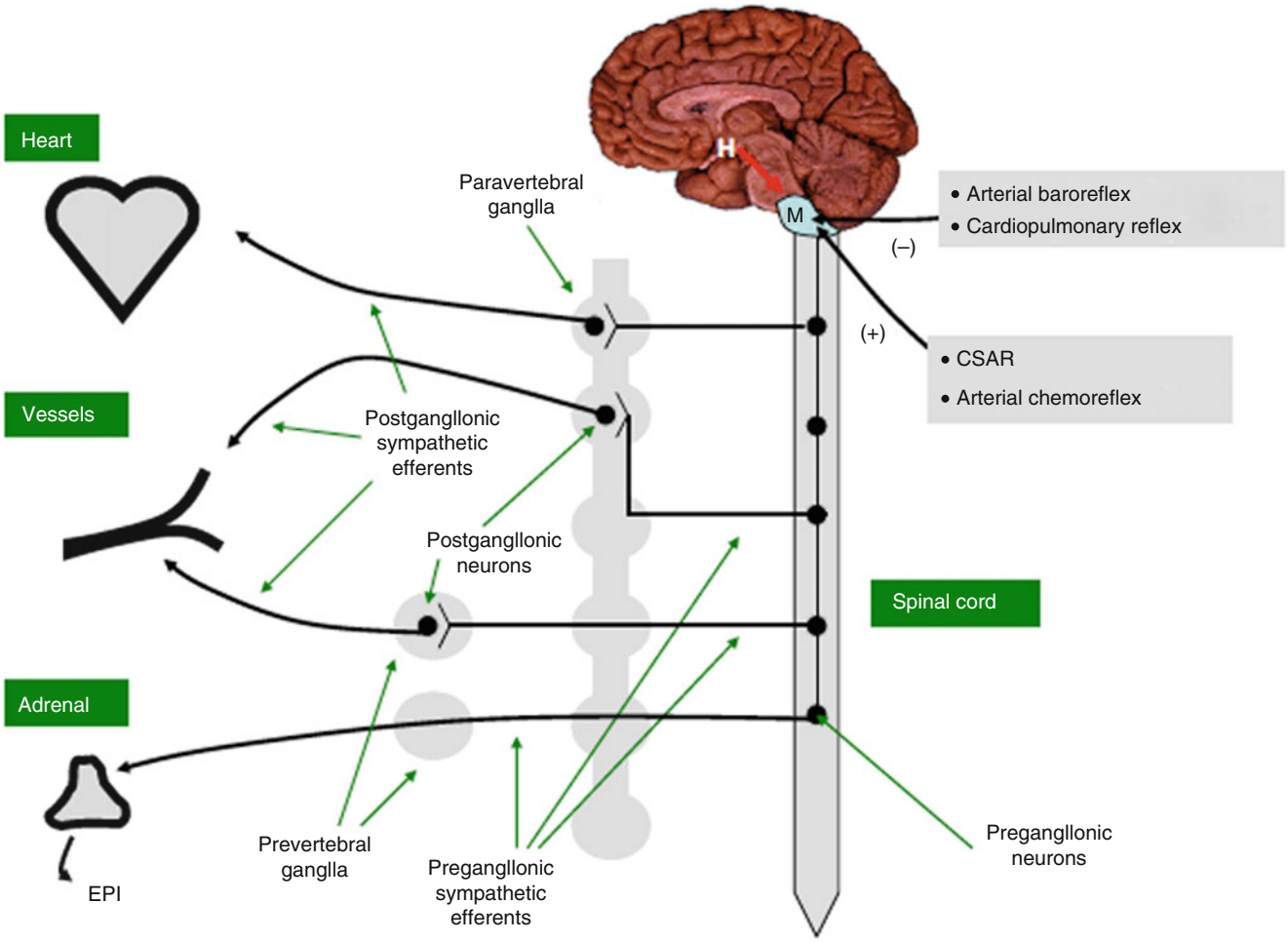


Fig. 30.3 The sympathetic nervous system. The most important level of integration of sympathetic nervous system efferent activities to the cardiovascular system resides in the dorsolateral reticular formation of the medulla. The hypothalamus modifies the activity of the medullary centers and is important in stimulating cardiovascular responses to emotion and stress. Sympathetic activity is attenuated (–) by the arterial baroreflex and the cardiopulmonary reflex and increased (+) by the cardiac sympathetic afferent reflex (CSAR) and the arterial chemoreceptor reflex. The arterial baroreflex manifests as a decrease in vagal tone in response to a decrease in blood pressure. The CSAR refers to a reflex increase in sympathetic activity of the heart in response to chemical mediators such as bradykinin, capsaicin etc., or by direct stimulation of sympathetic nerve endings. The chemoreceptor reflex is an increase in sympathetic activity in response to hypoxia and/or hypercarbia elicited through the peripheral chemoreceptors of the carotid body and the central chemoreceptors of the brain stem. *EPI* epinephrine, *H* hypothalamus, *M* medulla

Care Society evidence-based review and consensus statement on monitoring of hemodynamics and oxygen transport balance was recently published and can serve as a thorough information source [33]. The scope of this discussion is limited to the more established monitoring techniques, including the pulmonary artery catheter (PAC), pulse contour analysis and continuous CO monitor (PiCCO), near infrared spectroscopy (NIRS), central and mixed venous saturation, lactate, and B-type natriuretic peptide (BNP).

PAC

Swan and colleagues introduced the PAC in 1970 [34], and over the last 40 years, the PAC has provided valuable hemodynamic data in critically ill children. The appropriately placed PAC provides directly measured right cardiac pressures, pulmonary artery occlusion pressure (PAOP), optical measurement of mixed venous saturation, and thermodilution measurement of flow (i.e., cardiac output). The combination of these measurements and the mean arterial blood pressure measured by an arterial catheter allows calculation of pulmonary and systemic vascular resistances. The PAOP is equivalent to the left ventricular end-diastolic pressure, assuming that there is no downstream obstruction from the pulmonary arterial tree to the left ventricular cavity. These data are extremely valuable in patients with ADHF whose systemic oxygen delivery depends on a fine balance between cardiac output, systemic vascular resistance, and LV diastolic function. The data allow harmonization of

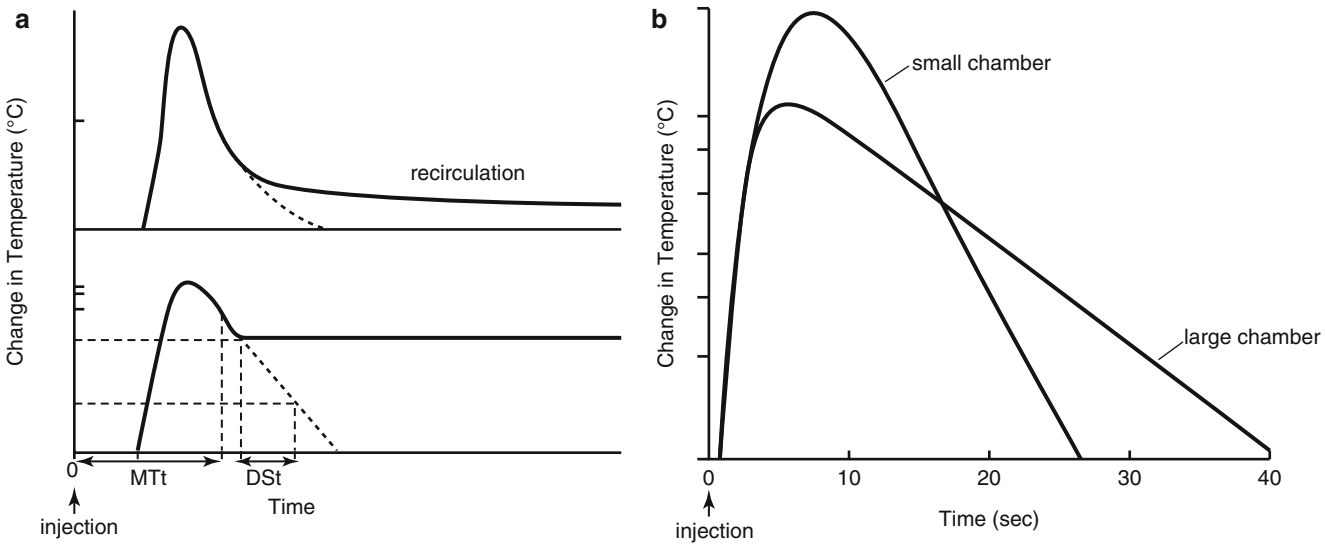


Fig. 30.4 Transpulmonary thermodilution technique. (**a**) Diagrammatic representation of temperature-time *curve* during a thermodilution measurement, plotted on linear-linear (*top*) and log-linear scales (*bottom*). The *dotted lines* in each case represent what the curve would have looked like in the absence of recirculation of the thermal indicator. Note that the decay of the thermal curve becomes linear when graphed on the semi-log scale (*bottom*). Also shown are typical points used to measure the mean transit time (*MTt*) and the downslope time (*DSt*). (**b**) Diagrammatic representation of temperature-time curves, obtained during a thermodilution measurement, graphed on a semi-log scale, from the large and small mixing chambers. Note that the curve from the smaller chamber reaches a peak sooner and decays sooner than that obtained from the large chamber. Thus, if the 2 chambers were in series, the downslope of the thermodilution curve obtained at a point distal to the 2 chambers would be dominated by the larger chamber (Reprinted from Isakow and Schuster [47]. With permission from the American Physiological Society)

inotropic support, vasodilators, and positive pressure ventilation to achieve optimal oxygen delivery.

PiCCO

The PiCCO, unlike the PAC utilizes a standard central venous catheter, as well as a proprietary thermistor-tipped arterial catheter to perform transpulmonary thermodilution measurements. To compensate for inter-individual differences in compliance and resistance of the arterial vessel system and to track changes of these variables as a result of changing clinical conditions, manual calibrations are necessary. The temperature-time curves obtained during transpulmonary thermodilution measurements are broader and lower in magnitude than when obtained via a PAC. Thus these measurements are more vulnerable to errors caused by baseline drift and miscorrections for indicator recirculation. On the other hand, and for the same reason, the transpulmonary technique is less vulnerable to errors caused by respiratory variation in blood temperature.

A high degree of correlation between thermodilution measurements of CO using a PAC (CO_{pa}) or an arterial catheter (CO_{tp}) has been established in multiple experimental and clinical settings, including cardiac surgery patients, intensive care patients, septic patients, and burn victims [35–43]. However, Bein et al., in a more recent work, observed large differences between the arterial wave form-based CO and reference methods during hemorrhage, shock, and vasodilatation [44]. It has become more and more evident that frequent recalibration is necessary in these patients to obtain reasonable accuracy [45]. In children, comparisons of measurements of CO_{tp} and calculations based on the Fick principle were highly correlated as well [28, 46]. Indicator dilution methods (including thermodilution) can be used not only to measure flow but also to measure the volume through which flow is measured. The distribution volume for the indicator is the product of the CO multiplied by the mean transit time for the indicator (Fig. 30.4). A detailed discussion of the measurements of intrathoracic thermal volumes can be found elsewhere [47].

PiCCO measures both static and dynamic hemodynamic variables. Based on recent studies it appears that changes in the PiCCO's global end-diastolic volume index (GEDVI), a static variable derived from thermal measurement of intrathoracic blood volume (ITBV), has better correlation with cardiac index (CI) and stroke volume index (SVI) than central venous pressure (CVP) or PAOP [48]. However, other studies show that neither GEDVI, nor CVP/PAOP predict patient response to fluid resuscitation. On the other hand, dynamic PiCCO variables as the pulse pressure variability and stroke volume variability have better correlation with fluid responsiveness. Unfortunately, adequate assessment of these dynamic variables is possible only in deeply sedated

and mechanically ventilated patients whose tidal volume is greater than 8 mL/kg ideal body weight [49]. The PiCCO method may give incorrect thermodilution measurements in patients with intracardiac shunts, aortic aneurysm, aortic stenosis, pneumonectomy, macro lung embolism and extracorporeal circulation (if blood is either extracted from or infused back into the cardiopulmonary circulation). It is therefore of limited use in the perioperative care of children with complex congenital heart defects, but may be useful in children with normal segmental anatomy who present with decompensated heart failure or in the postoperative care of children after heart transplantation.

NIRS

In children with CHD, obtaining vascular access is challenging because of previous thrombosis. Clot formation in central veins and arteries is caused by sheaths placed in the cardiac catheterization laboratory (CCL) and central venous catheters placed either in the operating room (OR) or the CICU. Therefore, using noninvasive hemodynamic monitoring devices is very appealing in the pediatric patient population. Regional NIRS monitoring is becoming an integral part in the care of the pediatric cardiac surgery patient as well as the care of children with ADHF. The NIRS probe provides continuous measurement of oxyhemoglobin in venous weighted vascular beds. Multisite NIRS monitoring includes the cerebral, mesenteric, and renal vascular beds. It is commonly used as a surrogate for systemic oxygen delivery and consumption in the OR, CCL, and CICU. Studies over the course of the last decade showed that NIRS has a favorable risk-benefit profile and can be effective and beneficial as a hemodynamic monitor for the care of critically patients [50, 51]. Dynamic NIRS measurements in critically ill patients monitored by tissue rather than regional NIRS device provide another layer of information and possibly earlier warning prior to the development of shock. Ischemia and reperfusion tissue oxygenation slopes (Fig. 30.5) obtained by inflation/deflation of a blood pressure cuff above the probe reflect tissue oxygenation reserve and flow respectively [52].

Biomarkers

Biochemical markers of perfusion and myocardial stress are used to support decision-making in children with ADHF. Central or mixed venous saturation, lactate, and BNP are used extensively and provide vital information on the relationship between oxygen delivery and oxygen consumption as well as response to interventions. Central or mixed venous saturation might provide warning prior to evolution of shock; however, elevated lactate levels reflect an ongoing anaerobic state. BNP is used as a baseline marker of heart failure, and its level following various therapeutic interventions might reflect the effectiveness of these interventions [53–55].

Care of the Pediatric ADHF Patient

Escalation of support in UNOS status 1 patients should be performed in a step-wise fashion, depending on their cardiopulmonary status and oxygen delivery. The first is long-term single agent inotropic support. Different inotropes can be used as first-line support including milrinone, dobutamine, and dopamine. Milrinone is long acting and functions as an inotrope, lusitrope, and vasodilator [56]. The long half-life of milrinone is beneficial since interruption of the infusion will not cause immediate hemodynamic changes. However, the longer half-life might be problematic if immediate discontinuation of this medication is required because of malignant arrhythmias and/or hypotension. Another important consideration is renal function [57]. Since the kidneys clear milrinone, renal dysfunction (which is common in patients with ADHF) might lead to increased serum concentration of milrinone and hypotension. Accurate assessment of renal clearance is mandatory in patients with ADHF to determine their eligibility for HT and will help to determine the optimal milrinone dose. Dobutamine and dopamine are short acting. Dobutamine provides inotropy and vasodilation, whereas dopamine provides mainly inotropy and at higher doses vasoconstriction. Interruption of these inotropes might cause acute hemodynamic changes because of their short half-lives. On the other hand, their titration is easier. Close hemodynamic monitoring in the CICU is recommended during initiation of inotropic support because of possible development of tachycardia and increased systemic and myocardial oxygen consumption, malignant arrhythmias, hypertension or hypotension.

All intravenous inotropes and inodilators currently used in the United States to treat ADHF operate through either cAMP or cGMP to increase intracellular calcium levels, possibly leading to myocardial cell death and/or increased rates of lethal arrhythmias [58]. They all improve the patient's hemodynamic profile, but none has produced consistent improvement in symptoms or exercise tolerance, and many have shortened survival [59–61]. Several new agents for ADHF currently in clinical trials have mechanisms of action that do not involve the adenylate cyclase or guanylate cyclase pathway. These agents target neurohormones, ion channels, and contractile proteins. Levosimendan currently is being used in 38 countries and is undergoing phase 3 clinical studies in the United States and Europe [62, 63]. This agent has a dual mechanism of action: it enhances calcium myofilament

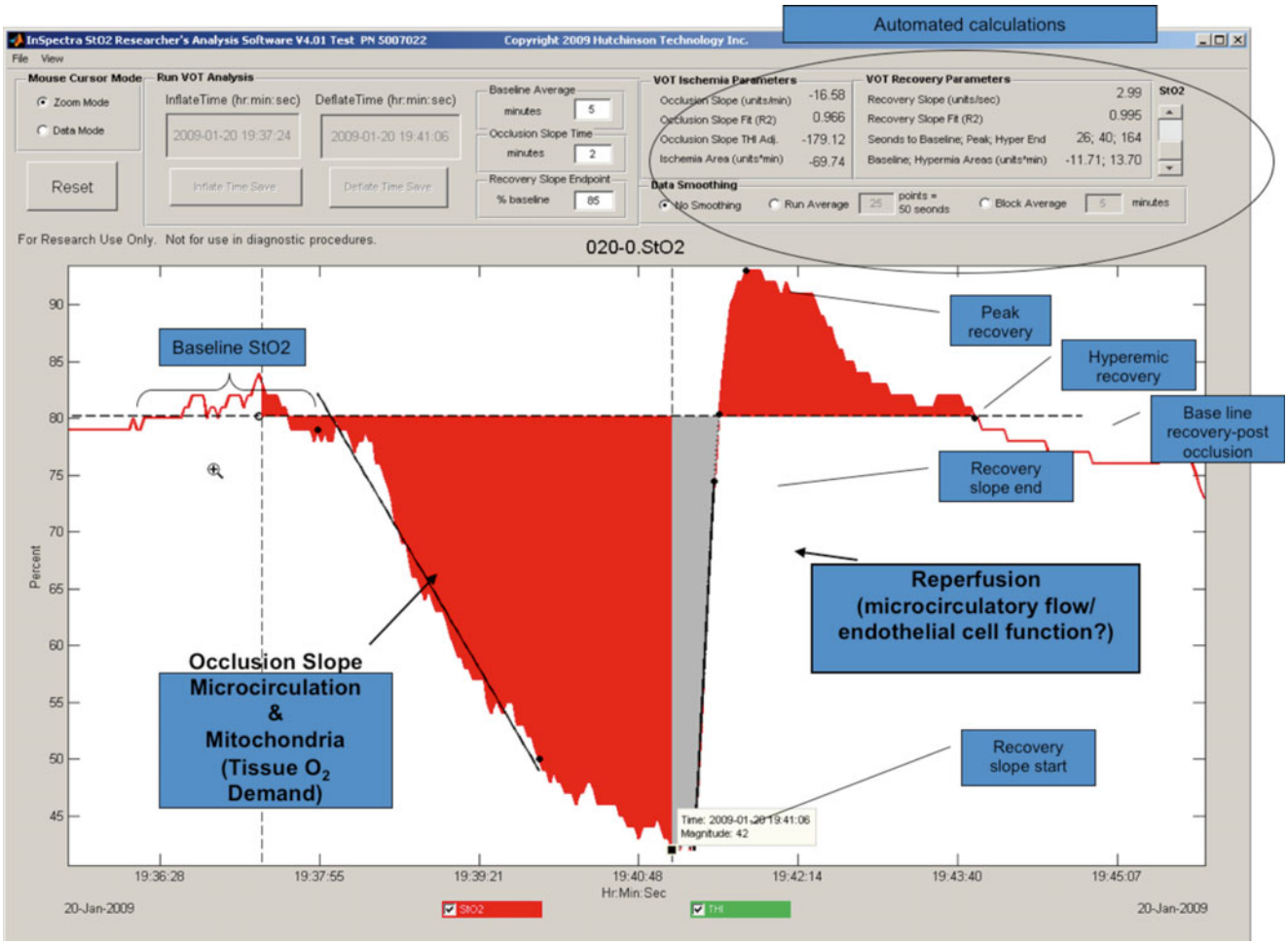


Fig. 30.5 Vascular occlusion test (*VOT*) derived tissue oxygen saturation (StO_2) phases and parameters. By inducing an artificial ischemic stress, emergent parameters of StO_2 are used to assess local oxygen uptake and delivery. These parameters serve as surrogates for systemic perfusion. Baseline parameters are established after the probe is placed on the thenar eminence of one hand. Blood pressure cuff is inflated to create arterial occlusion. This represents the beginning of ischemic phase. The arterial occlusion is maintained until a decay of 40 % below baseline StO_2 is seen. The ischemic slope represents the rate of tissue oxygen uptake. The cuff is then rapidly deflated, with corresponding increase in StO_2. The slope so obtained is referred to as the reperfusion slope. An over shoot of StO_2 above base line is seen after release of blood pressure cuff and referred to as the hyperemic phase of the VOT

responsiveness by binding to cardiac troponin C, thereby increasing contraction, and opens adenosine triphosphate–sensitive potassium channels in myocytes and vascular smooth muscle cells, promoting vasodilation [64]. Several clinical studies have indicated that levosimendan may reduce mortality compared with current therapy for AHFS [65–67]. Tezosentan, an intravenous endothelin-A and -B antagonist, has been studied in a series of ADHF clinical trials [68]. It has a high affinity and specificity for both endothelin receptors. Tolvaptan is a V_2-selective vasopressin receptor antagonist undergoing phase 3 clinical trials. It has been shown to increase urine output in patients with AHFS and to increase serum sodium with minimal sodium loss [69, 70]. Although the incidence of worsening heart failure was not affected by tolvaptan, post hoc analyses revealed that tolvaptan tended to reduce mortality in patients with renal dysfunction, and it significantly reduced mortality in patients with severe systemic congestion [70].

Regardless of the inotrope selected, safe administration requires placement of a stable central venous catheter. A peripherally inserted central catheter is preferred, as placement can be easily performed at the bedside and without general anesthesia. Evidence of inadequate systemic perfusion while supported with one IV inotrope requires escalation of care.

Escalation of care to the second treatment step requires transfer to the ICU for initiation of a second inotrope, since the combination of two inotropes increases the risk of malignant arrhythmias and increased systemic and myocardial oxygen consumption. Placement of an arterial line, application of advanced hemodynamic monitoring techniques such as NIRS and PiCCO, and obtaining lactate and central

venous saturation levels allow optimization of oxygen delivery. Another option prior to initiation of a second inotrope is treatment with nesiritide. Nesiritide is a recombinant B-type natriuretic peptide that acts by increasing cyclic guanosine monophosphate (cGMP), with the primary effect of causing vasodilation and a resultant decrease in left ventricular end-diastolic pressure. It is approved by the US Food and Drug Administration as a therapeutic agent for treating patients who have ADHF and dyspnea at rest or with minimal activity. Unfortunately, data related to the use of nesiritide in children with ADHF are minimal [71–73]. An association between nesiritide treatment and renal failure, as well as decreased survival at 30 days compared with conventional anti–congestive heart failure medications [74, 75], was reported, but has not been corroborated by large-scale prospective studies.

The clinical response to initiation of a second inotrope is a critical branching point. One possible outcome is stable improvement in systemic perfusion, as manifest by normalization of the oxygen extraction ratio either by regional or tissue NIRS saturations or by direct central venous co-oximetry, and improved end-organ function (resolving irritability, improved appetite, better urine output, etc.). This new plateau is considered a new stable baseline and allows de-intensification of monitoring and even transfer to a step-down patient floor. The second possible outcome is further deterioration of systemic perfusion as manifest by increasing regional and/or central oxygen extraction ratio. This is an ominous sign and requires escalation of support.

The initial third step intervention is endotracheal intubation and initiation of positive pressure ventilation. The assumption at this point is that oxygen extraction ratio is critical or close to critical and therefore, a trial of non-invasive positive pressure ventilation might tip the balance between oxygen delivery and consumption, since the work of breathing would remain significant. Based on the Law of LaPlace, the ventricular wall tension is directly proportional to the ventricular transmural pressure. The transmural pressure is determined by the difference between the intra-ventricular pressure and the pleural pressure with normal resting pleural pressure being zero. Pulmonary edema caused by elevated left-ventricular end-diastolic pressure leads to increased work of breathing and markedly negative pleural pressure. This pathologic state results in significantly increased ventricular wall tension and hence ventricular afterload. Application of positive pressure ventilation results in positive pleural pressure, which leads to decreased ventricular wall tension and reduced ventricular afterload. Another significant benefit of mechanical ventilation that cannot be achieved with non-invasive means is marked reduction in oxygen uptake by the accessory respiratory muscles and reduced overall oxygen consumption.

Tracheal intubation should be performed in a timely fashion to avoid end-organ dysfunction. It is an extremely risky procedure in patients with end-stage heart failure and should be performed by experienced individuals. These patients rely on circulating endogenous catecholamines to maintain oxygen delivery. An acute decrease in the endogenous catecholamine level with induction and neuromuscular blockade can lead to acute hemodynamic compromise, manifest by hypotension and bradycardia and result in cardiovascular collapse. In order to reduce the risk of decompensation, induction should be performed with medications that have minimal anxiolytic effect and minimal direct effect on the determinants of cardiac output.

The pulmonary pathophysiology of patients with end-stage heart failure is mainly related to long-standing elevation of left ventricular end-diastolic pressure, causing pulmonary vascular congestion and pulmonary vascular remodeling. The goal of mechanical ventilation in these patients is to minimize work of breathing, optimize oxygenation and ventilation, and avoid mechanical pulmonary injury, oxygen toxicity, and compromised cardiac output.

In patients awaiting cardiac transplantation treated with intravenous inotropic agents and mechanical ventilation whose clinical status continues to deteriorate, mechanical circulatory support should be considered to prevent end-organ compromise. A recent report by Blume et al. [76] documented favorable outcome in children supported by long-term ventricular assist devices (VAD). The report utilized the Pediatric Heart Transplant Study (PHTS) database to analyze outcomes in children listed for heart transplantation between 1993 and 2003 placed on VAD support. In the current era (2000–2003), 86 % of the VAD supported patients underwent successful heart transplantation. Survival to transplant was significantly poorer in patients with congenital heart disease and in smaller, younger patients. This report demonstrated that posttransplantation survival for VAD supported children was not significantly different from that of other status 1 patients who did not require mechanical circulatory support and was significantly superior to status 1 patients supported with ECMO.

In the United States, the only US Food and Drug Administration (FDA)-approved VAD currently designed for use in children is the DeBakey VAD Child (MicroMed Technology Inc., Houston, TX), but its approval is limited to children aged older than 5 years and with a body surface area (BSA) greater than 0.7 m^2 [77]. The DeBakey VAD is able to support the left ventricle effectively but has not been widely applied due to thromboembolic issues. Thus, ECMO remains the predominant technology for mechanically bridging neonates, infants, and children to cardiac transplantation. ECMO has substantial associated morbidity and mortality, particularly if the duration of support extends beyond 2 weeks [78]. To address the lack of mechanical circulatory support for

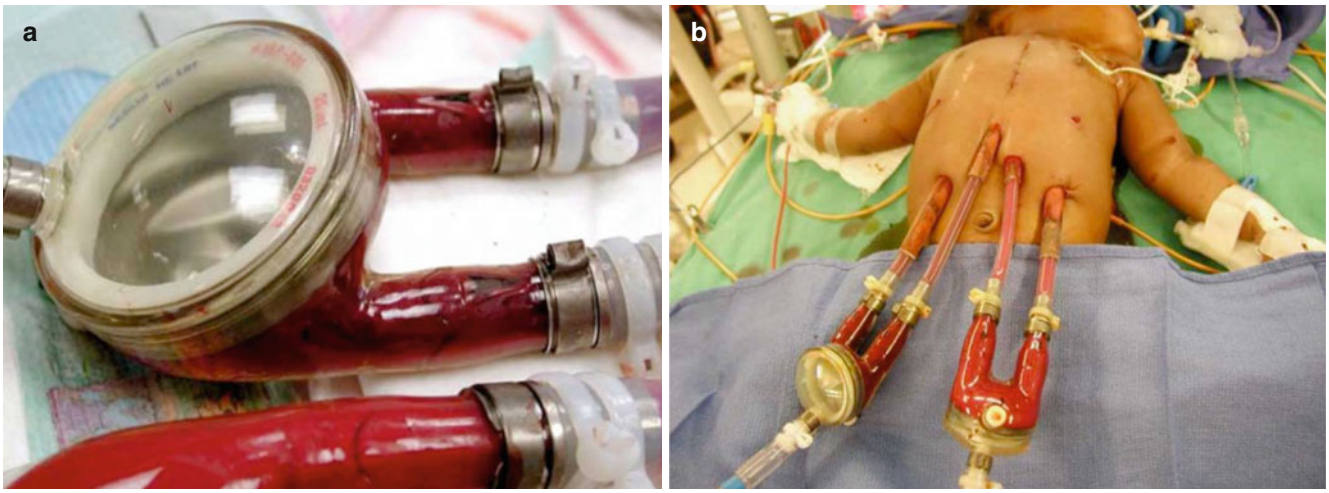


Fig. 30.6 The Berlin Heart VAD (Berlin Heart AG, Berlin, Germany) consists of a paracorporeal, pneumatically driven pump (**a**). The pump is made of a translucent, semirigid housing of polyurethane divided into a blood chamber and an air chamber by a three layer flexible diaphragm. Cannulae are designed in various configurations to allow biventricular support for all age groups. They are made of silicone rubber with a smooth internal surface. The outside of the cannulae is covered with a Dacron (C. R. Bard, Haverhill, Pennsylvania) velour surface at the contact site with the abdominal wall to encourage scar tissue ingrowth, thereby minimize ascending infections (**b**)

neonates and infants awaiting cardiac transplantation, a pneumatically driven pediatric-specific VAD, the EXCOR, was developed in Germany by Berlin Heart GmBH. This long-term pulsatile device can serve either as a univentricular or a biventricular VAD for children between 3 kg and adult sizes (Fig. 30.6). Berlin Heart Inc. applied for an investigational device exemption (IDE) trial in North America, which was approved and started in May 2007 for children from 3 kg to a BSA of 1.5 m^2. Before approval, the device was implanted in 97 patients in North America under compassionate use regulations. The pre-IDE data (June 2000–May 2007) were collected and analyzed by Morales et al. [79]. Seventy-three patients from 17 institutions were included in the study. Their median age and weight at device implant were 2.1 years (range, 12 days to 17.8 years) and 11 kg (range, 3–87.6 kg), respectively. Their primary diagnoses were dilated cardiomyopathy in 42, congenital heart disease in 19, myocarditis in 7, and other cardiomyopathies in 5. More than 50 % of the children were in cardiogenic shock with survival expected to be less than 24 h, and 48 % were in progressive decline with worsening end-organ function despite the use of inotropic and ventilatory therapy. In addition, approximately 33 % of patients were already supported with ECMO at the time EXCOR support was initiated. Device selection was left VAD (LVAD) in 42 (57 %) and biventricular assist devices (BiVAD) in 31 (43 %). The EXCOR bridged 51 patients (70 %) to transplant and 5 (7 %) to recovery. Mortality on the EXCOR was 23 % (n = 17) overall, including 35 % (11 of 31) in BiVAD versus 14 % (6 of 42) in LVAD patients (P = 0.003). Multi-variate 434 Pediatric and Congenital Heart Disease analysis showed younger age and BiVAD support were significant risk factors for death while on the EXCOR. Overall, these data suggest that the Berlin Heart is suitable for mechanical support of small children awaiting heart transplantation.

Conclusion

Care of the pediatric ADHF patient requires a step-wise multi-disciplinary approach in a medical center that provides specialized pediatric heart failure service, state of the art cardiac imaging, invasive cardiology, pediatric cardiac surgery, and pediatric cardiac intensive care. An in depth understanding of heart failure pathophysiology is required to make timely management decisions. The team's main objective is to avoid development of end-organ failure by timely escalation of cardiopulmonary support. The emphasis is on timing, and timing depends on early detection of inadequate oxygen delivery by state of the art hemodynamic monitoring and readily available expertise and equipment to provide specialized care.

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Diseases of the Pericardium

31

Katja M. Gist and Derek S. Wheeler

Abstract

Pericarditis, pericardial effusion, and cardiac tamponade are conditions that affect the pericardium in either isolation or association with systemic disease. The clinical presentation of these diseases are classic and should be easily recognized. Pericardiocentesis can be diagnostic and therapeutic (and potentially life-saving).

Keywords

Pericarditis • Pericardial effusion • Cardiac tamponade • Pulsus paradoxus • Pericardiocentesis

Introduction

The pericardium is composed of two layers, the visceral pericardium and the parietal pericardium. The visceral pericardium is in direct contact with the myocardium, while the parietal pericardium is composed of several layers of elastic and collagen fibers and is separated from the visceral pericardium by a small amount of fluid. The potential space created by the visceral and parietal pericardium is lubricated by lymph and normally contains <30 mL of fluid in an adult, and much less in infants and children [1]. The neurovascular bundles and lymphatic supply are located beneath the visceral pericardium and surround the parietal pericardium. The pericardium encloses the great arteries superiorly at the junction between the ascending aorta and the transverse aortic arch, the pulmonary artery just beyond its bifurcation, and the superior vena cava below the azygous vein. The inferior pericardial attachment includes a segment of the inferior vena cava and the posterior attachment includes the proximal pulmonary veins.

Illnesses affecting the pericardium can be categorized into four general categories, but all occur along a spectrum (Fig. 31.1) [2]. The vast majority of cases are subclinical. Pericarditis is a nonspecific term denoting inflammation of the pericardium that is usually associated with clinical signs and symptoms, usually not resulting in a medical emergency. Pericardial effusion describes a condition, in which there is more than a normal quantity of fluid in the pericardial space. The clinical presentation, as well as the need for intervention are dependent upon the rate at which fluid accumulates in the pericardial space. Cardiac tamponade is a true medical emergency requiring immediate attention secondary to impaired venous return and consequential impaired ventricular filling during diastole and decreased cardiac output. Constrictive pericarditis is characterized by a thickened and adherent pericardium that restricts filling of the ventricles, and is the endpoint of acute or chronic pericardial inflammation.

The innervation of the pericardium is via the vagus and phrenic nerves, as well as the sympathetic nerve fibers. Because of this innervation, pericardial inflammation may produce severe pain and trigger vagally mediated reflexes.

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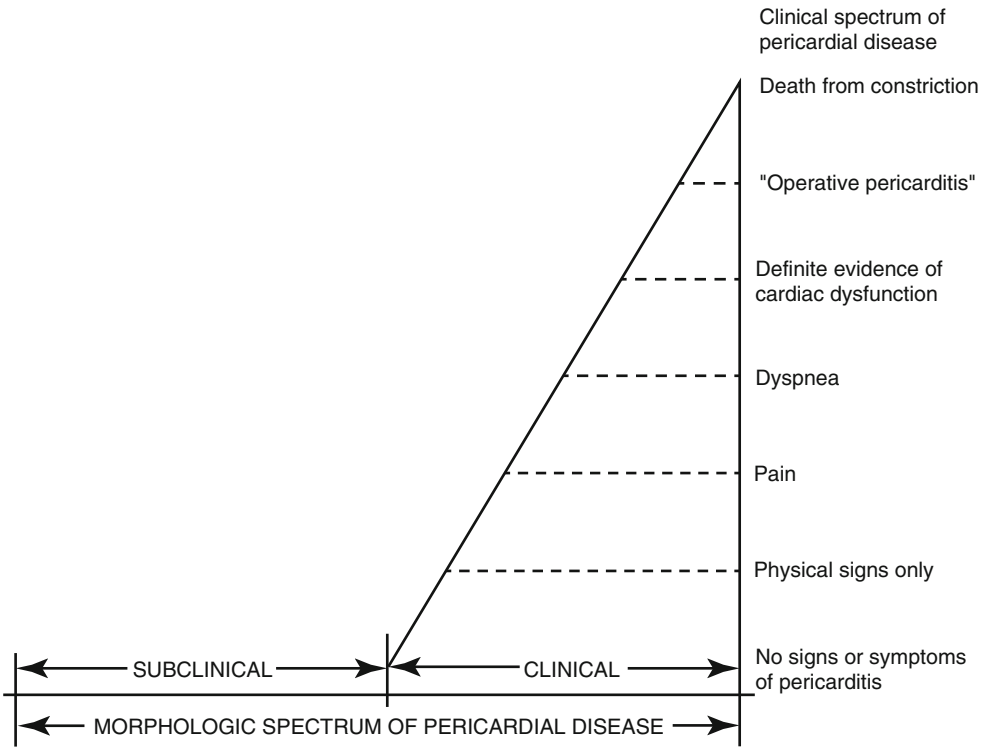


Fig. 31.1 Spectrum of pericardial heart disease. Pericardial disease is more often subclinical than clinical. The most severe form of clinical disease is pericardial constriction that can result in death (Reprinted from Roberts [2]. With permission from Baylor Proceedings)

As a result, the most common manifestation of pericarditis is a sharp, retrosternal chest pain. Because of the attachments of the pericardium, pain is usually worse during inspiration and in the supine position, and is relieved by sitting forward in the "tripod" position. Pain may be referred to the scapular region when there is accompanying irritation of the phrenic nerves that pass adjacent to the pericardium [3].

Pericarditis

Etiology

The etiology of pericarditis in children is variable and is summarized in Table 31.1. When considering the cause of pericardial disease or other systemic diseases in which the pericardium is involved, it is important to remember that the pericardium is not only adjacent to the heart, but it is in continuity with the surrounding intrathoracic structures. Thus, any inflammatory condition or process in which the heart, pleura, mediastinal structures, or the diaphragm are involved, may affect the pericardium as well. Although the course is often self-limiting, pericarditis can be complicated by a pericardial effusion, pericardial constriction or recurrent pericarditis [4]. These complications increase both morbidity and mortality.

Viral Pericarditis: Infectious diseases are the most common etiologic source of pericarditis in childhood. Causes of pericarditis are reported to be idiopathic in 40–86 % of cases [5]. The majority of these idiopathic cases are considered to

Table 31.1 Causes of diseases of the pericardium

Infectious
Bacterial
Viral
Fungal
Parasitic
Tuberculous
Idiopathic
Noninfectious/Inflammatory
Acute rheumatic fever
Systemic lupus erythematous
Juvenile idiopathic arthritis
Uremia
Kawasaki disease
Drug-induced
Traumatic
Postpericardiotomy syndrome
Chest wall injury (blunt or penetrating)
Foreign body contact with the heart
Oncologic
Leukemia
Lymphoma
Radiation pericarditis
Blood dyscrasias
Other
Hypothyroidism
Chylopericardium
Intrapericardial and cardiac tumors
Chronic
Constrictive pericarditis
Subacute effusive pericarditis

be viral in etiology despite, no confirmatory diagnosis (for which pericardial fluid is required). In recent years, advances in polymerase chain reaction (PCR) technology have helped to increase the yield of confirmatory etiologies, particularly for Coxsackie (group B) and other enteroviruses [2, 5–9]. Other viruses traditionally thought to play a role include adenovirus, influenza, Ebstein-Barr virus, rubella, mumps, HIV, and CMV. Importantly, cardiac tamponade physiology is less commonly associated with a viral etiology of pericarditis. Viral causes can be presumed if a patient has had a recent upper respiratory tract infection, with response to anti-inflammatory treatments and no recurrence.

Bacterial Pericarditis: Bacterial pericarditis, otherwise known as purulent pericarditis, comprises about 5 % of cases of pericarditis [7]. Bacteria can infect the pericardium by hematogenous spread or via direct extension from adjacent structures, mainly the lungs [4]. Onset of symptoms and disease progression are typically rapid and fatal if left undiagnosed. Prior to the widespread use of immunizations and antibiotics, *Streptococcus pneumoniae* was the most commonly identified organism [10]. Currently, *Staphylococcus aureus* is the most common cause of purulent pericarditis [10] and is often associated with concomitant distal sites of infection including osteomyelitis. Other bacterial culprits include, but are not limited to *Neiserria meningiditis* and *Hemophilus influenzae*. Since the advent of routine immunizations for *H. influenzae* in the developed world, non-typeable *H. influenzae* is responsible for invasive disease, including purulent pericarditis [11], and is most often preceded by an upper respiratory tract infection.

Meningococcal disease accounts for 6–16 % of all cases of purulent pericarditis [12], with Serotype Y being the most commonly reported. Similar to other bacteria, direct hematogenous seeding is the most common mechanism of infection. However, additional mechanisms include an immune mediated reaction or isolated meningococcal pericarditis. Reactive meningococcal pericarditis is thought to be an immunologic mediated reaction that occurs in the convalescent period. Tamponade physiology is common, but the pericardial fluid is typically sterile [12]. Isolated meningococcal pericarditis occurs commonly in young patients and should be considered in a patient with presumed viral or idiopathic pericarditis that does not respond to conventional therapy [12].

Mycobacterium tuberculosis accounts for approximately 4 % of cases of purulent pericarditis and 7 % of cases of cardiac tamponade [4]. The HIV epidemic in underdeveloped countries has contributed to the increased number of cases of tuberculosis and tuberculosis associated pericarditis [13]. Unfortunately, tuberculous pericarditis is associated with a high incidence of constrictive pericarditis secondary to calcification of the pericardium, and a high morbidity and mortality [13].

Post-pericardiotomy Syndrome: Post-pericardiotomy syndrome is a frequent cause of noninfectious pericarditis in children following cardiac surgery. The constellation of findings includes symptoms consistent with pericardial inflammation or effusion, fever, leukocytosis, and elevated inflammatory markers (erythrocyte sedimentation rate and C-reactive protein) [14–16]. The onset of the syndrome most commonly occurs 1–4 weeks following cardiac surgery, and the disease is typically limited to patients who have had the pericardium opened, occurring at a frequency of 10–40 % [14, 15]. However, there are reported cases of pericardial effusion and post-pericardiotomy syndrome occurring following transvenous pacemaker implantation, pulmonary artery banding, palliative shunt procedures (Blalock-Taussig shunt) and heart transplantation [17, 18]. In addition, cases have been reported to occur earlier than 1 week following the procedure [17].

Other forms of pericarditis: Less common forms of noninfectious pericardial inflammation include those occurring in association with collagen vascular and oncologic diseases, particularly lymphomas of the mediastinum. Pericardial inflammation may also occur in patients following radiation therapy. Certain endocrinologic disorders such as hypothyroidism may also be an underlying cause. Rheumatic fever and Kawasaki disease remain other important inflammatory diseases with pericardial involvement as one of the cardiovascular manifestations. Finally, blunt or penetrating chest wall injury may also lead to pericarditis or a more severe effusion with or without tamponade. Blunt chest trauma is the major risk of motor vehicle accidents, with the deceleration force leading to myocardial contusion and intrapericardial hemorrhage, cardiac rupture or pericardial rupture [19].

Clinical Presentation and Diagnosis

As described previously, the innervation and attachments of the pericardium are such that pericarditis will often present with chest pain that typically increases with inspiration. While chest pain is a common complaint in children, it is uncommon for pericarditis to be the etiology. Common associated symptoms in children include cough, dyspnea, abdominal pain, vomiting and fever [20]. No specific clinical feature is used to differentiate the various causes, and the diagnosis of pericarditis is based primarily on history with an antecedent respiratory tract infection being commonly reported. In the presence of a large effusion or restriction to filling, signs and symptoms of congestive heart failure may be evident. These include tachycardia, tachypnea, pallor, hepatomegaly and cool extremities. The tachycardia occurs as a compensatory mechanism for augmentation of cardiac output, the tachypnea is a result of pulmonary venous congestion due to increased pulmonary venous pressure from decreased cardiac output, and the hepatomegaly is a consequence of increased right heart pressures [20].

Cardiac auscultation findings are dependent upon the degree of fluid accumulation in the pericardium. The pericardial friction rub is pathognomonic for pericarditis and

is described as a scratching sound heard throughout the cardiac cycle. It is best heard at the left lower sternal border during expiration and with the patient leaning forward [7]. The friction rub is usually absent when there is a moderate to large amount of fluid in the pericardial space. Quiet or muffled heart sounds and a weakened apical impulse are common when there is substantial fluid accumulation. These findings, in association with the symptoms previously described, should alert the clinician to the possibility of cardiac tamponade [18]. The hallmark bedside finding in cardiac tamponade is pulsus paradoxus (see below). The finding of a paradoxical pulse greater than 10–15 mmHg is direct evidence of restrictive cardiac filling and cardiac compromise.

Management

As previously discussed, pericarditis most commonly has a benign clinical course and typically responds well to treatment despite lack of cause. Further investigation with invasive testing is warranted if the cause is complicated by tamponade or failure to respond to non-steroidal anti-inflammatory drugs (NSAIDs) within 1 week or with recurrence. Children with a pericardial effusion should be closely monitored for the development of pulsus paradoxus. If this develops, these children typically require close monitoring in an intensive care unit setting.

A recent international collaborative systematic review on the treatment of pericarditis reported that NSAIDs (ibuprofen, aspirin, indomethacin or naproxen) appear satisfactory for the treatment of pericarditis, with duration of use of 1 to several weeks [21]. The use of corticosteroids for the treatment of pericarditis has resulted in conflicting reports of benefit [21]. Steroids are associated with a high rate of side effects, and their use should only be considered in refractory pericarditis [21]. Steroids have however been reported as being successful for the treatment of tuberculous pericarditis in patients with HIV. Hakim et al. demonstrated decreased morbidity and mortality in this patient population [13]. Several other agents have been studied in adults and have been reported as successful for the treatment of pericarditis, with no data for use in young children. Colchicine, an anti-inflammatory agent (blocking effects on tuberculin, mitosis and white blood cell function) and statins (HMG-CoA reductase inhibitors that have pleotropic anti-inflammatory effects) have been used with success in the treatment of recurrent pericarditis [22–24]. Colchicine has been reported to be effective for the treatment of pericarditis in the adolescent age group [25].

Pericardiocentesis is an invasive procedure that is both diagnostic and therapeutic. Indications for pericardiocentesis include tamponade, concern for purulent pericarditis and concern for malignancy. It is not routinely performed for diagnostic purposes alone [4]. The fluid should be evaluated for gram stain, cell count and culture (bacterial, viral and PCR for infectious pathogens). Purulent hypercellular effusion is typically associated with bacterial pericarditis, fibrous/serofibrous effusion with lymphocyte predominance is viral, and fibrous/serofibrous is commonly immune-reactive. Hemorrhagic effusion is associated with trauma, tuberculosis or malignancy [4]. If purulent pericarditis is suspected, prompt drainage and initiation of antibiotic therapy is indicated. Table 31.2 summarizes the management of patients with purulent pericarditis. Intra-pericardial administration of streptokinase has been reported to allow for improved catheter drainage without requirement for surgical drainage in a small group of patients with purulent pericarditis [26–28]. Open drainage procedures may need to be considered in order to prevent the long-term sequelae of constrictive pericarditis and myocardial compromise [29]. Thompson et al. reported their experience on a subset of patients requiring pericardiectomy for either inflammatory or constrictive pericarditis and suggest that early referral for pericardiectomy should be considered in patients with refractory disease and continued symptoms. They describe two approaches for the removal of the pericardium. A complete pericardiectomy from a median sternotomy approach is

Table 31.2 Management of purulent pericarditis

1.	Ensure adequate ventilation and cardiac output
2.	Administer oxygen
3.	Provide cardiorespiratory monitoring
4.	Obtain laboratory studies (simultaneous with step 5)
	Complete blood count (including platelets)
	Electrolytes and glucose
	Blood urea nitrogen and creatinine
	Arterial blood gas
	Blood culture
	CXR
	ECG
	Echo
5.	Establish venous access
6.	Perform pericardiocentesis (with ultrasound guidance) and send specimen for:
	Culture (bacterial, viral, tuberculous)
	Gram stain, cell count and cytology
	Viral titers
	Antinuclear antibody
	Chemical profile
7.	Administer antibiotics:
	Broad spectrum directed toward S. Aureus and H. influenza
	Should include a penicillinase-resistant penicillin and third generation cephalosporin
	In regions with a high incidence of methicillin-resistant staphylococci, vancomycin should be used
	Once culture and sensitivity results are known, specific intravenous antibiotic therapy should continue for 3–4 weeks

considered for inflammatory pericarditis in order to remove the pericardium from around the right atrium in addition to the ventricles. This is to prevent a further nidus for future relapses. Constrictive pericarditis is approached from a left thoracotomy, in which the pericardium from both ventricles is removed in order to improve hemodynamics [22–24]. Outcomes following these procedures were excellent with decreased morbidity and mortality [4].

While the underlying condition certainly influences outcome, in most young patients pericardial disease resolves without long-term sequelae. However, the outcome is not entirely predictable from the initial presentation and the results of early management. Thus serial assessment even after resolution of the initial process is an important component of effective management.

Cardiac Tamponade

Pathophysiology

In addition to protecting and restraining the heart, the normally non-compliant pericardium is an important determinant of cardiac filling patterns. The normal pericardial constraint limits chamber dilation, particularly of the thin walled right atrium and right ventricle, and also equalizes compliance between the right and left ventricles. The thicker walled left ventricle produces interdependence of filling between the ventricles that is usually of little importance. However, when the intra-pericardial pressure is increased or the pericardial cavity size becomes fixed (with associated constriction), ventricular interdependence is exaggerated [4, 18].

The pericardium exhibits an exponential stress–strain relationship. Physiological changes in circulating pericardial volume produce minimal changes in intra-pericardial pressure. With an abrupt or large increase in intravascular volume that exceeds the pericardial reserve volume, the pericardium exerts a constraint to filling [3]. Intrapericardial pressure is similar to pleural pressure (−6 mmHg at end inspiration and −3 mmHg at end expiration). Under normal conditions, lowering of pericardial pressure in inspiration raises transmural pressures in the right atrium and ventricle, leading to increased filling of the right heart, whereas left heart output is decreased slightly because of the aortic transmural pressures and delayed pulmonary transit.

In the presence of acutely accumulating pericardial fluid, a small amount (typically less than 200 mL) is sufficient to produce cardiac tamponade. This is due to the non-compliant pericardium. However, chronic accumulation of fluid may occur with little to no hemodynamic derangements as the pericardium slowly stretches to accommodate the excess volume. Tamponade is therefore determined by

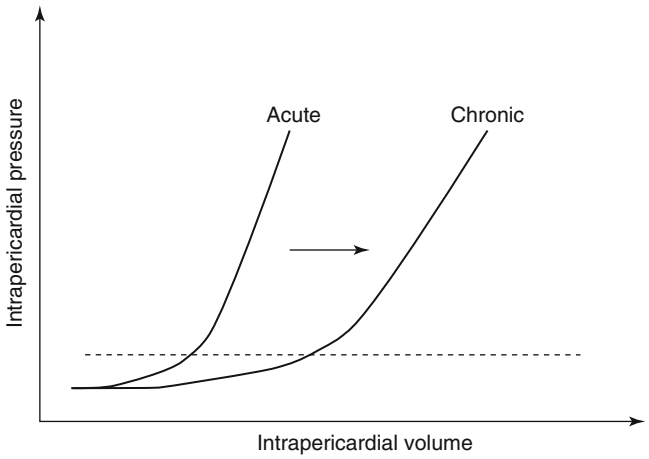


Fig. 31.2 Pericardial compliance curves, acute (*left*) and chronic (*right*) accumulation of pericardial fluid. The rapid accumulation of pericardial fluid is compensated at first by expansion of the pericardium. However, once a critical threshold is attained (*dotted line*), there is a rapid, steep increase in intra-pericardial pressure for a given increase in pericardial volume, at which time signs and symptoms of cardiac tamponade are observed. The slow accumulation of fluid allows passive stretch of the pericardium, such that the increase in intra-pericardial pressure is less significant for any given increase in pericardial volume

the compliance of the pericardium (Fig. 31.2). As pericardial fluid accumulates acutely, the pericardial tissue stretches to accommodate the additional volume, such that the increase in intra-pericardial pressure for a given increase in intra-pericardial volume is small (flat portion of the compliance curve). However, once a certain threshold is attained, a small change in intra-pericardial volume results in a steep increase in intra-pericardial pressure (J-shaped compliance curve). Conversely, a slow increase (over days to weeks) in intra-pericardial volume is compensated, as the compliance curve is shifted to the right and the slope of the compliance curve flattens. Therefore, the rise in intra-pericardial pressure for a given change in volume is much less. The therapeutic implications of an acute versus chronic pericardial fluid accumulation are also important. For example, removal of even a small volume of pericardial fluid from an acute effusion or hemopericardium will decrease the intra-pericardial pressure significantly and relieve symptoms of cardiac tamponade. Conversely, due to the change in compliance curves, a large volume of pericardial fluid from a symptomatic, chronic effusion will need to be removed to attain comparable relief of tamponade.

Cardiac tamponade is produced by compression of the heart by accumulation of pericardial fluid beyond a certain threshold (i.e., the steep, J-shaped portion of the pericardial compliance curve). The true filling pressure of the heart is represented by the myocardial transmural pressure (i.e., intracardiac pressure minus intra-pericardial pressure).

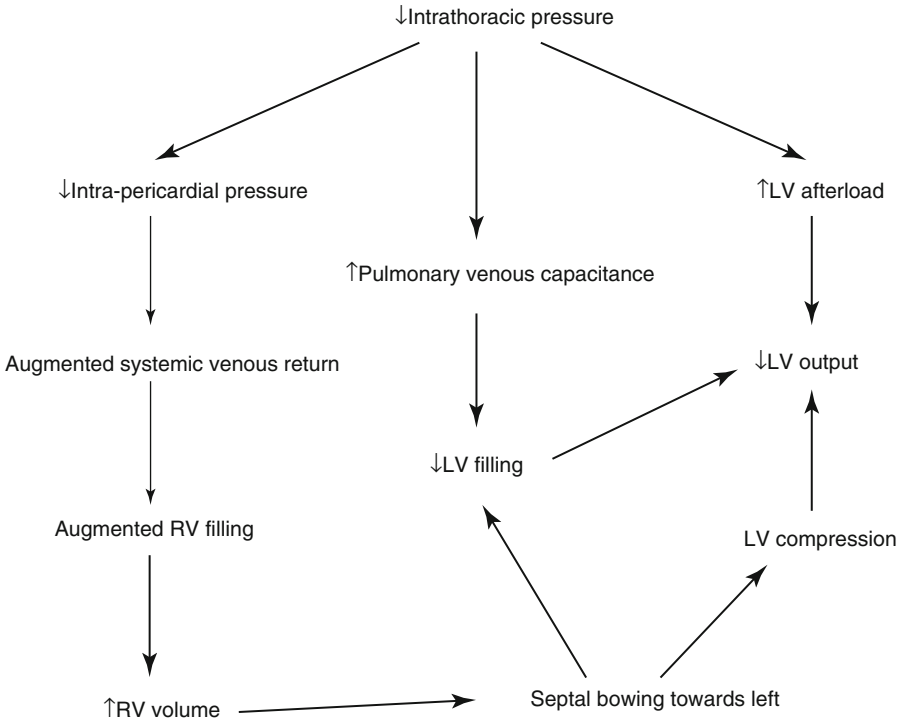


Fig. 31.3 Flow diagram demonstrating the mechanism of pulsus paradoxus

Therefore, as intra-pericardial pressure rises, the filling pressure of the heart decreases and stroke volume falls. The body attempts to compensate for the increase in intra-pericardial pressure (and hence transmural pressure) by increasing systemic central venous pressure and pulmonary venous pressure, so that the left and right ventricular filling pressures are higher than the intra-pericardial pressure. Left atrial and right atrial pressures increase and equilibrate with the rising intra-pericardial pressure – this equalization of pressures is the hallmark of cardiac tamponade [29, 30]. Despite the subsequent fall in stroke volume, cardiac output is, at least temporarily, preserved due to the body's compensatory mechanisms.

Clinical Presentation and Diagnosis

Initial signs and symptoms of cardiac tamponade are readily identified in older children and include tachycardia, tachypnea, and hypotension. However, in neonates and infants, tachycardia may be the only presenting sign. Becks triad of hypotension, distended neck veins and muffled heart tones is pathognomonic for cardiac tamponade and was first described in 1935 [31]. Pulsus paradoxus is a key diagnostic finding in cardiac tamponade, and is highly specific for a pericardial effusion [32]. There are however several clinical situations in which pulsus paradoxus can be present. These include forceful respiratory efforts, status asthmaticus, tension pneumothorax, profound shock, pulmonary embolism and restrictive cardiomyopathy [33]. Cardiac tamponade can also exist in the absence of pulsus paradoxus, including scenarios of extreme hypotension, hypovolemia and pericardial adhesions from prior cardiac surgery [18, 33]. The latter can lead to a highly localized compression of the heart called regional cardiac tamponade [18]. Aortic regurgitation with or without ventricular dysfunction will dampen respiratory variations in blood flow and pressure, and children with elevated right heart pressures from pulmonary hypertension or right ventricular hypertrophy will also have dampened respiratory variation in blood flow and pressure.

Pulsus paradoxus is defined as a greater than 10 mmHg inspiratory decrease in systolic blood pressure [9]. It was first described by Kussmaul in 1873 in relation to "adhesive mediastino-pericarditis" [34]. Kussmaul described these changes as paradoxic because he was unable to palpate a radial pulse during inspiration despite a palpable heartbeat. Gauchat and Katz further described the pulsus paradoxus as a rhythmic pulse occurring in natural breathing, which shows a waxing and waning in size during respiration, evident on palpation in all accessible arteries in 1924 [35]. The mechanism of pulsus paradoxus relies on the fact that right heart filling is favored during inspiration, while left heart filling is favored during expiration as previously described (Fig. 31.3). Under normal cardiac physiologic conditions, there is a small, less than 10 mmHg, decrease in systolic blood pressure with inspiration. During normal inspiration, negative intrathoracic pressure (relative to atmospheric pressure) causes an increase in systemic venous return. However, there is an even greater increase in the pulmonary vascular capacitance such that there is a decrease in filling of the left ventricle. Concurrently, diaphragmatic excursion exhibits a traction effect on the

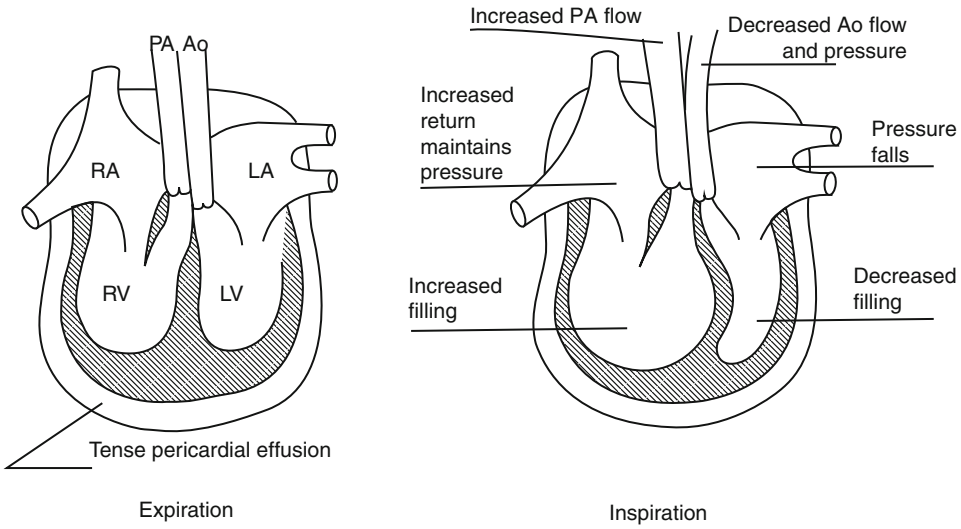


Fig. 31.4 Line diagram demonstrating the effect of inspiration in the setting of pericardial effusion. During inspiration (*right*), right heart filling is enhanced at the expense of systemic output, which is diminished secondary to a decrease in left atrial pressure and left ventricular filling. *RA* right atrium, *RV* right ventricle, *PA* pulmonary artery, *LA* left atrium, *LV* left ventricle (Reprinted from Darsee and Braunwald [36].With permission from Elsevier)

heart, limiting filling and ejection. Hence, left-sided cardiac output is decreased, resulting in a normal decrease in systolic blood pressure during inspiration (less than 10 mmHg under normal conditions). Finally, under normal conditions, intrathoracic pressure and intra-pericardial pressure vary almost equally during the respiratory cycle. However, in cardiac tamponade physiology, intra-pericardial pressures remain elevated relative to intrathoracic pressure. As right ventricular filling is augmented during inspiration, intra-pericardial pressure increases further and compresses the left ventricle via ventricular interdependence, thereby accentuating the fall in cardiac output during inspiration (Fig. 31.4).

Pulsus paradoxus may be measured non-invasively using a standard blood pressure cuff or invasively using an indwelling arterial catheter. For example, non-invasive measurement for detection of pulsus paradoxus starts with establishing the baseline blood pressure, and then repeating the blood pressure measurement by inflating the sphygmomanometer cuff several mm Hg above the baseline systolic blood pressure followed by slow deflation of the cuff. As the pressure falls, the Korotkoff sounds disappear with each inspiration. At the point at which they cease to disappear, becoming equal to that auscultated during expiration, the measured blood pressure is recorded. The pulsus paradoxus is the difference between the initial maximum systolic blood pressure and this final measurement. Tamburro et al. and Amoozagar et al. described the use of the pulse oximetry waveform as a non-invasive measure of the pulsus paradoxus in children with large pericardial effusions in the intensive care unit and in those following cardiac surgery respectively, and demonstrated that it was an effective method of detecting pulsus paradoxus (Figs. 31.5, 31.6) [37, 38]. Central venous pressure monitoring can provide useful data in patients with tamponade physiology. The waveform

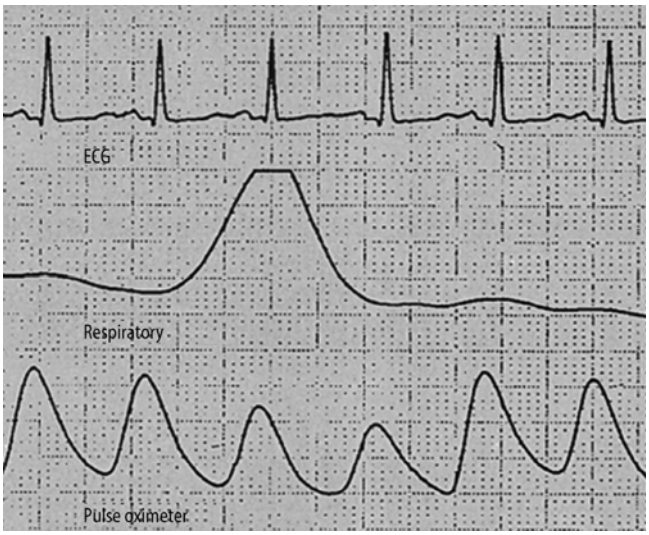


Fig. 31.5 Simultaneous tracings of ECG and respiratory and pulse-oximetry waveforms during a single respiratory cycle. The highest value of the upper plethysmographic peak of the pulse-oximetry waveform falls dramatically with inspiration (Reprinted from Tamburro et al. [37]. With permission from American Academy of Pediatrics)

is characterized by a rapid X descent, and a blunted Y descent because of the inability of the heart to fill during diastole (Fig. 31.7) [39].

Serum laboratory evaluation is not typically necessary in the presence of a large pericardial effusion or tamponade, and does not typically add diagnostic utility. Cardiac troponin levels have been demonstrated to be elevated in patients with pericarditis, reflecting injury to the underlying myocardium. However, they cannot be used to reliably distinguish myocardial disease from pericardial disease [40, 41].

Electrocardiogram (ECG), chest x-ray (CXR) and echocardiogram (echo) are useful in the diagnosis of pericarditis,

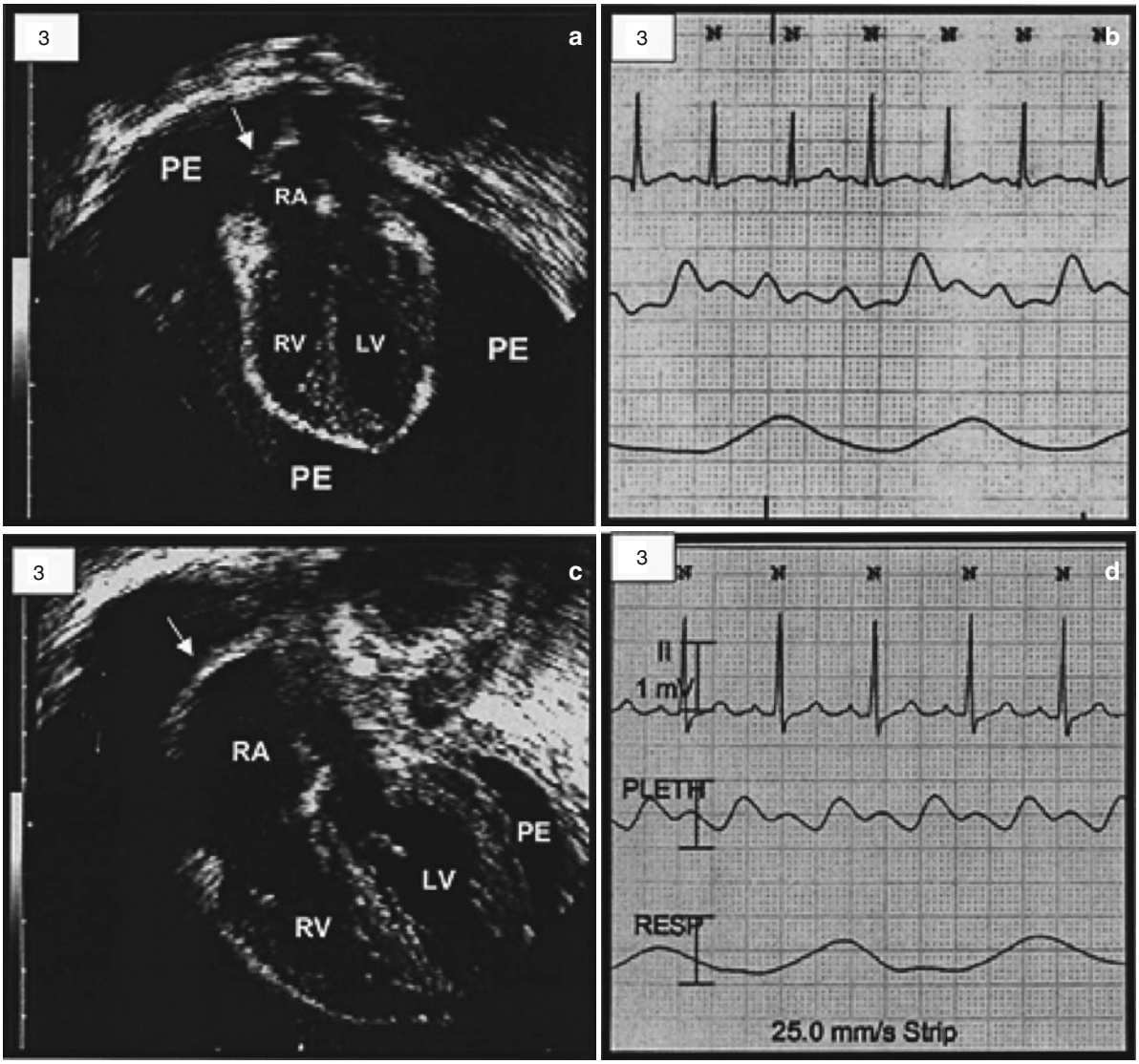


Fig. 31.6 Echocardiographic findings and associated pulse-oximetry waveform findings. (**a**) Echocardiogram before pericardiocentesis. PE designates the large circumferential pericardial effusion. The *arrow* demonstrates considerable flattening of the right atrial (*RA*) wall during diastole, a sign of compromised cardiac filling (*RV* right ventricle, *LV* left ventricle). (**b**) Simultaneous ECG, pulse-oximetry, and respiratory tracings demonstrate a marked decrease in the highest value of the upper plethysmographic peak of the pulse-oximetry waveform upon inspiration before pericardiocentesis. (**c**) Echocardiogram after pericardiocentesis. The circumferential pericardial effusion (*PE*), although still present, is smaller. The right atrial wall (*arrow*) remains convex during diastole, indicating reexpansion of this chamber after the procedure. (**d**) Simultaneous tracings document that the highest value of the upper plethysmographic peak of the pulse-oximetry waveform (PLETH) is well-maintained on inspiration after the procedure (Reprinted from Tamburro et al. [37]. With permission from American Academy of Pediatrics)

pericardial effusion and tamponade. Additional imaging such as cardiac magnetic resonance imaging (cMRI) and computed tomography (CT) are useful in chronic disease. Most patients with acute pericardial disease do not require an extensive work-up to determine the exact cause because the clinical course is most often benign and self-limited [42]. ECG is abnormal in 90 % of patients with pericardial disease and changes occur in stages as the disease progresses [4]. While sinus tachycardia is a common finding, it is non-specific. Low-voltage QRS complexes or electrical alternans (Fig. 31.8) are more specific for cardiac tamponade [44, 45]. The most classic ECG findings for pericarditis are

described in four stages. Stage 1 occurs within hours to days and is characterized by diffuse ST segment elevation in leads I, II, III, aVL, aVF, and pericardial leads V2–V6 (Fig. 31.9). In addition, the PR interval decreases in most leads. Stage II occurs within days to weeks, and is characterized by normalization of the ST and PR segments, with flattening or inversion of the T waves. Stage III is considered to be chronic, with normalization of the ECG, but the possibility of continued T wave inversion (likely from superficial myocardial injury). Stage IV is characterized by normalization of T wave inversion [4, 7, 46, 47]. Chest X-ray is often normal in pericarditis. The presence of calcifications suggests constriction [4]. A large quantity if fluid needs to be present in order to cause the characteristic boot-shaped heart [4] (Fig. 31.10).

Echocardiogram is the diagnostic modality of choice for presence of a pericardial effusion. The echocardiogram is typically normal in isolated pericarditis. The earliest sign of hemodynamic impairment by echocardiogram is right heart chamber compression; specifically collapse of the right ventricular free wall during diastole [48, 49] (Fig. 31.11). With a large effusion, a swinging motion of the heart within the pericardial cavity may be seen, as well as abnormalities of septal motion (Fig. 31.12). Dilation of the inferior vena cava (IVC) is seen, as well as loss of inspiratory compression of the IVC. Doppler echocardiography often demonstrates inspiratory decrease in transmitral flow in the presence of cardiac tamponade. With inspiration, the mitral E wave decreases by greater than 30 % as compared to expiration (Fig. 31.13). Transtricuspid flow in tamponade demonstrates an E wave that is increased by greater than 70 % in inspiration. Similar findings are seen with Doppler flow across the aortic and pulmonary valve [50].

CT and cMRI are used as adjunctive modalities when the echo is inconclusive or nondiagostic. cMRI has the ability to characterize fluid and facilitate the diagnosis (pericarditis vs. constrictive pericarditis vs. restrictive cardiomyopathy) (Fig. 31.14). Both imaging modalities may also delineate important structures and invasion of the pericardial space in the presence of mediastinal tumors or other cardiac tumors [51].

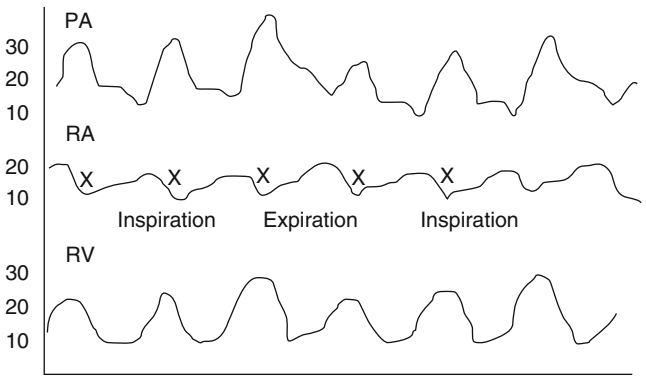


Fig. 31.7 CVP tracing in a child with cardiac tamponade showing equalization of RA, PA diastolic and RV diastolic pressures at 15 mmHg. Also note that there is marked attenuation of the *y* descent on the RA tracing

Management

Pericardiocentesis is the lifesaving procedure of choice for children with cardiac tamponade. Medical stabilization



Fig. 31.8 Electrical alternans. Alternation of QRS complexes, usually in a 2:1 ratio, on electrocardiogram findings is called electrical alternans. This is due to movement of the heart in the pericardial space (Reprinted from Lau et al. [43]. With permission from Texas Heart Institute. Copyright 2002 by the Texas Heart Institute, Houston)

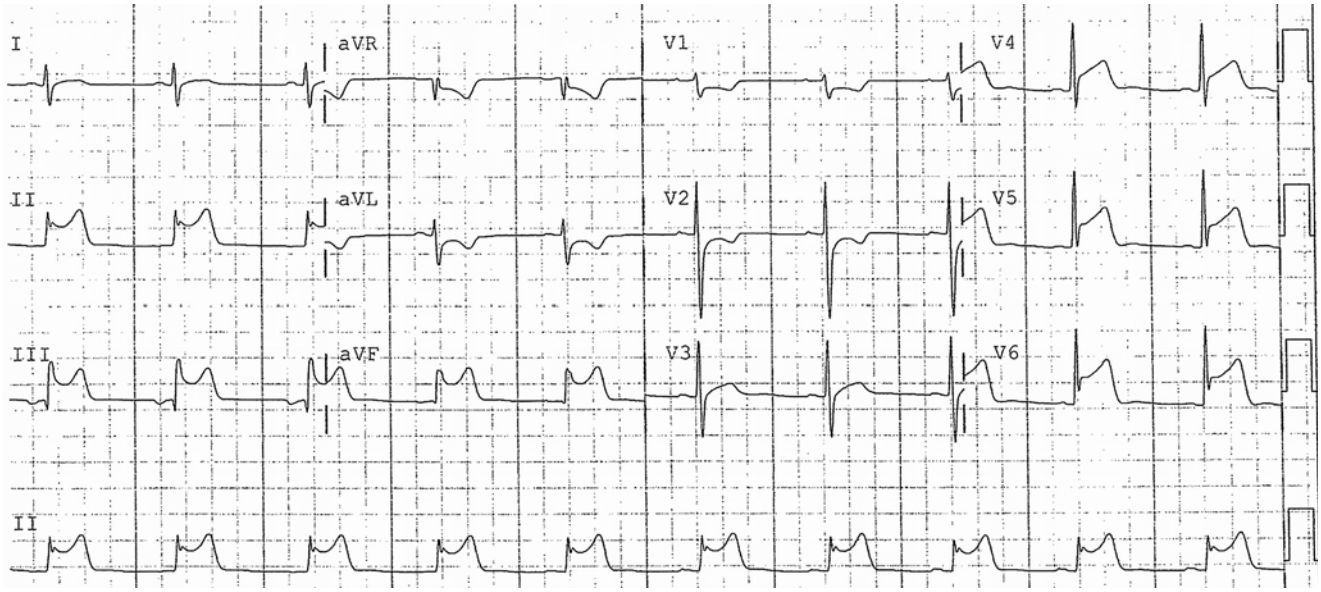


Fig. 31.9 ECG demonstrating diffuse ST segment elevation

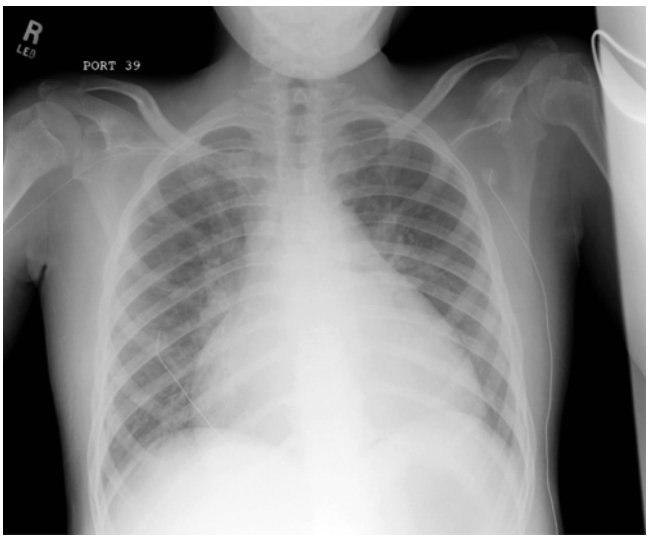


Fig. 31.10 Chest radiograph demonstrating that classic findings of cardiomegaly in the absence of pulmonary edema (*water bottle-shaped heart*) in a child with a pericardial effusion

with fluid resuscitation and inotropic support is controversial and temporary at best. However, fluid resuscitation may precipitate (i.e., in the case of low-pressure tamponade) or worsen tamponade physiology, especially in children who are either normovolemic or hypervolemic. In the latter scenario, fluid administration will increase intracardiac pressures further, hence increasing intrapericardial pressures and worsening tamponade [52–54]. Sagristà-Sauleda et al. demonstrated in their study that volume expansion resulted in a small rise in arterial pressure and index, but an increase in intrapericardial pressure, right atrial pressure and left ventricular end-diastolic pressure. Despite this, none of the patients reported increased dyspnea or other signs/symptoms of increased pulmonary edema [55]. They concluded that volume expansion should be considered in patients with cardiac tamponade as a temporary emergency measure while stabilizing for pericardiocentesis [55]. Animal studies suggest that naloxone counteracts the hypotensive effects of cardiac tamponade, though the use of this therapeutic modality in the clinical setting has not been attempted [56]. Mechanical ventilatory support may worsen tamponade physiology, though if unavoidable (e.g., cardiac tamponade in the post-operative setting), excessive swings in intrathoracic pressure with high airway pressures are best avoided [18]. Chest compressions in this setting

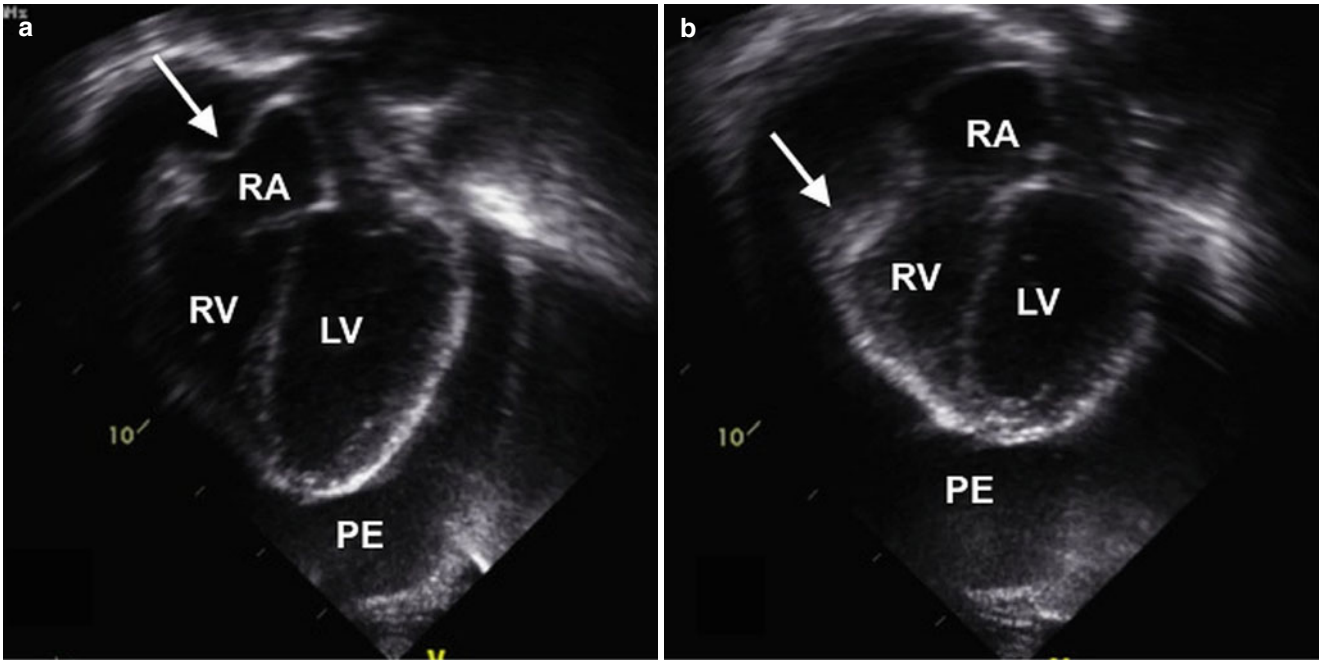


Fig. 31.11 Apical 4-chamber echocardiographic view demonstrating right atrial and right ventricular wall collapse. (**a**) The large circumferential pericardial effusion can be seen with collapse of the right atrial wall (*arrow*). (**b**) During ventricular diastole, the right ventricular wall is collapsed (*arrow*). This is the most common finding in pericardial tamponade. *RA* right atrium, *RV* right ventricle, *LV* left ventricle, *PE* pericardial effusion

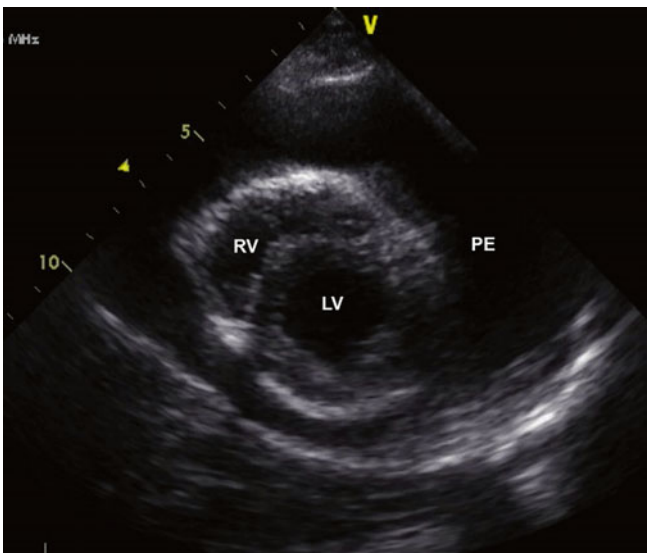


Fig. 31.12 Parasternal short axis view of the heart on echocardiogram demonstrating a circumferential pericardial effusion. *PE* pericardial effusion, *RV* right ventricle, *LV* left ventricle

may have limited efficacy, as there is very little room for additional filling of the heart. In addition, even if systolic pressure rises, diastolic pressure falls and worsens coronary perfusion [18].

Closed needle pericardiocentesis via the subxiphoid approach is the preferred approach for removal and drainage of a pericardial effusion. The subxiphoid approach minimizes the risk of pleural or coronary artery laceration, though complications are further minimized when using echocardiographic guidance [18, 57–59]. A pericardial pigtail catheter may be placed via the Seldinger technique and left in place for drainage of chronic effusions for a period of up to 5–7 days [60]. Tsang et al. reported complications for 1127 echo-guided pericardiocentesis. Major complications occurred at a frequency of 1.2 %, and included death, chamber perforation, ventricular tachycardia and pneumothorax. Minor complications included pleuro-pericardial fistula, small pneumothorax and catheter occlusion [61].

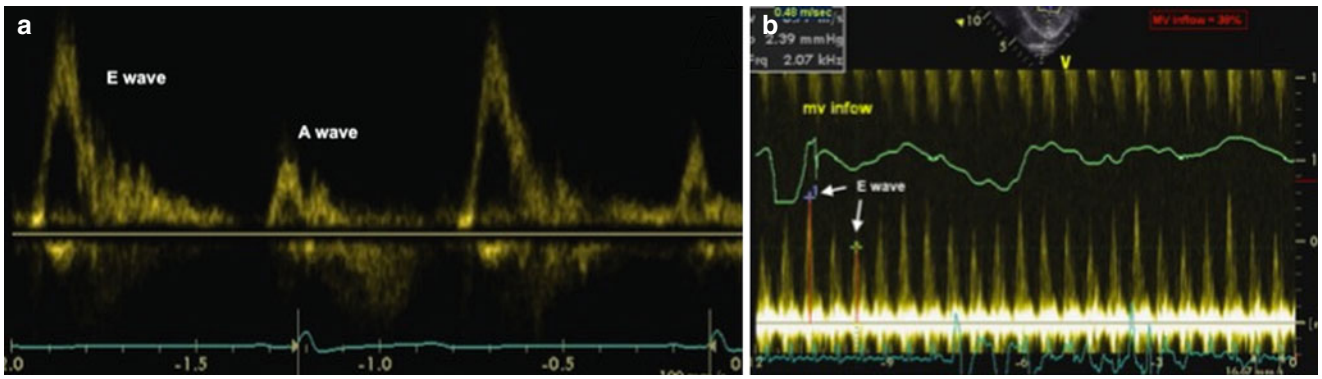


Fig. 31.13 Mitral valve inflow Doppler. (**a**) Normal mitral valve inflow Doppler. Note the consistence in the height of the E wave. (**b**) Mitral inflow Doppler in cardiac tamponade. With increased sweep speed, one can appreciate the variation in the E wave with respiration. The variation seen is 38 % that meets criteria for cardiac tamponade

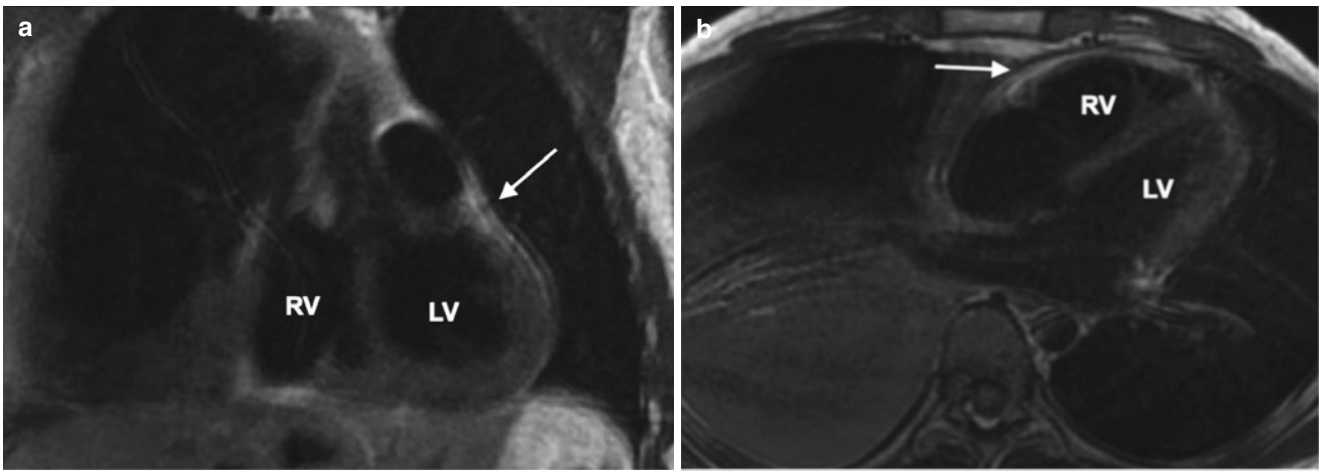


Fig. 31.14 Cardiac MRI demonstrating constrictive pericarditis. (**a**) Coronal section and (**b**) transaxial section through the apex of the heart, demonstrating thickening of the pericardium (*arrows*). *RV* right ventricle, *LV* left ventricle

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Hypertensive Emergencies

32

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Abstract

Beginning with the definitions, this chapter will explore the pertinent information about Hypertensive Emergencies and Urgencies for the Pediatric Critical Care Physician. It provides an in depth review of the reliable ways to measure blood pressure in the PICU. Once sure of the blood pressure reading, the reader is then taught the normal renal, endothelial and cerebral controls over systemic blood pressure as a way to understand the pathophysiology behind hypertension. The most common pediatric etiologies and appropriate diagnostic testing are then outlined in the context of the clinical presentations of hypertensive emergency. Lastly, the medications used in hypertensive emergency are then presented by class and a table of available continuous infusions provides an easy reference guide for the critical care physician.

Keywords

Hypertensive emergencies • Hypertensive urgencies • Cerebral autoregulation • Renin-angiotensin • End-organ damage • Blood pressure measurement • PRES • Vasodilators

Definitions of Terms Related to Hypertension

Hypertension in children and adolescents is defined as systolic and/or diastolic blood pressure greater than the 95th percentile for age, height, weight, and sex [1–3]. Reference values obtained for each age group by ausculatory method are available in the Fourth Report on the Task Force for Blood Pressure in Children [4]. Hypertensive crises are designated as **hypertensive urgencies**, markedly increased blood pressure without end-organ damage, or **hypertensive emergencies**, severely elevated blood pressure in the presence of end-organ damage. The organs most affected are the central nervous system, cardiovascular system, and the kidneys [5, 6]. Immediate intervention is necessary in hypertensive emergencies to prevent progression of end-organ damage [2–4, 7, 8].

Measurement of Blood Pressure

Prior to initiation of any therapy, it is important to ensure reliable and frequent blood pressure readings [8, 9]. Blood pressure may be measured by many techniques including **ausculatory**, **oscillometric**, **Doppler** or **arterial catheters**. As each technique has strengths and weaknesses, choice must be determined within the context of the clinical situation. When values are in doubt, confirmation of blood pressure by more than one technique is indicated.

The **ausculatory** method uses a cuff to obstruct an artery and a stethoscope to detect the phases of arterial filling upon release of the cuff pressure. Sound disappears when the cuff is inflated, and the reappearance of sound represents systole

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and is called phase 1 or K1. As the cuff deflates, turbulent flow progresses into laminar flow producing different Korotkoff sounds appreciable by auscultation. Diastole occurs upon disappearance of the sound at a lower cuff pressure, phase V or K5 [4]. This method depends entirely upon arterial flow, so it can be affected by arterial wall compliance. The **oscillometric** method also uses cuff inflation to occlude a vessel. Turbulent flow during systole causes small vibrations in the wall of the artery which are detected as oscillations in cuff pressure. The mean blood pressure is the point of maximal oscillation [10]. In this method, systolic and diastolic blood pressures are not measured directly but determined by calculation with an algorithm. Oscillometric blood pressures tend to be higher than those by the auscultatory method [10].

Doppler devices detect the apparent change in frequency of turbulent flow as it diminishes to laminar flow [10]. Like the auscultatory and oscillometric methods, standard technique for cuff size and position is required to provide reproducible measures. In all three methods, the cuff should cover 80–100 % of the upper arm and the bladder should cover 40 % of the arm circumference midway between the olecranon and acromion. A small cuff will factitiously elevate blood pressure [3, 9, 11].

The most reliable method is through continuous monitoring using invasive catheters in either a peripheral or central artery [9]. The catheters are attached to tubing, creating a continuous column of fluid with a pressure transducer which converts the pressure transmitted to an electrical signal. The influence of electrical damping can influence systolic and diastolic measures. An overdamped signal will underestimate both systolic and diastolic blood pressures resulting in a narrow pulse pressure, but maintain an accurate mean pressure. This can be the result of vasospasm and may be temporized with a monitor fluid containing papaverine. Conversely, an underdamped system will overestimate systolic blood pressure but will report accurate diastolic and mean arterial blood pressure [12].

Pathophysiology

According to Ohm's law, blood pressure is a product of cardiac output and systemic vascular resistance [8]. Hypertension results from either an abrupt increase in cardiac output by increasing stroke volume or heart rate and/or an increase in systemic vascular resistance [8]. Hypertensive crises can arise de novo or more often as a complication of underlying essential or secondary hypertension [2, 3]. The absolute level of the blood pressure is not as important as the rate of its rise [3]. Regardless of the inciting event, an abrupt rise in blood pressure causes mechanical stress and endothelial injury leading to increased vascular permeability, activation of the coagulation cascade, and deposition of fibrin. Fibrinoid necrosis of the arterioles occurs, and this leads to ischemia and subsequent release of vasoactive mediators and inflammatory cytokines. The renin-aldosterone-angiotensin system is activated leading to further increases in systemic vascular resistance and release of interleukin-6 (IL-6) and other mediators of inflammation. In the glomerulus, pressure diuresis leads to volume depletion and further renin-aldosterone-angiotensin stimulation [6]. A vicious inflammatory and hormonal cycle begins which can lead to end-organ damage and death if unchecked [2, 3, 7].

Table 32.1 Hormonal mediators by system and the vaso-active effect each produces

	Vasoconstrictors	Vasodilators
Renin-angiotensin system	Renin	Bradykinin
	Angiotensin II (AII)	
Central nervous system	Vasopressin	Atrial natriuretic peptide
Sympathetic nervous system	Norepinephrine and epinephrine on alpha and beta-1 receptors	Epinephrine on beta-2 receptors
Endothelium	Endothelin	Nitric oxide

Homeostasis is maintained with reflexive changes in the kidney, endocrine system, endothelium, and brain and one or all of these can be dysfunctional in hypertension. This section will describe normal physiologic control over blood pressure by system (Table 32.1).

Renal Regulation of Blood Pressure

Hemodynamics of the Kidney

Regulation of sodium, the principal extracellular solute, is primarily responsible for extracellular fluid content [13]. As extracellular fluid increases, the increase in blood pressure produces increased renal excretion of sodium and water, pressure natriuresis and diuresis respectively. With prolonged hypertension, extracellular fluid is depleted; thus, diuretics and fluid restriction are not standard therapy for patients presenting in hypertensive crisis [5]. A number of vasoactive substances alter the glomerular filtration rate and renal blood flow to regulate renal perfusion pressure by modulating resistances of the afferent and efferent arterioles.

Renin-Aldosterone-Angiotensin System

Renin is released from the juxtaglomerular apparatus in response to hyponatremia (as sensed by the macula densa), decreased glomerular perfusion pressure (as sensed by baroreceptors), and β-adrenergic agonists [8]. Conversely, renin release is inhibited by sodium excess, increased perfusion pressure with resultant stretching of afferent arterioles, and β-adrenergic antagonists. Renin cleaves angiotensinogen

to form angiotensin I. Angiotensin-converting enzyme (ACE), which is found primarily in the lungs, converts angiotensin I to angiotensin II (AII). ACE also serves to inactivate bradykinin, blocking systemic vasodilation. Angiotensin II acts on receptors in the peripheral vasculature leading to vasoconstriction, stimulates norephinephrine release and NADPH oxidase causing increased reactive oxidative species, and inhibits nitric oxide production [7]. Lastly, AII stimulates aldosterone production. Aldosterone is synthesized in the adrenal cortex and promotes renal sodium reabsorption by the cortical collecting tubule leading to an increase in the effective circulating blood volume. Aldosterone also further stimulates the sympathetic nervous system, generates reactive oxidative species, and increases tissue sensitivity to AII [8].

Hormonal Mediators

Arginine vasopressin (antidiuretic hormone), released by the posterior pituitary secondary to increased plasma osmolarity, stimulates sodium and water reabsorption by the kidney and vasoconstriction in peripheral blood vessels. Volume expansion produces stretching of the atria of the heart and release of atrial natriuretic peptide [8]. This peptide suppresses renin secretion by increasing cyclic guanosine 3′, 5′-monophosphate (cGMP) in the juxtaglomerular cells. Atrial natriuretic peptide also dilates vessels pre-constricted by other vasoactive agents, such as norepinephrine, angiotensin II, and arginine vasopressin.

Circulating catecholamines, epinephrine and norepinephrine, released in times of physiologic stress, act on α (alpha) and β (beta) adrenergic receptors to increase cardiac output. At initial release, epinephrine acts on β_1 (beta-1) receptors to increase heart rate and systolic blood pressure and on β_2 (beta-2) receptors to cause vasodilation in somatic vascular beds. As epinephrine levels increase, α (alpha) adrenergic effects predominate leading to an increase in systemic vascular resistance. Norepinephrine exerts both α (alpha) and β_1 (beta-1) effects but no β_2 (beta-2) activity and, therefore, serves to raise blood pressure through primary increases in systemic vascular resistance [8, 14, 15].

Endothelial Control over Systemic Vascular Resistance

Nitric Oxide

Nitric oxide is a clear, colorless gas synthesized from arginine by nitric oxide synthases. Given its extremely short half-life, it is implicated as a potent local vasodilator. Nitric oxide is released continuously from arteries and arterioles, but not veins, and enters the vascular smooth muscle cell, where it increases the intracellular concentration of cGMP and causes relaxation. Shear stress on the cell surface of the endothelium of arteries causes increased nitric oxide release and resultant vasodilation [16]. Multiple hormonal systems inhibit and stimulate nitric oxide release to modulate basal vasomotor tone. For instance, bradykinin stimulates the release of nitric oxide to produce vasodilation [16]. Inhibition of nitric oxide synthase results in increased vascular resistance, decreased renal blood flow, and diminished sodium excretion, and this effect is attenuated by pretreatment with an angiotensin II receptor antagonist [13].

Endothelin

Endothelin is a 21-amino acid peptide produced by the endothelium in response to multiple inflammatory and hormonal mediators including hypoxia, AII, vasopressin, thrombin, IL-1 and mechanical stress. Conversely, it is inhibited when guanylyl cyclase is activated in response to nitric oxide. It has potent local vasoconstrictor effects by linkages between its receptors and intracellular secondary messengers [17]. Bosentan and other exogenous endothelin antagonists show promise for local vasodilatory properties in pulmonary hypertension and renovascular hypertension [18].

Autoregulation of Cerebral Blood Flow

Cerebral blood flow (CBF) is governed by the relationship between cerebral perfusion pressure (CPP) and cerebrovascular resistance (CVR) as displayed in this equation: CBF = CPP/CVR. Cerebral perfusion pressure is the difference between the mean arterial pressure and intracranial pressure, or central venous pressure if higher [19, 20]. Cerebral autoregulation is the process by which a stable CBF is maintained in the face of variations in perfusion pressure. In adults, stable CBF is maintained at 50 ml/100 g/mint or 50 ml per 100 g tissue per minute over a mean blood pressure range of about 50–150 mmHg [6, 20]. Cerebral blood vessels use the "Bayliss effect" to alter their caliber to compensate for changes in cerebral perfusion pressure [21]. When blood pressure falls, cerebral vessels dilate to maintain CBF until they become maximally dilated and further falls in blood pressure decrease CBF [20]. Similarly, cerebral vessels constrict in the face of rising blood pressure until maximum vasoconstriction is attained. At higher blood pressures, cerebral vessels dilate with resultant increase in CBF [22] (Fig. 32.1).

The lower limit of autoregulation is usually 25 % below the basal mean blood pressure and the upper limit is around 30–40 % above it [6, 23]. In chronic hypertension this curve is shifted to the right, so that autoregulation may fail below a mean arterial pressure of 110 mmHg [20, 23]. Thus, in clinical practice, patients with hypertensive emergency should have mean blood pressure lowered acutely by no more than 25 % to avoid going below the lower limit of cerebral autoregulation [5, 6, 20, 23].

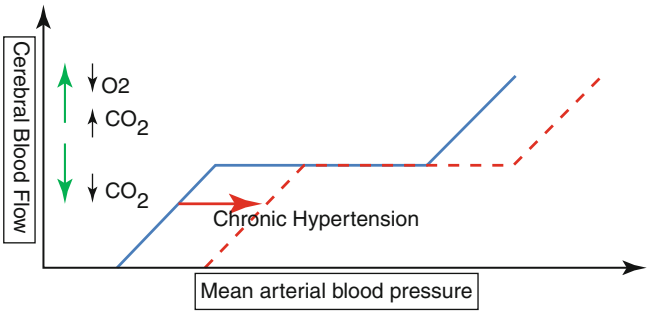


Fig. 32.1 The cerebral autoregulatory curve and the impact of chronic hypertension and acute changes in the partial pressures of oxygen and carbon dioxide on cerebral blood flow

There are three mechanisms which maintain cerebral autoregulation: myogenic, metabolic and sympathetic [19, 20]. The myogenic mechanism involves smooth muscle contraction in the arteriolar walls when mean arterial pressure rises. This allows for near-immediate response to changes in blood pressure. The metabolic mechanism invokes local nitric oxide and adenosine levels to divert CBF to areas of highest cortical metabolic activity. The sympathetic nervous system protects the brain in chronic hypertension by shifting the autoregulatory curve to the right. It is postulated that lack of sympathetic nerves in the posterior circulation is the reason this region is most affected in posterior reversible encephalopathy syndrome (PRES). Further evidence for sympathetic control is found in the exaggerated diminution in CBF when intracranial hemorrhage occurs with an intact sympathetic nervous system compared with hemorrhage after sympathectomy [20].

Other factors affecting CBF include intracranial pressure, blood viscosity, oxygen saturation, and arterial carbon dioxide. While acute hypercapnia and hypoxia can increase CBF, hypocapnia decreases CBF [20]. This is the mechanism invoked in situations of severely elevated ICP when hyperventilation is used emergently to decrease CBF to lower ICP. Recent studies show that cerebral autoregulation is attenuated during isocapnic hypoxia and only increased in hypercapnic hypoxia implying that the partial pressure of CO_2 has more of an effect than that of oxygen [24]. When cerebral autoregulation is altered by hypertension, the impact of oxygen saturation and carbon dioxide content on cerebral blood flow may increase [20].

Etiologies

Hypertension is either essential (primary) or secondary to an underlying condition. In patients less than 10 years old, essential hypertension is a rare diagnosis of exclusion. Secondary hypertension is far more common in this age group and is most often caused by underlying renal pathology [8, 25]. Table 32.2 shows the etiologies of secondary hypertension as delineated by system. It is important to remember that in the critical care unit, inadequately treated pain and agitation are probably the most common etiologies of elevated blood pressure. This circumstance may be difficult to detect, particularly if neuromuscular blockade is also administered. Concurrent tachycardia is a good clue to this problem, as is tearing of the eye with noxious interventions [14]. In adolescents, however, essential hypertension is becoming more common especially in the context of obesity [1, 2].

Obesity and Metabolic Syndrome

Body mass index is a major determinant of blood pressure [26]. With the obesity epidemic, more adolescents are being diagnosed with essential hypertension and metabolic syndrome. Estimated to occur in 4–11 % of all children, the metabolic syndrome involves obesity, dyslipidemia, inflammation, hypertension, and insulin resistance [2, 27]. As the severity of obesity worsens, the prevalence of metabolic syndrome increases. Recent NIH data reports that 17 % of newly diagnosed Type II diabetic children have hypertension on their first visit [27]. Autopsies of children with metabolic syndrome reveal early atherosclerosis of the aorta and coronaries [1, 27].

Clinical Presentation

Hypertensive urgency presents as vague symptoms such as headache or nausea and vomiting. In hypertensive emergency, presentation depends on the affected end-organ [2, 3].

Neurologic Manifestations

Hypertension can alter cerebral autoregulation and lead to intracranial hemorrhage, cerebrovascular ischemia, seizures, hypertensive encephalopathy, or PRES. Acute increases in systemic blood pressure above the extreme of cerebral autoregulation causes a chain of events beginning with arterial spasm and local autoregulatory failure [8, 19, 21]. Local hyperperfusion and exudation of plasma through vessel walls leads to cerebral edema and increased intracranial pressure. Elevations in blood pressure also structurally change vasculature, causing damage and necrosis leading to further leakage and edema even after return to normotension [21]. Increased ICP causes capillary compression and decreased CBF ultimately causing hypertensive encephalopathy [19, 20]. Focal areas of ischemia may develop and lead to lateralizing neurologic signs and stroke [21]. Blood pressure

Table 32.2 Etiologies of secondary hypertension by system with specific diagnoses, symptoms and pertinent diagnostic tests

Organ system	Pathology	Symptoms	Tests
Renal	Up to 60 % of all secondary hypertension [8, 24]	Anuria or oliguria, hematuria, peripheral edema	Blood urea nitrogen, serum creatinine, urine protein:creatinine ratio
Parenchymal	Vesiculo-ureteral reflux nephropathy, glomerular disease (FSGS), hemolytic uremic syndrome, obstructive uropathy, polycystic kidney disease	Recurrent urinary tract infections, dysuria, nocturia or enuresis, anemia, growth failure	Urinalysis, renal ultrasound, complete blood count with peripheral smear
Vascular	Renal artery stenosis Fibromuscular dysplasia Emboli from umbilical or central vascular catheter	Flank pain, hematuria	Angiography with or without ACE-I stimulation, CT or MRI of the abdomen
High Renin states	Coarctation of the aorta, Hypotension from shock, Intravascular depletion	Blood pressure gradient in the extremities	ECHO, renin and aldosterone levels, electrolytes
Sympathetic nervous system	Inadequately treated pain Post-operative hypertension	Tearing with noxious stimuli (if under neuromuscular blockade), tachycardia	Response to analgesia
Central nervous system	Seizures	Tachycardia with hypertension	EEG
	Elevated ICP from ICH, hydrocephalus or space-occupying lesions	Cushing's triad, Altered mental status	Head CT or MRI
Endocrine	Pheochromocytoma Neuroblastoma Hyperthyroidism, Hyperaldosteronism Cushing's Syndrome Congenital adrenal hyperplasia	Tachycardia, weight loss, hypertension, sweating, palpitations, family history, abdominal mass, goiter, proptosis	TSH and free T4, cortisol, free plasma and 24 h urine metanephrines, serum electrolytes
Toxicology			
Related to treatment	Corticosteroids, chemotherapy, immunosuppressants, sympathomimetics, dextroamphetamine or methylphenidate, phenylpropanolamine (cold medicine), abrupt stop of clonidine or Beta-blocker	Correspondent hypertension with therapy and improvement with withdrawal	Follow drug levels if possible (e.g. tacrolimus)
Illicit or OTC	Cocaine, MDMA, amphetamines, phencyclidines, antihistamines, Neem tree oil, blue cohosh, licorice, ma Huang	Accessibility to these agents	Urine and plasma drug screen, arterial blood gas to determine anion gap
Heavy metals	Mercury, arsenic, lead, cadmium	Exposure history, pica, paresthesias	Serum levels Abdominal x-ray for lead chips
Miscellaneous	Burns and immobilization Abdominal compartment syndrome	Trauma history, ascites, abdominal distension with elevated bladder pressure	Ionized calcium
	Sleep apnea	Stertor, daytime sleepiness	Abdominal drainage Sleep polysomnography

reductions must be gentle and are sometimes contraindicated in stroke to avoid further hypoperfusion and extension of the ischemic area [3, 11].

Similar mechanisms are theorized to be the cause of PRES which is a clinical and radiographic diagnosis. Specific patient populations have been identified at higher risk for PRES including those with an allogenic bone marrow or solid organ transplant, chemotherapy, hemolytic uremic syndrome or thrombotic thrombocytopenic purpura, a renal vascular disorder, sepsis and systemic inflammatory response syndrome, or an underlying vasculitis such as lupus or polyarteritis nodosa [28–30]. Typical presentation includes headaches, visual changes, nausea, paresis, altered mental status, coma, and generalized seizures [28, 30]. Blood pressure is elevated upon presentation in 70–80 % of cases [30]. Brain imaging displays a unique pattern of symmetric vasogenic edema predominantly in the parietal and occipital regions [29]. Despite the syndrome's name, the basal ganglia, brain stem, and deep white matter can be affected in isolation [28].

The mechanism of PRES is not well understood [28–30]. In animal studies, blood pressures over 150–160 mmHg can cause hyperperfusion, breakdown of the blood–brain-barrier, and hemispheric edema [19, 30]. However, 25 % of patients do not present with blood pressures exceeding the upper limits of autoregulation. An alternate theory implicates endothelial injury from either hypertension or neurotoxic medications

causing cytokine release. Cytokine effect on injured endothelium leads to extravasation of fluid and proteins out of vessels and resultant edema. Local cytokines and impaired autoregulation can cause vasoconstriction and hypoperfusion, disrupting the blood–brain-barrier and worsening cerebral edema. Focal vasospasm has been suggested by angiography revealing string-of-beads patterns in cerebral arteries in PRES [19, 30]. On laboratory examination, evidence of endothelial damage is present with platelet consumption, elevated lactate dehydrogenase, and red blood cell fragmentation [28, 30].

Treatment of PRES focuses on gradual blood pressure control, withdrawal of offending agents, hydration, and control of seizures [28]. Both the imaging changes and clinical symptoms usually completely reverse with removal of the neurotoxin and normalization of the blood pressure [8]. In those few patients with intracranial hemorrhage or infarction, prognosis is worse and neurologic damage may not be reversible [30].

Cardiovascular Manifestations

Cardiac injury is manifested as acute heart failure with pulmonary edema, myocardial ischemia, or aortic dissection [31]. Any patient who presents with acute chest pain in the setting of severe hypertension must be evaluated for aortic dissection with chest imaging. If left untreated, 75 % of adults with aortic dissection die within 2 weeks of presentation [3]. Dissection is propagated by the velocity of left ventricular ejection and systolic blood pressure and heart rate. Vasodilator therapy alone is not ideal because of the reflexive tachycardia that increases aortic ejection velocity and can increase the area of dissection [3].

Renal Manifestations

Vascular injury to the kidney as a result of hypertension is manifested by hematuria, proteinuria, and azotemia. Hypertension can disrupt renal autoregulation and cause direct glomerular damage with overwhelming hydrostatic pressure. Patients may present in oliguria or anuria due to severely depressed renal function or acute renal failure [4].

Ophthalmologic Manifestations

Even small changes in blood pressure by 10 mmHg can produce focal narrowing of retinal arterioles and lead to hypertensive retinopathy [4]. Severe hypertension can cause retinal vessel occlusion, leakage, hemorrhages, or micro-aneurysms. Optic neuropathy from venous congestion can result in flame hemorrhages and optic disc edema [3].

Evaluation

A thorough history and physical examination may uncover likely etiologies, determine duration of the problem, and identify end-organ damage. Past medical history should start with birth history including presence of umbilical catheters and birth weight, as low birth weight infants are at increased risk for essential hypertension in adolescence [1]. Developmental and growth failure or weight loss may suggest an underlying endocrinopathy. Review of systems should include symptoms consistent with sleep apnea or with increased sympathetic tone such as flushing, sweating, and palpitations [25]. A social history should include tobacco, alcohol, and drug use including over-the-counter, herbal, or illicit drugs [3, 14]. Relevant family history includes any cardiovascular or renal disease, diabetes, stroke, obesity or hereditary endocrinologic tumors, such as pheochromocytoma or multiple endocrine neoplasm Type 2 [15]. Family history may also give clues to prescription medicines available to ingest.

A thorough physical examination of all pertinent end-organs involved in hypertensive emergency should start with confirmation of blood pressure in all extremities using the ausculatory method. Focusing on fluid status, neurologic, cardiac, and pulmonary systems may identify both etiology and consequences of hypertensive emergency. Please see Table 32.2 for symptoms of each affected system. Initial laboratory investigations are directed at further evaluation of current status and screening for underlying causes and end-organ dysfunction. Upon presentation, a complete blood count with a peripheral smear, electrolytes including blood urea nitrogen and creatinine, urinalysis, and chest x-ray should be obtained [7–9].

Management

Therapeutic Goals

In hypertensive emergency therapeutic goals depend on underlying etiology, clinical presentation, and the patient's baseline blood pressure. Abrupt lowering of the blood pressure below the lower limit of cerebral autoregulation may cause hypoperfusion and worsen cerebral ischemia [2, 3, 7–9, 19, 21, 22]. Current recommendations suggest decreasing blood pressures by 25 % over the first 6–8 h and then gradually lowering the blood pressure to closer to baseline levels in the next 24–48 h as tolerated [4–6, 11, 19]. In aortic dissection, blood pressure should be lowered faster with a goal

Table 32.3 Medications available as a continuous infusion for blood pressure control and their effects on SVR, CO and cerebral blood flow

Medication	Mechanism of action	Dose	Primary indication	Effect on systemic vascular resistance and cardiac output	Effect on cerebral blood flow
Sodium Nitroprusside	Metabolized into nitric oxide producing direct vaso- and veno-dilation	0.3–8 mcg/kg/min (with sodium thiosulfate infusion)	Hypertensive emergency without elevated ICP	Decreases preload and afterload by dropping SVR	Dilates cerebral vessels to increase CBF and ICP
Fenoldopam	Dopamine-1 and alpha-2 receptor agonist	0.1–1.6 mcg/kg/min	Hypertensive emergency with acute renal failure	Arterial dilation, decreases afterload	Dilates cerebral arteries to increase CBF and ICP
Esmolol	Cardio-selective beta-1 receptor antagonist	100–500 mcg/kg/min after load of 0.3–0.5 mg/kg	Aortic dissection (with Nicardipine)	Reduces CO by decreasing heart rate and stroke volume	Little to no effect on CBF
Labetalol	Selective alpha-1 and non-selective beta-antagonist	0.25–3 mg/kg/h after load of 0.2–1 mg/kg	Aortic dissection, ICH or CVA	Reduces SVR without decreasing CO, no tachycardia	Little to no effect on CBF
Nicardipine	Second generation Ca-channel blocker acting on smooth muscle in all blood vessels and the myocardium	0.5–5 mcg/kg/min	Hypertensive encephalopathy, Aortic dissection (with esmolol), Hypertensive emergency with acute renal failure, CVA, Sympathetic crisis (with benzodiazepine), Perioperative hypertension	Arterial and venous dilation, decreases cardiac contractility and heart rate by slowing conduction through the AV node	Cerebral vasodilation and increased CBF and increased ICP if mean arterial pressure is still elevated
Clevidipine	Third generation Ca-channel blocker, selective arterial vasodilator	0.5–3.5 mcg/kg/min	Same as nicardipine although not approved by FDA for pediatric use	Arterial dilation only decreasing afterload without affecting preload	Cerebral vasodilation and increased CBF and increased ICP if mean arterial pressure is still elevated

systolic of <100. Precise control is best achieved with short-acting continuous infusions which can be titrated to avoid inadvertent hypotension [3] (Table 32.3). After end-organ damage and hypertensive emergency have been controlled, appropriate oral maintenance therapy should be instituted. In hypertensive urgency oral and intermittent medications can be used to control blood pressures over 24–48 h [3].

Therapeutic Agents by Class

Vasodilators

Sodium nitroprusside is metabolized into nitric oxide and causes direct arterial and venous dilation through smooth muscle relaxation. By decreasing systemic vascular resistance, nitroprusside reduces both afterload and preload [8]. With an onset of seconds and duration of action of 1–2 min, it is easily titrated to effect. Theoretically, it is contraindicated in cerebral ischemia and elevated intracranial pressure because it vasodilates cerebral vessels while decreasing mean arterial pressure and cerebral perfusion pressure [3, 9, 22]. The drop in afterload caused by nitroprusside may decrease coronary arterial flow and should be avoided in heart failure or myocardial ischemia [3, 9].

Although common side effects include nausea and vomiting, diaphoresis, flushing, and muscle twitching, the most important side effect of nitroprusside is cyanide toxicity. Nitroprusside contains 44 % of cyanide by weight which is released non-enzymatically in a dose-dependent manner [3, 9]. Cyanide can cause metabolic acidosis, cardiac arrest, encephalopathy, seizures, and coma through direct respiratory arrest of the cells. Cyanide is metabolized in the liver to thiocyanate by the enzyme rhodanese requiring thiosulfate for the reaction. Thiocyanate is 100 times less toxic than cyanide and is excreted by the kidneys [3, 8, 9]. In renal failure, thiocyanate may accumulate and create toxicity characterized by tinnitus, blurred vision, confusion, seizures, psychosis, nausea, abdominal pain, and hyperreflexia. Thiocyanate also inhibits iodine uptake by the thyroid and may produce hypothyroidism [32].

The therapeutic range of nitroprusside is 0.3–8 mcg kg^{-1} min^{-1}; however, doses greater than 4 mcg kg^{-1} min^{-1} induce cyanide formation faster than humans can detoxify [3]. Therefore, at doses over 4 mcg kg^{-1} min^{-1}, a solution of 0.1 % sodium nitroprusside

and 1 % sodium thiosulfate, or a 1:10 ratio by weight, in light-protected tubing, is recommended [33]. Alternatively, hydroxocobalamin, vitamin B_{12a}, can be used to trap the cyanide ion by forming cyanocobalamin [9, 34]. Of note, methylene blue is contraindicated in treating methemoglobinemia attributable to cyanide toxicity, since the conversion of methemoglobin to hemoglobin may liberate large amounts of cyanide [34].

Fenoldopam acts on peripheral dopamine-1 receptors and α_2 (alpha-2) receptors to cause potent arterial dilation. Upregulation of cyclic AMP leads to smooth muscle relaxation in coronary, renal, mesenteric, and peripheral arteries [7]. Because of stimulation of dopamine receptors in the proximal and distal tubules, fenoldopam also improves creatinine clearance and inhibits sodium reabsorption. It has an onset of action of 5 min and duration of 30–60 min [9]. Tolerance can develop within 48 h of continuous administration [7].

Adrenoreceptor Antagonists

Alpha-Adrenergic Antagonists

Under normal physiologic conditions, arterial and venous vascular tone is dependent largely on α (alpha)-adrenergic receptor input to vascular smooth muscle. Agents that provide α (alpha) adrenergic antagonism lead to arterial and venous dilation, decrease systemic vascular resistance, and lower arterial blood pressure.

Phentolamine is a pure alpha-adrenergic antagonist with equal effect on α_1 (alpha-1) and α_2 (alpha-2) receptors. It has an onset of action of 1–2 min and duration of 10–30 min. Side effects are due to the reflex cardiac stimulation and unopposed β (beta)-adrenergic effects: tachycardia, arrhythmias, flushing, and headache [22]. This is a first-line agent in control of hypertension secondary to pheochromocytomas [9]. **Phenoxybenzamine** is an oral agent similar to phentolamine for more chronic control. **Prazocin** is an oral (alpha) α_1 blocker with a long-half life and not indicated in hypertensive emergencies. **Clonidine** is a centrally acting α_2 (alpha-2) agonist which causes decreased sympathetic output and resultant decrease in blood pressure, heart rate and cardiac output and secondary diuresis. Only available in oral or transdermal forms, clonidine is not indicated for acute blood pressure control [22].

Beta-Adrenergic Antagonists

β (beta)-adrenergic antagonists are first-line therapy for hypertension secondary to coarctation of the aorta [35]. Renin secretion is regulated in part by β (beta)-adrenergic receptors, therefore, β (beta)-blockers decrease blood pressure in high-renin states [36]. However, without concurrent alpha-blockade, β (beta)-blockers may cause increased systemic vascular resistance, decreased cardiac output, and impaired renal blood flow due to unopposed alpha action [6, 36]. β (beta)-antagonists are also contraindicated in asthma or obstructive lung disease as β_2 (beta-2) receptors mediate bronchial dilatation [8, 9].

Esmolol has an onset of action of 60 s and duration of 10 min making it the easiest to titrate in its class [3, 8, 36]. It is a cardio-selective β (beta)-blocker that decreases blood pressure by decreasing cardiac output. Esmolol is metabolized by rapid hydrolysis of ester linkages by red blood cell esterases and is safe in renal or hepatic failure [3, 9]. **Labetolol** is a combined selective α_1 (alpha-1) and β (beta)-blocker that reduces systemic vascular resistance without affecting cardiac output or causing tachycardia [8]. The ratio of α (alpha) to β (beta)-blockade effect is approximately 1–7 [3, 9]. Labetolol has a short onset of action of 2–5 min and duration of 2–4 h. Labetalol maintains cerebral, renal, and coronary blood flow and is safe in pregnancy and elevated intracranial pressure [8].

Calcium-Channel Antagonists

These agents cause vasodilation through inhibiting transport of calcium ions into vascular smooth muscle by blocking voltage-dependent calcium channels. Calcium channel blockers also decrease cardiac contractility, heart rate, and conduction through the AV node [22]. Additionally, calcium channel blockers promote natriuresis [37].

Nicardipine is a second-generation dihydropyridine derivative calcium channel blocker with high vascular selectivity and strong cerebral and coronary vasodilatory activity. By increasing stroke volume and cerebral blood flow, it reduces cerebral and cardiac ischemia [3, 8, 9]. Onset of action is within 5–15 min and its duration is 4–6 h [3, 9]. **Clevidipine** is a third-generation dihydropyridine calcium-channel blocker which is an ultra-short acting arteriolar vasodilator [3, 9]. Clevidipine decreases afterload without affecting preload and thus leads to better stroke volume and cardiac output maintaining renal, splanchnic, and coronary flow without reflexive tachycardia [3, 8, 9]. Its onset and duration of action are both less than a minute, so clevidipine can be used for precise blood pressure control [8]. This drug is metabolized by red blood cell esterases and does not rely on intact renal or hepatic function [9].

Angiotensin Converting Enzyme Inhibitors

These agents competitively inhibit ACE, the endogenous enzyme which converts angiotensin I to angiotensin II. By lowering systemic levels of AII, not only do ACE-Is diminish the vasoconstrictor effects of AII, they also increase circulating levels of bradykinin. Therefore, ACE-inhibitors decrease peripheral vascular resistance without changing heart rate and cardiac output. There is evidence that this class of drug may shift the cerebral autoregulatory curve to shorten the plateau

range making the cerebral circulation more susceptible to extremes of blood pressure; thus, ACE-I should be avoided in increased ICP or cerebral ischemia [22]. ACE inhibitors may provoke renal insufficiency when given in the presence of renal artery stenosis. Since the renin-angiotensin system influences erythropoietin synthesis, anemia may result [37].

Enalaprilat is the only ACE-inhibitor available in intravenous form. It blocks conversion of angiotensin I to AII by inhibiting peptidyl peptidase, the enzyme that hydrolyzes the reaction [22]. It may cause a precipitous fall in blood pressure in high renin states and has variable effect in other patients [8]. Despite a rapid onset of 15–30 min, its duration of action is 6–12 h [9].

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Part III

The Central Nervous System in Critical Illness and Injury

Molecular Biology of Brain Injury: 2012

33

Michael J. Whalen, Phoebe Yager, Eng H. Lo, Josephine Lok, Heda Dapul, Sarah Murphy, and Natan Noviski

Abstract

Here we will cover a number of topics relevant to the molecular biology of acute brain injury beginning with an introduction to basic neurotransmitter systems and function, including excitatory (glutamate, acetylcholine, others) and inhibitory (GABA, glycine) neurotransmitters. To illustrate how these systems can interact with systemic processes we describe the cholinergic anti-inflammatory response, one way that the brain communicates with the peripheral immune system to downregulate an inflammatory response. Glutamate receptor physiology is introduced and the concept of excitotoxicity, central to all forms of acute central nervous system injury, is explained including the roles of metabotropic and ionotropic signaling. This leads to analysis of modes and mechanisms of programmed cell death after acute brain injury with an emphasis on programmed necrosis, apoptosis, caspases, poly-ADP-ribose polymerase, mitochondrial permeability transition, and oxidative stress, including coverage of the new field of oxidative lipidomics, which has provided a link between reactive oxygen species generation, release of mitochondrial cytochrome C, and cell death via specific oxidation of cardiolipin after acute brain and cellular injury. Links between oxidative and nitrosative stress and neuroinflammation and how these fundamental processes relate to brain injury are also included. Finally, extracellular matrix proteases, including matrix metalloproteinases and tissue plasminogen activator and their role in neurodegeneration and neuroprotection, as stroke biomarkers, and as mediators of blood–brain barrier damage are elucidated.

Keywords

Cell death • Inflammation • Neurotransmitters • Oxidative stress • Autonomic nervous system • Necrosis • Oxidative lipidomics • Brain injury

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Neurotransmitters and Their Receptors

Introduction

The concept that electrical activity between neurons is transmitted via chemical messengers was first demonstrated in 1921 by an Austrian physiologist, Otto Loewi. Using two frog hearts, he placed the first heart (still connected to its vagus nerve) into a saline-filled chamber. This chamber was connected to a second saline-filled chamber into which he placed the second heart. Electrical stimulation of the vagus nerve caused the first heart to slow. After a short delay, he noticed the second heart also slowed. From this experiment,

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he hypothesized that the electrical stimulation of the vagus nerve released a chemical into the first chamber, which flowed into the second and caused the second heart to slow just as the first. He referred to the chemical as "Vagusstoff". We now know this chemical to be acetylcholine, by far the best studied neurotransmitter [1].

Neurotransmitters: Definition

Neurotransmitters are the chemical messengers synthesized and utilized by neurons to propagate electrical impulses from one neuron to the next. Neurotransmitters are produced and stored within presynaptic neurons, which, when depolarized, release neurotransmitters into the synaptic cleft. Neurotransmitters bind and activate specific membrane-bound receptors in the postsynaptic cell, leading to ion fluxes such as inward sodium, calcium, or chloride current, and outward potassium efflux. Following their release, neurotransmitters are rapidly inactivated by reuptake and/or degradation.

Neurotransmitters fall into two main categories: peptide neurotransmitters, and small-molecule neurotransmitters such as acetylcholine, biogenic amines, and amino acids. We will focus primarily on the role of several major classes of neurotransmission in the normal brain, and on the role of amino acid neurotransmitters in excitotoxicity, the process by which over-stimulation of glutamate receptors induces cell death.

Neurotransmitter Receptors

There are over 100 putative neurotransmitters, and a vast array of neurotransmitter receptors; the same neurotransmitter may be excitatory or inhibitory, depending on whether binding to a specific receptor results in depolarization versus hyperpolarization, respectively. In general, all neurotransmitter receptors function by opening or closing ion channels in the postsynaptic cell membrane. They can do this directly if the receptor functions as an ion channel, or indirectly if the receptor lacking an ion channel activates a second messenger system. The former is referred to as an ionotropic or ligand-gated receptor, the latter as a metabotropic receptor.

Ionotropic receptors are generally composed of five membrane-spanning subunits that together form a central channel. The receptor is a multimer with several extracellular neurotransmitter binding sites, a number of transmembrane domains, and a single central ion channel connecting the extra- and intra-cellular compartments. In contrast, metabotropic receptors are monomeric, membrane-spanning proteins that stimulate intracellular G-proteins that interact with separate membrane-spanning ion channels. When neurotransmitters bind the extracellular sites of metabotropic receptors, G-proteins linked to the intracellular domain are activated, dissociate, and interact with ion channels or through intermediary proteins to alter conductance of neighboring ion channels. Metabotropic receptors generally modulate the function of ionotropic receptors, and have longer lasting electrical effects as well as effects on gene expression and intracellular signaling important for synaptic plasticity, learning, and memory.

Acetylcholine

The two types of acetylcholine (Ach) receptors are nicotinic and muscarinic, named for synthetic chemicals that activate extracellular binding sites. Nicotinic ACh (nAch) receptors are excitatory ligand-gated channels localized at the neuromuscular junction, as well as within the brain, autonomic nervous system, and central and peripheral immune cells. Nicotinic ACh (nACh) receptors, found throughout the cortex, induce arousal, euphoria, and relaxation. Nicotine and other nACh receptor agonists improve attention, enhance learning, and shorten reaction time. Muscarinic ACh receptors are metabotropic and are responsible for the majority of acetylcholine effects in the brain. These receptors are found in abundance in the striatum and other forebrain regions in addition to postganglionic parasympathetic neurons.

The Cholinergic Anti-inflammatory Response

In addition to its role in neurotransmission, recent studies over the past several years demonstrated an intriguing role for the parasympathetic nervous system, and the vagus nerve in particular, as a modulator of the brain and peripheral immune response to central nervous system (CNS) injury [2–6]. After stroke or TBI, damaged cells release signaling molecules termed alarmins (e.g., HMGB1, ATP, nucleic acids) which bind to Toll-like and other receptors on CNS and peripheral immune cells (microglia, blood monocytes, macrophages) initiating an inflammatory response that contributes to secondary injury [7, 8]. Increased vagal activity that occurs after acute brain injury is hypothesized to counterbalance this "sterile" immune response. Acetylcholine released from efferent terminals of the vagus nerve binds to the α7 nicotinic acetylcholine receptor (α7nAchR) expressed on microglia, macrophages, and other cytokine-producing cells. Stimulation of the α7nAchR in these cell types recruits the anti-inflammatory Janus kinase-2/signal transducers and activators of transcription-3 cascade, inhibits nuclear factor kappa B activity, and decreases production of pro-inflammatory cytokines, suppressing peripheral and CNS inflammation [9]. This adaptive response to CNS

injury, intended to restore homeostasis in injured tissue, can also be detrimental if it becomes prolonged and/or exaggerated. Over activity of the parasympathetic nervous system may contribute to immune paralysis and increased systemic infections observed in patients with traumatic brain injury (TBI) and stroke [10]. On the other hand, vagal nerve stimulation and α7nAchR agonists reduce infarct size in focal stroke and attenuate glutamate release in global stroke models [11, 12]. These observations suggest that modulation of the cholinergic anti-inflammatory pathway, either by vagal nerve stimulation or specific α7nAchR agonists, may have therapeutic potential to reduce inflammation and secondary damage in patients with acute CNS injury [13]. Conversely, reduction of cholinergic signaling may prevent infectious complications in these patients by limiting immune paralysis and improving neutrophil function and bacterial clearance mechanisms. Hopefully, future studies aimed at understanding how modulation of cholinergic signaling influences outcome after acute CNS injury will lead to new therapeutic options.

Serotonin

Serotonin or 5-hydroxytryptamine (5-HT) is implicated in the pathophysiology of a number of psychiatric diseases, including depression, eating disorders, anxiety disorders, and obsessive-compulsive disorder. Serotonin-containing neurons predominate in the raphe region of the pons and upper brainstem and project into the forebrain. A wide variety of 5-HT receptors have been discovered, most of which are metabotropic. These receptors influence sleep and wakefulness, emotion, motor behaviors, and satiety. Once serotonin has been released into a synaptic cleft, its action is terminated by the serotonin reuptake transporter (SERT). The selective serotonin reuptake inhibitors (SSRIs) interfere with SERT and prolong the action of serotonin in the synaptic cleft.

GABA and Glycine

The majority of inhibitory synapses in the brain utilize either GABA or glycine as neurotransmitters, which act on ionotropic and metabotropic receptors to decrease excitation by causing hyperpolarization of the post-synaptic membrane. In the normal brain, glucose is metabolized to glutamate via the tricarboxylic acid cycle. Glutamate is then converted to GABA by glutamic acid decarboxylase (GAD). GAD requires a cofactor, pyridoxal phosphate (derived from vitamin B_6), for normal function. Pyridoxine dependency is an autosomal recessive disorder manifest by intractable infantile seizures responsive to vitamin B_6 administration. The disorder is associated with high levels of glutamate in the CSF and impaired GAD activity.

There are 2 types of GABA receptors, referred to as GABA-A and GABA-B. GABA-A receptors are ligand-gated and function by enhancing Cl^- conduction through the central pore, inducing hyperpolarization and reducing membrane excitability. Benzodiazepines and barbiturates induce sedation, anxiolysis, and increase the seizure threshold by binding GABA-A receptors. GABA-B receptors are metabotropic and inhibit depolarization via recruitment of a G-protein second messenger that blocks neighboring K^+ and Ca^{++} channels.

Glutamate

Glutamate is a nonessential amino acid that does not cross the blood–brain barrier and therefore must be produced by neurons within the central nervous system to function as a neurotransmitter. Glutamine, the primary precursor to glutamate, is supplied by glial cells to neurons. Once within the presynaptic terminal of the neuron, glutaminase converts glutamine to glutamate. Glutamate is stored in vesicles until release by neuronal depolarization, and then is transported back to glial cells, reconverted to glutamine via glutamine synthetase, and returned to the neuron.

Glutamate Receptors

Glutamate receptors are composed of five monomeric subunits that assemble in various combinations to form a variety of glutamate receptors, several of which may respond simultaneously to glutamate in a given postsynaptic neuron. Three ligand-gated (ionotropic) glutamate receptors have been described– *N*-methyl-D-aspartate (NMDA), 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl)propanoic acid (AMPA), and kainite receptors. All three are excitatory. Three specific properties make NMDA receptors unique. First, their central pore conducts Na^+, K^+, and Ca^{++}. Ca^{++} influx serves as a second messenger to initiate intracellular signaling cascades and new gene expression. Second, magnesium binds to glutamate receptors within the central pore, which inhibits channel function by maintaining hyperpolarization of the postsynaptic membrane. Magnesium is extruded from the pore during depolarization to allow free flow of other cations. This unique property adds voltage-dependence to ionic flow across the pore and has been linked to brain functions such as learning and memory. Finally, a glycine-binding site modulates channel opening in response to glutamate binding, and glycine is required for optimal NMDA receptor function.

NMDA receptor activation underlies the formation of novel memories by modulating the strength of the effect of

a synapse on a postsynaptic cell [14]. For example, frequent and repetitive stimulation of a synapse containing NMDA receptors leads to augmentation of the postsynaptic response during future synaptic stimulation; this electrophysiological phenomenon is known as long-term potentiation (LTP) and is mediated by calcium influx through the NMDA receptor. Conversely, a low frequency of synaptic stimulation, and failure to recruit firing from additional synapses, leads to long term depression (LTD) and inhibitory effects on the postsynaptic cell. Long-term depression is also mediated by calcium currents in NMDA receptors. Long term potentiation/depression are ways in which synaptic strength is regulated, both acutely and on a long term basis, and both are necessary for normal learning and memory. Both LTP and LTD are inhibited by NMDA receptor antagonists that impair memory function in rodents. Thus, NMDA receptors induce memory formation by calcium-dependent mechanisms that include LTP or LTD, in hippocampal as well as cortical brain regions.

In addition to the ligand-gated glutamate receptors, three known metabotropic receptor subtypes modulate neurotransmission by activating intracellular second messenger systems that lead to altered postsynaptic Ca^{++} and Na^{+} flux, and thereby modulate excitability of the postsynaptic neuron. For example, group I mGlu receptors coupled to phospholipase C modulate intracellular calcium signaling, while group II and group III receptors inhibit adenylyl cyclase. Metabotropic glutamate receptors play important roles in synaptic plasticity by potentiating the effects of NMDA receptor activity in brain regions involved in learning and memory. In addition, metabotropic glutamate receptors on non-neuronal cell types modulate the response to CNS injury, as we shall see below.

Excitotoxicity

Drs. Lucas and Newhouse first described the concept of excitotoxicity in 1957 by feeding glutamate to young mice and demonstrating neuronal loss in the retina [15]. The relationship between increased extracellular glutamate concentrations and neuronal cell death was subsequently described in a number of acute brain injury models [16–20]. During acute insults to the brain, such as stroke, infection, trauma, seizures, hypoglycemia, or hemorrhage, glutamate is released by neurons and glia into the brain extracellular space [20]. High concentrations of glutamate overstimulate NMDA and calcium-permeable AMPA receptors and induce transient, massive influx of extracellular calcium. Calcium may also enter the neuron from voltage-gated calcium channels, sodium/calcium transporters, and from intracellular stores. Intracellular calcium activates proteolytic enzymes that cleave substrates essential for cellular survival, such as cytoskeletal proteins, DNA repair enzymes, and other key cellular constituents. In addition, increased intracellular calcium induces mitochondrial electron transport chain dysfunction and subsequent generation of oxygen free radicals that, in concert with activation of proteases and other "death effectors", leads to necrotic or apoptotic cell death [21]. Recent studies have shown that calpains and caspases (two classes of death proteases activated by increased intracellular calcium) contribute to prolonged increases in intracellular calcium following excitotoxic stimuli by cleaving and inactivating membrane calcium pumps [22, 23]. Thus, following an initial (sub lethal) calcium increase, defective cellular calcium clearance magnifies the initial insult by prolonging the duration of increased intracellular calcium. Cell injury and death that occur because of over activity of glutamatergic neurotransmission is referred to as excitotoxicity.

Despite a wealth of preclinical data implicating excitotoxicity in the pathogenesis of CNS injury, efforts to interrupt excitotoxicity using glutamate receptor antagonists are only effective if given before or shortly after the time of ischemic or traumatic injury in experimental animals [24–27]. In human trials, administration of NMDA receptor antagonists up to several hours after stroke and traumatic brain injury was not effective and actually increased mortality and morbidity in some patients [18, 28–32]. One explanation for these negative results is that following traumatic brain injury, NMDA receptor deactivation occurs between 15 min and 1 h in regions of injured cortex and hippocampus; NMDA receptors remain deactivated for at least 7 days, and NMDA receptor deactivation correlates with deficits in a working memory task at 2 weeks after injury [33]. Interestingly, administration of NMDA reversed the cognitive deficits associated with NMDA receptor deactivation after acute traumatic brain injury [33]. Taken together with other studies implicating acute CNS inflammation as one cause of NMDA receptor deactivation [34], the data suggest that long-term memory deficits induced by acute CNS injury may be initiated by an acute neuroinflammatory response that inhibits NMDA receptor function in cortical and hippocampal brain regions critical for learning and memory. This hypothesis, testable in the laboratory, may elucidate relationships between acute brain injury, the associated inflammatory response, and lasting learning and memory dysfunction in experimental animals and patients with acute brain injury.

Metabotropic Glutamate Receptors in Acute CNS Injury

The first demonstration that excitatory amino acids can activate receptors other than ligand-gated ion channels involved cultured striatal neurons stimulated with glutamate, which stimulated inositol phosphate formation, rather than ion flux [35]. The mGlu5 receptor is coupled to Gq/G11 protein and

its activation stimulates phosphatidylinositol hydrolysis. mGluR5 also stimulates mRNA translation by activating the ERK/MAPK-interacting kinase (Mnk1)/eukaryotic initiation factor 4E (eIF4E) pathway, and the phosphatidylinositol-3-kinase/mammalian target of rapamycin (mTOR)/p70S6K pathway [36]. In postsynaptic elements, mGlu5 receptors are physically linked to NMDA receptors and enhance their function [37, 38]. Currently, potent and subtype-selective ligands currently under clinical development are among the most promising drugs in the treatment of inherited and acquired neurological and psychiatric disorders (reviewed in [36, 39]).

The mGluR5 is particularly interesting because of its role in acute CNS injury paradigms. Chronic activation of microglia and persistence of biochemical indices of inflammation such as TNF-α and NF-κB activity occurs for months to years after acute brain and spinal cord injury [40]. These observations suggest that chronically activated microglia may contribute to progressive neuronal cell death and white matter loss in chronic neurodegenerative conditions such as CNS trauma [41], through release of pro-inflammatory cytokines and reactive oxygen and nitrogen species [40, 42]. Interestingly, mGlu5 receptors are expressed in astrocytes, oligodendrocytes, and microglia as well as neurons. In microglia, stimulation of mGluR5 induces potent anti-inflammatory effects that are mediated in part via inhibition of membrane bound NADPH oxidase. Microglia express functional mGluR5 receptors which, when stimulated by specific agonists, inhibit NADPH oxidase and down regulate the release of pro-inflammatory factors, rendering microglia less toxic to neighboring cells [43, 44]. Intrathecal administration of the mGluR5 agonist (RS)-2-Chloro-5-hydroxyphenylglycine (CHPG) for 7 days after spinal cord injury in rats improved recovery for up to 28 days and reduced brain tissue and white matter loss, and attenuated microglial-associated inflammatory responses [45]. CHPG also reduced infarct volume in a rat stroke model [46]. Although more work needs to be done to distinguish effects of mGluR5 signaling via glia versus other cell types (including neurons as well as non-neural cell types outside the CNS), and truly specific mGluR5 agonists remain to be developed, stimulation of mGluR5 receptors is a promising therapeutic strategy to limit neuroinflammation and improve outcome in acute and chronic CNS disorders, including traumatic brain and spinal cord injury.

Cell Death After Acute Brain Injury

A number of insults to the CNS may initiate complex cascades of intracellular biochemical events that lead to delayed neuronal death, as well as death of other vulnerable cell types remote from the injury center [21, 47–53]. Because cell death may occur hours to weeks after CNS injury, it is hoped that a better mechanistic understanding will result in novel treatments to preserve tissue and neurologic function. The last 30 years has witnessed impressive advances in understanding basic mechanisms of how cells die after acute brain injury. Excitotoxicity, oxidative stress, and programmed cell death are major pathways that are central to the pathogenesis of ischemic and traumatic brain cell death [54]. Understanding how injured brain cells die is difficult because numerous interrelated, complex mechanisms contribute to the execution phases, and little is known about the mechanisms that initiate death programs after acute brain injury [53, 55, 56]. This section will present an overview of three modes of cell death, the major pro-cell death pathways, and initiating mechanisms involved in acute brain cell death. Figure 33.1 shows a simplified overview of some of the pathways involved.

Necrosis

In the past 5 years, the cell death field has undergone dramatic advances, particularly in the understanding of mechanisms governing necrosis. Long regarded as an uncontrolled mode of cell death that occurs during overwhelming cellular stress, necrosis has recently been understood as a genetically programmed mode of death executed by serine/threonine kinases with mechanisms fundamentally different from caspase-mediated apoptosis. Here, we will briefly review the history of the discovery of programmed necrosis pathways [57, 58] and discuss programmed cell death after CNS injury in terms of what is known about programmed necrosis and apoptotic mechanisms.

Severe ischemic, infectious, epileptogenic, or traumatic insults to the brain induce early cell death that is characterized by cell membrane permeability, organelle swelling, cellular and nuclear shrinkage, metabolic failure and depletion of cellular energy reserves, loss of ion pump function, and cell death that induces a marked local inflammatory response that propagates tissue injury. This mode of neuronal cell death is referred to as necrosis [59]. Necrosis was traditionally viewed as passive resulting from physical cellular disruption or severe ischemic/metabolic insults that induce profound energy failure. This view of necrosis as an unregulated entity was first challenged in 1988 by the discovery that TNF alpha could induce cell death with necrotic-like morphology [60]. A role for mitochondrial reactive oxygen species in the execution of necrosis was discovered in 1992, and in 1996 interaction between TNF receptor 1 and receptor interacting protein kinase 1 (RIPK1) was established as one trigger for programmed necrosis [61, 62]. In 2000, a landmark study showed that RIPK1 mediates TNF induced necrosis independent of caspases [63], and in 2003, Chan and colleagues introduced the term

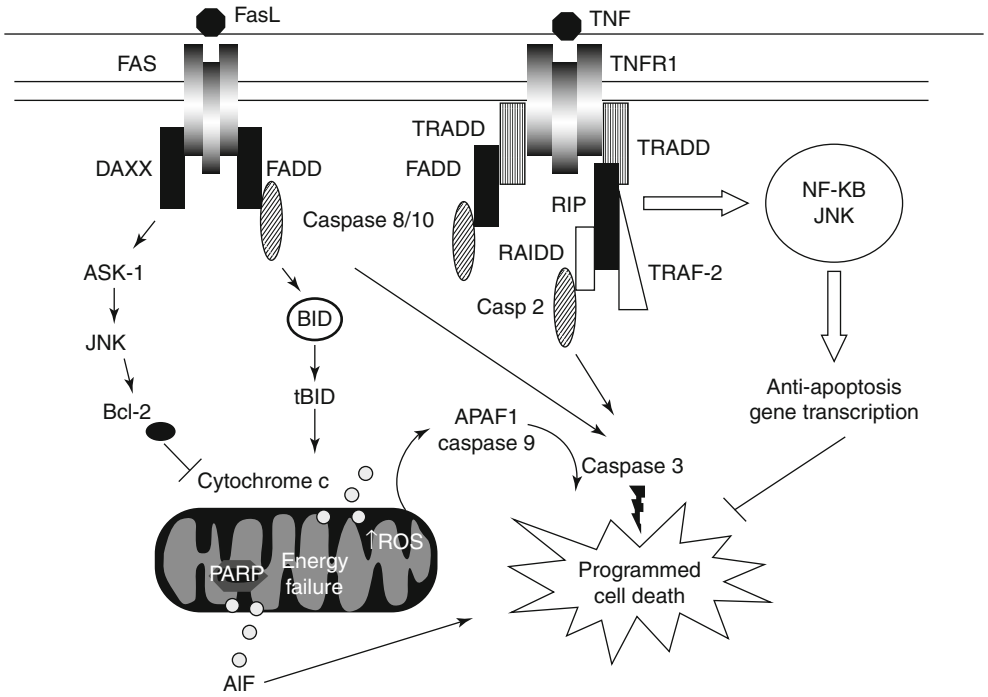


Fig. 33.1 Cell death pathways and acute brain injury. Fas and Tumor Necrosis Factor receptor 1 (*TNFR1*) are prototype death receptors that signal apoptosis through Fas Associated Protein with a Death Domain (*FADD*), by activating initiator caspases such as caspases 8, 10, and 2. Mitochondria release cytochrome c and other apoptogenic factors (e.g., apoptosis inducing factor) leading to programmed cell death. In addition, TNFR and bid activation can also induce necrosis through oxidative stress and mechanisms that remain to be clarified. Abbreviations: *FasL* Fas ligand, *TRADD* TNFR associated protein with a death domain, *RIP* receptor interacting protein, *RAIDD* RIP-associated ICH-1 homologous protein with a death domain, *TRAF-2* TNF receptor-associated factor-2, *JNK* jun-N-kinase, *NF-kB* nuclear factor-kappa B, *ASK-1* apoptosis signal-regulating kinase 1, *bcl-2* B-cell lymphoma-2, *PARP* poly-ADP[ribose] polymerase), *AIF* apoptosis inducing factor, *ROS* reactive oxygen species

"programmed necrosis" in the setting of viral infection [64]. In 2005, Degterev and Yuan used a chemical library screen and identified the tryptophan derivative, necrostatin-1, as a specific and potent inhibitor of programmed necrosis, and coined the term "necroptosis" to describe necrostatin-inhibitable necrosis [65, 66]. Following this discovery, the same group identified RIPK1 as the specific target of necrostatin-1 in 2008 [67].

Necrostatin-1 reduces acute cell death and improves functional outcome in stroke, traumatic brain injury, and neonatal hypoxia/ischemia models, suggesting that programmed necrosis contributes to acute CNS injury [65, 68, 69]. Although the exact biochemical mechanisms that mediate necrosis are still relatively unknown, several key pathways have been implicated, including poly-ADP-ribose polymerase (PARP) and apoptosis inducing factor (AIF) activation, oxidative stress via cytosolic NADPH oxidase or mitochondrial dysfunction, activation of calpains and other proteolytic enzymes, and energy failure resulting from collapse of the mitochondrial transmembrane potential and rapid depletion of intracellular ATP stores [56, 70]. Excitotoxic death can be necrotic in the context of extreme insults, whereas milder forms of excitotoxic injury in CNS insults may trigger delayed caspase-mediated cell death sometimes referred to as apoptosis.

Caspase-Dependent Apoptosis

Caspase-mediated apoptosis is an evolutionarily conserved, genetically programmed cell suicide process that is mediated by activation of a family of death-inducing cysteine proteases termed caspases [71–73]. At least 14 known cysteine proteases promote apoptosis by cleaving substrates at specific tetrapeptide amino acid sequences [59, 74]. Caspases exist as proforms that when cleaved at specific aspartate residues form tetrameric active complexes that cleave and inactivate diverse cellular substrates, such as cytoskeletal proteins, inhibitors of DNA endonucleases, and cellular enzymes required for survival. Activity of effector caspases results in classic apoptotic cellular morphology and cell death. Initiator caspases, such as caspases 2, 8, and 9, cleave and activate effector caspases 3, 6, and 7. Other caspases are involved in inflammatory responses and do not directly mediate cell death. Activated caspases are found in ischemic and traumatic brain tissue and cerebrospinal fluid of humans

[53, 56]. Genetic or pharmacologic inhibition of caspases reduces tissue damage in experimental stroke and TBI, but does not always improve functional outcome [75].

Apoptosis is characterized by morphologic and biochemical features distinct from necrosis. Caspase-dependent apoptosis, for example, is characterized by cell shrinkage, chromatin condensation, internucleosomal DNA fragmentation in multiples of 280 bp (known as DNA laddering due to the classic pattern produced by DNA gel electrophoresis), formation of nuclear apoptotic bodies, and engulfment of dying cells by phagocytes or neighboring cells in the absence of a local inflammatory response [76]. At the molecular level, activated caspases and proteolytic products of their substrates are detectable, as well as externalization of membrane phosphatidylcholine (which signals phagocytosis) and internucleosomal DNA fragmentation that reacts with terminal transferase in the TUNEL assay, a commonly used in situ marker for apoptosis.

Caspase-independent programmed cell death is mediated by apoptosis-inducing factors released from mitochondria, without concomitant activation of caspases [77–80]. One such factor, AIF, is a phylogenetically ancient flavoprotein encoded by a gene on the X chromosome and expressed in most tissues [81]. AIF functions as an electron acceptor/donor in the mitochondrion, and has a second apoptogenic function as well. Following acute cellular injury, AIF translocates to the cytosol and to the nucleus, where it induces nuclear chromatin condensation and large scale (approximately 50 kb) DNA fragmentation. This mode of cell death produces margination of nuclear chromatin and cellular morphology distinct from that of caspase-dependent apoptosis.

Intrinsic Pathway of Apoptotic Cell Death

The "intrinsic pathway" is a major apoptotic pathway that involves release of pro-apoptotic factors from injured mitochondria. Proteins involved in the intrinsic cell death pathway include the BCL-2 family of pro-apoptotic proteins (i.e., bax and bad), mitochondrial oxidoreductases such as cytochrome c and AIF, some caspases, and DNA fragmentation factors such as caspase activated DNAse and endonuclease G. Following acute brain injury, apoptosis may be triggered by a number of pathologic mechanisms, including ischemia, trauma, excitotoxicity, oxidative stress, energy failure, and others [48, 56]. These pathologic events can lead to depolarization of the mitochondrial inner membrane and release of cytochrome C (or other apoptogenic factors such as AIF in caspase-independent death). Cytochrome C interacts with an adapter protein "apoptotic protease activating factor" (Apaf-1), ATP, and procaspase-9 in the cytosol to form an "apoptosome", where caspase-9 is autoactivated by self-oligomerization. Caspase-9 cleaves and activates caspase-3, leading to caspase-dependent apoptosis. Other mechanisms of mitochondrial-mediated cell death include generation of reactive oxygen species in response to excitotoxic and other stimuli, and energy failure through overactivation of the DNA repair enzyme poly(ADP)-ribose polymerase (PARP, discussed below). Thus, the mitochondrion not only controls cellular respiration but also is a rheostat for cellular damage and a central mediator of cell death after acute CNS injury.

The Extrinsic Cell Death Pathway

Another route to programmed cell death involves activation of membrane bound "death receptors" of the tumor necrosis factor receptor (TNFR) superfamily, such as Fas and TNFR1 [82–85]. Ligand binding induces activation of death receptors, which then recruit cytosolic adapter proteins such as Fas associated protein with a death domain (FADD) and TNFR associated protein with a death domain (TRADD). Binding between death receptors and their adapter proteins occurs via homotypic interactions between evolutionarily conserved death domain sequences. Activated adapter proteins bind initiator procaspases, such as procaspase 2, 8, and 10, through death effector domain (DED) sequences present in adapter proteins and procaspases. The resulting complex formed by a death receptor, adapter protein(s), and procaspase is a death inducing signaling complex (DISC). Self-aggregation of initiator procaspases at the DISC induces their autoactivation, and activated initiator caspases process and activate procaspases 3, 6, and 7, which mediate cell death. Alternatively, activated caspase-8 can cleave and activate cytosolic bid, a pro-apoptotic Bcl-2 family member that induces release of cytochrome c from mitochondria [86, 87]. Of note, mice deficient in bid have reduced infarct volume and caspase-3 activation after experimental cerebral ischemic injury [88], and bid can also induce necrotic cell death [89]. Thus, activation of bid links the extrinsic death pathway, initiated by death receptor activation, to mitochondrial (intrinsic) pathways that may culminate in apoptosis or necrosis. In the case of programmed necrosis, the signaling complex is comprised of RIPK1, RIPK3, cytosolic adapter proteins such as FADD, and others that initiate necrotic death signaling pathways [90].

In addition to cell death pathways, activated TNFRs may induce intracellular signaling pathways and new gene expression that favor cell survival. For example, activation of NF-κB is anti-apoptotic in the setting of CNS injury, whereas activation of Jun-N-kinase (JNK) by death receptors is pro-apoptotic in ischemic brain. In neuronal cells, JNK activation is involved in apoptosis in response to stress or withdrawal of survival signals, whereas NF-κB protects against TNF- and Fas-induced apoptosis by promoting transcription of antioxidant and anti-apoptotic genes including Bcl-2 family members that inhibit

cytochrome c translocation and other apoptotic and necrotic death pathways [91–94]. Thus, TNFR family members may activate multiple intracellular signaling pathways that initiate complex, redundant, and often opposing responses, the net effect of which determines cell survival or death.

Our group and others have studied death receptor signaling in acute brain injury. In experimental cerebral ischemia, inhibition of TNFα and Fas ligand together reduces infarction volume by as much as 80 % [95]. Following cerebral contusion in mice and humans, a Fas-FADD-procaspase-8 DISC assembles in brain early after trauma and is associated with activation of caspases and ongoing cell death [96]. Because death receptor signaling is highly redundant, it is not surprising that genetic inhibition of Fas alone fails to reduce lesion volume or acute cell death after experimental cerebral contusion [97], although Fas inhibition does reduce cerebral ischemic infarction volume [98] and sequelae of traumatic spinal cord injury [99–101]. We have found that genetic or genetic/pharmacologic inhibition of TNFα and Fas receptor together reduces posttraumatic brain lesion volume, and more importantly seems to improve neurologic function, after controlled cortical impact in adult and immature mice [97]. Based on these preliminary findings, we believe that TNFRs, and their downstream adapter proteins, are attractive therapeutic targets to ameliorate tissue damage and functional neurologic deficits after ischemic, traumatic, and other forms of CNS injury and degenerative CNS diseases.

The PARP Suicide Hypothesis

Poly(ADP-ribose) polymerase-1 (PARP-1) is an abundant nuclear DNA repair enzyme that stabilizes DNA damaged by oxidative stress. Upon activation by severe DNA damage, PARP-1 hydrolyzes NAD(+) to nicotinamide and transfers ADP ribose units to histones and other nuclear proteins, including PARP-1 itself. ADP-ribosylation inhibits protein function and facilitates DNA repair, but overactivation of PARP-1 can deplete cellular stores of NAD(+) and ATP, resulting in energy failure and cell death. DNA damage by oxygen radicals or excitotoxicity induces PARP-1 activation during acute ischemic and traumatic brain injury. Lesion size after experimental stroke is dramatically reduced in PARP-1 knockout mice. Following traumatic brain injury, PARP-1 knockout mice had similar lesion size but improved neurologic function compared to wild type [102]. Excessive PARP-1 activation is also implicated in models of Parkinson's disease and traumatic spinal cord injury [103–105]. In addition to necrosis via depleted energy reserves, PARP-1 induces release of AIF from mitochondria leading to programmed cell death [106]. Finally, PARP-1 is a transcription factor that modulates expression of genes involved in cell death and survival. Recent studies using specific PARP-1 inhibitors show that partial inhibition of PARP-1 preserves brain NAD(+) stores and improves functional outcome after traumatic brain injury in mice, whereas more complete pharmacologic PARP-1 inhibition impairs spatial learning in naïve as well as injured mice [107]. These studies highlight the multiple roles of PARP-1 in traumatic and ischemic brain injury, and underscore the difficulties involved in development of therapies targeting proteins with complex and multiple diverse functions in the brain.

Studies in experimental traumatic brain injury often demonstrate very little correlation between cell death and functional outcome, and interventions that inhibit cell death may or may not influence motor and memory function. Thus, it is not yet clear that inhibiting apoptotic cell death will prove beneficial to patients with head injury [56]. The most effective therapeutic strategies will probably target multiple mechanisms in addition to cell death, such as derangements in cerebral blood flow and energy metabolism, or neurotransmitters and their receptors that are involved in the motor and cognitive functions adversely affected by acute brain injury (discussed below).

The Mitochondrial Permeability Transition Pore

The mitochondrial permeability transition (MPT) pore is a voltage-gated channel that, when open, allows molecules and ions with a mass < 1,500 Da to pass through the inner mitochondrial membrane to the intermembrane space. Oxidative stress, or rapid and extreme increases in intracellular calcium associated with excitotoxicity, triggers the assembly of an MPT pore, which has as its critical components cyclophilin D binding to an adenine nucleotide translocator [108]. Opening of the MPT pore releases stored calcium into the cytosol, and dissipation of the mitochondrial inner transmembrane potential uncouples the electron transport system from ATP hydrolysis. These events lead to energy failure, enhanced production of reactive oxygen species (ROS), a secondary increase in intracellular calcium, release of apoptogenic factors from the mitochondria, and cell death [109]. Compounds that block the MPT pore, such as cyclosporine A and its derivatives, are protective in experimental stroke and TBI models, suggesting that the MPT pore is a key regulator of cell death mechanisms, both necrotic and apoptotic [108].

Oxidative Damage in Acute Brain Injury

Under normal conditions, a critical balance exists between the production of oxidant free radicals and the antioxidant defense that protect cells in vivo. Free radicals are defined

as molecular species that contain one or more unpaired electrons. During normal metabolism, they are involved in enzymatic reactions, mitochondrial electron transport, signal transduction, activation of nuclear transcription factors, gene expression, and the antimicrobial action of neutrophils and macrophages [110]. The balance between oxidants and antioxidants in injured brain may be disturbed by increased production of free radicals because antioxidant defenses in brain (such as superoxide dismutase, catalase, glutathione, ascorbate, and alpha-tocopherol) are not adequate to completely neutralize upregulated oxidant species after trauma or ischemia/reperfusion [111]. The severity of oxidant-antioxidant imbalance determines the magnitude of injury to the cell.

Free radicals can react with almost every molecule found in living cells, including DNA, membrane lipids, proteins, and carbohydrates. A major consequence of oxidative stress is damage to cellular macromolecules. During lipid peroxidation, peroxyl or hydroxyl groups may be added to unsaturated fatty acids, or fatty acid carbon chains may be cleaved during reaction with unpaired electrons in to generate aldehydes. Free-radical damage to proteins may cause cross-linking, carbonyl formation, and protein denaturation. DNA bases may also be modified by oxidation, resulting in single- and double-strand breaks or mispairing of purine and pyrimidine during DNA replication.

The brain has a number of characteristics, which make it especially susceptible to free radical mediated damage. Brain lipids are highly enriched in polyunsaturated fatty acids, and brain regions such as substantia nigra and striatum have high concentrations of iron, which catalyzes production of free radicals. Both of these factors increase the susceptibility of brain cell membranes to lipid peroxidation. Because the brain is critically dependent on aerobic metabolism, mitochondrial respiratory activity is higher than in many other tissues, increasing the risk of free radical "leak" from mitochondria; conversely, free radical damage to mitochondria in brain may be tolerated relatively poorly because of this dependence on aerobic metabolism.

Free radicals have been implicated in the pathogenesis of central nervous system injury, including TBI, spinal cord injury, cerebral ischemia, and neurodegenerative diseases [52, 110, 112–115]. Reactive oxygen species may modify excitotoxicity by downregulating ion flux through NMDA receptors, however, exposure to oxidative stress can also enhance NMDA receptor-mediated neurotoxicity particularly when antioxidant defenses are depleted. Free radicals contribute to cell death at several points in the apoptotic cascade, serving as initiators, early signals, and possibly late effectors of apoptotic neuronal death. As previously mentioned, oxidative stress can also contribute to cell death by facilitating mitochondria transition pore formation [111]. Proof that excessive oxygen radical generation is fundamental to the pathogenesis of acute brain injury derives from studies in which superoxide dismutase (SOD) knockout mice had increased brain damage, whereas mice overexpressing SOD had reduced brain damage and improved functional neurologic outcome, after experimental stroke and TBI [116–119].

Reactive Oxygen Species (ROS)

ROS formation during ischemia-reperfusion may originate from several sources (Fig. 33.2), including nitric oxide synthase (NOS) activity, mitochondrial electron transport, multiple steps in the metabolism of arachidonic acid and, in some species (e.g., rodents), xanthine oxidase, which is produced by hydrolysis of xanthine dehydrogenase. The oxygen molecule (O_2) qualifies as a radical because it has two unpaired electrons, each located in a different orbital, both "spinning" in the same direction. This parallel spin is one reason for poor reactivity of O_2 with cellular constituents, despite its potential as an oxidizing agent. Acceptance of a single electron by an O_2 molecule forms the superoxide radical, O_2^-, which has one unpaired electron. Superoxide itself has limited reactivity and is capable of inactivating only a few enzymes directly. The NADH dehydrogenase complex of the mitochondrial electron transport chain is one of the enzymes shown to be a direct target for superoxide attack [120]. Excess superoxide is removed by converting it to H_2O_2, a reaction that is catalyzed by SOD. This reaction is an important defense mechanism in aerobic organisms [120]. Overall, both O_2^- and H_2O_2 have limited chemical reactivity, but they can generate highly reactive hydroxyl radicals ($OH^\bullet$) by reacting with transition metals such as iron and copper. After closed head injury in rats, peak hydroxyl radical formation occurred by 40 min, and hydroxyl radicals are increased for several hours after experimental acute subdural hematoma [121–123]. Increased hydroxyl radical production also occurs in brain after focal cerebral ischemic injury in rodents [124]. Superoxide production has been detected after experimental spinal cord injury [125], CNS inflammation and ischemia-reperfusion [126], and fluid percussion TBI [127]. Superoxide radical is believed to be the principal mediator of microvascular damage after TBI, and superoxide dismutase attenuates brain microvascular damage after TBI [128, 129].

Reactive Nitrogen Species (RNS)

Nitric oxide synthase (NOS) has been identified as another source of ROS/RNS with special relevance to pathological conditions (Fig. 33.2). NOS is homologous to P450 cytochrome *c* reductase; cofactors in the reaction are FMN, FAD, tetrahydrobiopterin and NADPH. Three types of NOS have been identified: Ca^{2+}/calmodulin-activated neuronal

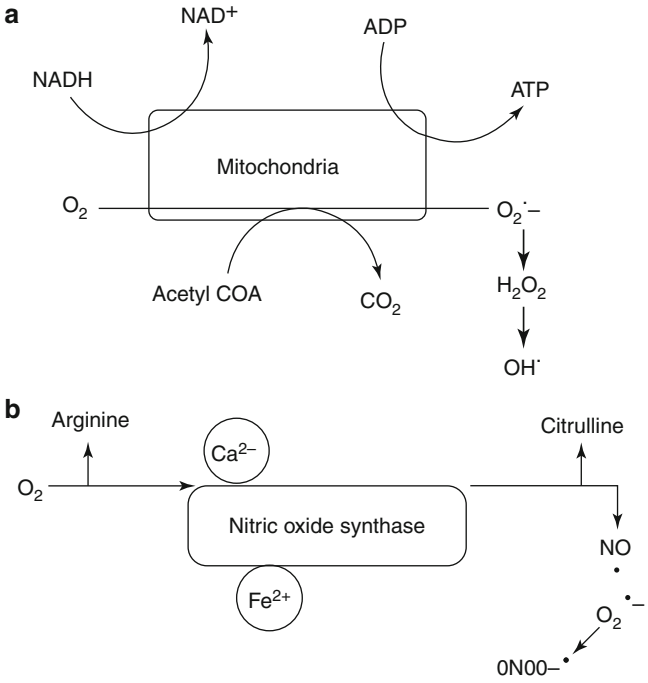


Fig. 33.2 Oxidative stress pathways. (**a**) Reactive oxygen species generated by mitochondrial electron transport and (**b**) reactive nitrogen species generated by nitric oxide synthase (*NOS*). Peroxynitrite (ONOO–) is a highly toxic species that signals apoptosis and necrosis after acute brain injury. Other oxidants are generated in damaged mitochondria by the electron transport chain and molecular oxygen. Abbreviations: *NO* nitric oxide, $O_2^{\bullet}$ singlet oxygen, H_2O_2 hydrogen peroxide, $OH^{\bullet}$ hydroxyl radical

NOS (nNOS), endothelial NOS (eNOS) and inducible NOS (iNOS). NOS normally converts arginine and molecular oxygen to citrulline and nitric oxide (NO), a free radical gas. Nitric oxide is lipid-soluble, readily crosses cell membranes, and functions in control of cerebral blood flow (NO mediates vasodilatation), neuronal communication, synaptic plasticity and memory formation, intracellular signal transmission, and release of neurotransmitters [130]. NO may exist as nitrosonium (NO^+), $NO^{\bullet}$, and nitroxyl anion (NO^-). NO^+ is thought to contribute to NMDA toxicity, whereas NO^- is thought to be neuroprotective by downregulating the NMDA receptor and inhibiting glutamate release presynaptically, through activation of guanylate cyclase. NO, which has limited radical reactivity, can combine readily with O_2 and possibly H_2O_2 to produce peroxynitrite (ONOO–), a highly oxidizing, non-radical compound that oxidizes lipids, proteins and DNA. Nitric oxide-mediated peroxynitrite contributes to acute brain injury in part by inducing DNA damage and activating PARP, as well as directly by oxidizing key cellular constituents. On the other hand, NO can inhibit excitotoxicity by downregulating NMDA receptor function via S-nitrosylation; NO may inhibit caspase activity in a similar manner. Thus, reactive nitrogen species may have both beneficial and detrimental effects in acute brain injury. Inhibition of the early peak of NO in brain following TBI, which is likely mediated by nNOS, improves neurological outcome after experimental TBI [130]. However, later after injury there is a relative NO deficiency associated with cerebral hypoperfusion; augmentation of NO during this time, by administering L-arginine, improves cerebral blood flow and outcome in several models [130]. A delayed increase in NO after traumatic injury, mediated by iNOS, is also observed in experimental TBI; experimental studies suggest both deleterious and protective effects of iNOS in rodent TBI models. Formation of peroxynitrite by iNOS early after injury is detrimental, and iNOS inhibition may therefore be protective [131]. In contrast, iNOS knockout mice have impaired long-term spatial memory acquisition after experimental TBI, suggesting that iNOS is critical for recovery mechanisms [132]. Recent studies support a beneficial role for iNOS in TBI by maintaining endogenous antioxidant reserves, and that iNOS contributes strongly to (deleterious) protein nitrosylation and nitration reactions [131]. Thus, NO can exert beneficial and detrimental effects in the injured brain, depending on the magnitude of its production, temporal distribution after injury, and other factors.

In the first comprehensive clinical study of oxidative injury in children with TBI, Bayir and colleagues found progressive depletion of antioxidant reserves and evidence for free radical-mediated lipid peroxidation in cerebrospinal fluid samples [133]. These investigators later reported increased S-nitrosothiols (transfer of NO groups to cysteine sulfhydryls on proteins) in CSF of children with severe TBI and decreased intracranial pressure, and postulated that S-nitrosothiols could be neuroprotective after TBI by virtue of nitrosylation and inhibition of NMDA receptors and caspases [134]. In adult patients, lipid peroxidation was noted early after severe TBI and was more prominent in males vs. females, suggesting that females have less oxidative damage than males during acute brain injury, and enhanced neuroprotection mediated by female gonadal hormones [135]. In that study, therapeutic hypothermia tended to decrease lipid peroxidation in males but not females. These data suggest that differences in susceptibility to oxidative injury may explain, at least in part, gender-specific differences in pathophysiology and outcome observed after acute and neurodegenerative brain injury [136].

Oxidative Stress and Neuroinflammation: Mediators of Neurologic Dysfunction After Brain Injury

Does the brain's endogenous inflammatory response to acute injury influence subsequent neurologic dysfunction observed in patients with TBI, meningitis, and other forms of acute CNS injury? In mice subjected to closed head

injury, an initial increase in NMDA receptor activation, consistent with acute excitotoxicity, is observed in brain regions proximal to the injury site. From 1 h to 1 week later, however, pronounced NMDA receptor deactivation is observed in cortex and hippocampal regions involved in learning and memory, and is associated with motor and cognitive dysfunction after TBI [33]. Downregulation of NMDA receptor function is also observed after injection of lipopolysaccharide into rat brain and is prevented by treatment with an antioxidant [34]. These observations led to the hypothesis that desensitization of NMDA receptors after stroke and TBI may in part account for the failure of clinical trials using NMDA receptor antagonists to improve outcome in patients with stroke and TBI [33].

More recently there have been an increasing number of studies linking neurodegeneration that occurs during the acute and chronic phases of CNS injury to microglial activation [42]. Part of the microglial activation response to CNS injury or exposure to toxins involves assembly and activation of NADPH oxidase, a multimeric protein comprised of four cytosolic subunits ($gp40^{PHOX}$, $p47^{PHOX}$, $p67^{PHOX}$, and p21-RAC-1, a GTP binding protein) and two membrane bound subunits ($gp91^{PHOX}$ and $p22^{PHOX}$). Different combinations of subunits yield several NADPH oxidase isoforms; NADPH oxidase 1 is comprised of gp91 as a core component. The NADPH oxidase complex plays a key role in microglial production of reactive oxygen species, particularly superoxide, which can react with nitric oxide and from highly neurotoxic oxygen metabolites including peroxynitrite. In addition, ROS induce proinflammatory gene transcription through redox sensitive transcription factors such as NF-κB, including upregulation of inducible nitric oxide synthase, TNFα, and other cytokines and chemokines. This leads to a vicious cycle of persistent microglial activation and inflammation [41, 137], that has recently been implicated in the pathogenesis of neuron loss in Parkinson's disease (a progressive CNS disorder that may begin with an acute exposure to environmental toxins) and neuron loss, white matter damage, and functional outcome in experimental stroke and spinal cord injury [40, 42, 138].

Chronically activated microglia upregulate NADPH oxidase and secrete superoxide, which is neurotoxic, and potentiates cell-autonomous microglial expression of proinflammatory cytokines by activating redox sensitive transcription factors. Thus, chronically activated microglia are hypothesized to lead to chronic neurodegeneration in a variety of CNS injuries and diseases including traumatic brain injury, meningitis, ischemic stroke, intracerebral hemorrhage, seizures, and peripheral nerve and spinal cord injury [40, 42, 43, 138–145]. This hypothesis has led to an active search for agents that deactivate microglia even in the chronic phase of CNS injury with the hopes of sparing tissue damage and restoring function; NADPH oxidase is a major target of this approach [146, 147]. Another approach would be to activate factors that induce microglial silencing, such as CD200 receptor signaling in order to prevent or attenuate the deleterious microglial response to CNS injury [148, 149]. Judging from the number of studies already reported on this subject in 2011, these concepts are likely to drive the acute CNS injury field for quite some time in the near future.

Oxidative Stress, Oxidative Lipidomics, and Apoptosis

Lipidomics is the study of lipids, their molecular interactions, and their function within the cell. Lipids are isolated from biological samples by exploiting the high solubility of their hydrocarbon chains in organic solvents [150]. Mass spectroscopy is employed to create a "lipid profile" for the composition and quantity of specific lipids contained in the sample. Using computer algorithms that identify lipid fragments formed during mass spectroscopy, information about the molecular identity, composition, and oxidation state of individual lipids can be obtained from cultured cells or brain tissue. The lipid profile can be used to monitor cellular responses to injury [151, 152]. The recent introduction of soft-ionization mass spectroscopy techniques, which allow for examination of intact biomolecules without requiring their fragmentation, has permitted rapid analysis of specific molecular species of lipids directly from tissue slices [151].

Phospholipids are a fundamental component of CNS tissue architecture and function. They have a crucial role not only in providing membrane structure in cells, but also as mediators of signal transduction [150, 153]. Phospholipids are composed of a glycerol backbone, a phosphoester-connected head group, and a mixture of polyunsaturated, monounsaturated, and saturated fatty acid chains. Polyunsaturated phospholipids are particularly vulnerable to oxidative modification because they possess a carbon group that has a weak energy bond with its protons [154]. Free radicals can act by abstracting these weakly bonded protons, leaving a carbon free radical with an unpaired electron, which can then form further free radicals and perpetuate oxidation. These processes of oxidative modification are thought to be involved in many disease states and in the response to oxidative stress [155, 156].

Oxidative lipidomics employs mass spectroscopy to examine oxidative modifications of lipids, lipid interactions with other molecules, and contribution of oxidized lipids to cellular functions. Recent studies have suggested that specific modifications of lipids may be critical for particular cellular functions and may play a role in disease states [151]. Markers of lipid peroxidation are increased in brain tissue, serum and CSF following clinical and experimental TBI [133, 157–159]. Some studies have suggested that

elevated markers of lipid peroxidation might also be associated with outcome after ischemic and hemorrhagic stroke and TBI [160–162]. Surprisingly, however, studies analyzing lipid oxidation following TBI using oxidative lipidomics techniques have not found oxidation of the most abundant lipid species in the brain, which would be expected if lipid peroxidation were occurring via free radicals. This evidence suggests that lipid peroxidation in TBI may not occur via random free-radical mechanisms, which would be expected in those tissues which are most susceptible to free radical oxidation – those with a higher concentration of polyunsaturated phospholipids [151]. Instead, specific phospholipids such as mitochondrial cardiolipin (CL) and extra-mitochondrial phosphatidyl serine (PS) appear to undergo the greatest amount of oxidative change following brain injury, whereas the most abundant phospholipid species escape damage.

What is the mechanism of phospholipid oxidation following TBI? One hypothesis is that lipid peroxidation following TBI results from the execution of an apoptotic program of cell death. Cytochrome c is known to act as a catalyst of peroxidation in apoptosis. Cytochrome c forms a high-affinity complex with mitochondrial CL when mitochondrial CL is translocated to the outer mitochondrial membrane early in apoptosis [163]. The cytochrome c/CL complex is a potent CL-specific peroxidase. Furthermore, CL peroxidation is necessary for the release of pro-apoptotic factors from the mitochondria into the cytosol [151]. Cytochrome c is also known to act on extra-mitochondrial PS after being released into the cytosol. These peroxidation events initiate caspase mediated apoptotic cell death, however their role in necrotic cell death is less explored. The study of oxidative lipidomics has suggested that non-random lipid oxidation following TBI may reflect targeted peroxidation processes in apoptosis. Inhibition of CL peroxidation may therefore suppress apoptosis and represents a potential avenue of neuroprotection in TBI [151]. In particular, small molecule inhibitors and regulators, such as 2,2,6,6-tetramthylpiperidine-N-oxyl (TEMPO) and a-synuclein (Syn) may have potential protective effects [164]. As more work is done in this field, greater understanding of how lipid oxidation initiates and propagates neuronal cell death may lead to new therapeutic targets for TBI and other forms of acute brain injury.

Extracellular Matrix Proteases

In addition to intracellular proteases, extracellular proteases may also play important roles in brain injury. Emerging data in the past 6 years implicate proteases from the matrix metalloproteinase (MMP) family of genes as well as serine proteases from the plasminogen axis [165]. These proteases are critical during brain development by altering extracellular matrix and allowing cellular migration and neurite and axonal extension [166]. Dysregulation of MMPs after brain injury leads to aberrant proteolysis of the neurovascular matrix, resulting in blood brain barrier (BBB) damage and cell death.

Matrix Metalloproteinases in Acute CNS Injury

In experimental models of cerebral ischemia, many MMPs are significantly increased [167–170]. Overall data point to a deleterious role for MMPs, at least acutely. MMP injection into brain is neurotoxic [171]. Treatment with inhibitors or MMP-neutralizing antibodies reduce edema and infarction in rat and mouse models of cerebral ischemia [168, 172–174]. Recently, it was demonstrated that MMP-9 knockout mice had significantly smaller lesion volumes compared to wild type mice after focal cerebral ischemia and traumatic brain injury, emphasizing the central role of this protease, at least in mouse systems [167, 168, 175]. A similar finding was obtained after transient global cerebral ischemia, with hippocampal neuron death being significantly ameliorated in MMP-9 knockout mice [176].

After neurovascular injury, MMPs may degrade basal lamina, weaken vessels, and predispose them to leakage and rupture. In experimental studies, activation of MMP-9 and degradation of critical protein components of cerebral blood vessels have been correlated with the development of hemorrhage and edema [177, 178]. In a recent study, pharmacological inhibition of MMPs significantly decreased the incidence of hemorrhage in a rabbit model of embolic stroke [167], and matrix degradation and subsequent BBB leakage was reduced after cerebral ischemia in MMP-9 knockout mice [167]. MMP activation and BBB disruption is associated with the generation of reactive radicals [179], thus interactions between oxidative stress and the proteolytic cascade may ultimately mediate the progression of edema and infarction. Within the context of early neurovascular inflammation, cytokines and vascular adhesion molecules may further amplify MMPs in activated endothelium [180–182]. Cell adhesion molecules themselves may also be substrates for MMPs, thus comprising a complex interactive system of response to brain injury.

In addition to vascular leakage, extracellular matrix proteases may also directly induce cell death. By disrupting homeostatic signals between cells and matrix, specialized modes of apoptosis called anoikis may be initiated [183]. In vivo and in vitro evidence is beginning to accumulate to support the importance of these novel mechanisms in stroke. In a nonhuman primate model of focal cerebral ischemia, areas in which vascular antigens are lost correlated with regions of neuronal injury [184]. Loss of neuron-matrix interactions promotes neurotoxicity by downregulating cell survival integrin signaling pathways [185]. The importance

and relevance of these matrix mechanisms has recently been underscored by the finding that fibronectin knockout mice suffered increased neuronal apoptosis and brain infarction after cerebral ischemia [186].

Matrix Metalloproteinases in CNS Recovery

In recent years, another facet of MMP biology has come to light – the fact that MMPs may have beneficial actions during stroke recovery [187]. During brain development, MMPs contribute to morphogenesis of the CNS [188, 189]. In this context, MMPs may allow precursors hidden in matrix compartments to be activated through its proteolytic activity. MMP9 has been found to increase angiogenesis in normal and neoplastic tissues through its ability to mobilize VEGF from the extracellular matrix [190]. In a demyelination model, MMP-9 knockout mice had impaired myelin formation [191]. The corresponding rescue experiment showed that MMP-9, expressed locally around a demyelinating lesion of the spinal cord, was able to facilitate remyelination [190]. It is note-worthy that while acute MMP inhibition improved locomotor recovery, extended treatment failed, consistent with the hypothesis that remodeling requires MMP activity in the CNS.

MMP9 has also been implicated in hippocampal-dependent associative learning [192]. Administration of the MMP inhibitor GM6001 interferes with LTP in mouse hippocampal slices, and hippocampal slices from MMP-9 deficient mice exhibited decreases in LTP, which resolved with the addition of exogenous MMP-9. In behavioral experiments, MMP-9 knockout mice displayed reduced memory when tested for hippocampus-dependent context conditioning [192]. In a rodent ischemic stroke model , administration of an MMP inhibitor reduced acute blood–brain barrier damage but produced impairments in long-term functional recovery [193].

In addition to MMP-9, MMP-2 may be involved in recovery after spinal cord injury [194]. After spinal cord injury, MMP-2 is upregulated at the time when reactive astrocytes promote glial scar formation [195]. In an experimental model of spinal cord injury, MMP-2 deficient mice had more white matter injury and decreased motor recovery [195].

These data are consistent with the hypothesis that MMPs have multiple roles in the process of central nervous system injury and recovery. In the acute injury phase, MMP activity appears to be deleterious. However, in the recovery phase MMPs may comprise key molecules for promoting the remodeling of ischemic brain via angiogenesis, vasculogenesis, or neurogenesis. Research that aims at developing therapies for neuroprotection and injury recovery will need to address this possible dichotomy in MMP function.

Matrix Metalloproteinases as Stroke Biomarkers

Peripheral blood MMP levels in stroke patients have increasingly become a promising clinical tool by providing potential biomarkers for diagnosis and prognosis [187]. High levels of MMP9 have been found in patients with ischemic and hemorrhagic strokes, compared with healthy individuals [196, 197]. More importantly, acute MMP-9 levels have been related to infarct size, poor neurological outcome, and hemorrhagic transformation complications [197–199]. MMP-9 levels assessed at hospital entry have been found to correlate with infarct volume seen on diffusion-weighted MRI [200], with stroke lesion growth, and even with the application of thrombolytic therapy [201]. MMP-9 levels have been found to be especially elevated in patients that received t-PA [202], with significantly higher levels in stroke patients treated with t-PA compared with untreated patients [203]. Consistent with the hypothesis of deleterious MMP actions during ischemic stroke, hyperacute MMP-9 blood levels emerged as a powerful predictor of further hemorrhagic complications after t-PA thrombolysis [204]. In a study comparing brain and blood MMP-9 levels in a middle cerebral artery occlusion ischemic model in rats, an early increase in MMP-9 was detected in blood, whereas brain MMP-9 levels showed a delayed elevation [205]. In another study examining the utility of minocycline as an MMP inhibitor in a rat embolic stroke model, t-PA treatment was associated with augmented MMP-9 levels in blood, while the ability of minocycline to protect against t-PA associated hemorrhagic transformation was correlated with decreased MMP-9 levels [206]. A recent clinical trial confirmed these experimental findings. In the MINOS trial, thrombolysis stroke patients who received minocycline had lower plasma levels of biomarker MMP-9 compared to patients that received tPA alone [207].

Investigations regarding other MMP blood levels in ischemic stroke have not yet yielded definite results [187]. However, experimental and clinical data regarding the use of MMP-9 as a stroke biomarker are promising and may contribute to clinical stroke management in the future.

Tissue Plasminogen Activator

Besides MMPs, proteases from the plasminogen system are also involved in brain injury. In ischemic stroke, the primary role for tissue plasminogen activator (tPA) is beneficial lysis of the offending clot. However, accumulating data now suggest that pleiotropic and deleterious actions of tPA may also participate in neurovascular pathology. Tsirka, Strickland, Lipton, and colleagues first demonstrated that tPA knockout mice were protected against excitotoxic hippocampal injury and focal cerebral ischemia [208, 209]. tPA knockout mice

suffered significantly less brain damage after trauma compared to wild type mice [210]. tPA may interact with the NR1 subunit of the NMDA receptor complex and amplify damaging calcium currents during excitotoxicity [211]. tPA (and plasmin) may also target non-fibrin substrates in brain extracellular matrix, as tPA augmented excitotoxic neuronal death in the hippocampus by degrading inter-neuronal laminin and disrupting pro-survival cell-matrix signaling [212]. Although the main effect of tPA in stroke certainly occurs within the targeted vessel, these findings suggest that extravascular actions of tPA may complicate its intended role in clot lysis.

High dysregulated levels of tPA in brain will surely be deleterious in terms of disrupting blood–brain barrier integrity and mediating neuronal excitotoxicity. However, similar to MMPs, this extracellular protease may also possess more subtle beneficial actions. tPA plays a central role in modulating synapses for long-term potentiation [213, 214]. Recent studies now suggest that tPA released from reactive astrocytes after focal ischemia can promote neuronal plasticity in recovering brain [215].

Most brain injury research has been focused on intracellular mechanisms of cell death. However, accumulating data now suggest that extracellular proteases can also play key roles by degrading neurovascular matrix and inducing both BBB disruption and cell death. Hence, targeting both intra- and extracellular proteases may offer more effective approaches for treating stroke and brain injury in the future.

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Tumors of the Central Nervous System

34

Robert F. Tamburro Jr., Raymond Barfield,
and Amar Gajjar

Abstract

Primary malignancies of the central nervous system (CNS) are the second most common malignancy during childhood. Data suggest that over 3,000 children under 20 years of age are diagnosed with a brain or spinal cord tumor annually in the United States. These tumors account for the majority of cancer-related deaths in children. The age of peak incidence varies with the histological type of CNS tumor. The presenting signs and symptoms also vary by age as well as by tumor location. Tumor location is an important prognostic factor as the extent of tumor resection has been associated with outcome for many histological types.

Tumors of glial origin constitute approximately 50 % of all primary CNS tumors in children, and are grouped into low and high grade gliomas based on their histopathology. Low grade gliomas are a heterogeneous group of tumors with long-term survival rates exceeding 80 % with appropriate treatment. Prognosis for high grade gliomas is much more discouraging. Examples of other CNS tumors include medulloblastomas which occur predominantly in the cerebellum and are the most common malignant CNS tumor in children. Long-term prognosis has improved dramatically for medulloblastoma with 5-year survival rates between 50 % and 80 %. Ependymomas are the third most common pediatric brain tumor. Survival rates in excess of 80 % are being reported for these tumors when gross total tumor resection is attained in conjunction with well designed three dimensional conformal radiation. Craniopharyngiomas represent a benign intracranial tumor with a high survival rate. However, craniopharyngiomas are associated with significant morbidity due to their proximity to the optic nerves and the hypothalamus. Although this chapter is focused primarily on intracranial tumors, acute spinal cord dysfunction from metastatic cord compression is a neurological emergency. Treatment requires timely recognition and prompt intervention as prognosis is most related to the degree of disability at diagnosis.

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Brain tumor • Glioma • Astrocytoma • Ependymoma • Medulloblastoma • Craniopharyngioma
Spinal cord tumor

Primary malignancies of the central nervous system (CNS) are the second most common type of malignancy during childhood, second only to the leukemias. They are now considered the leading cause of childhood cancer-related death. Although this chapter is focused primarily on CNS tumors and their treatment, it is important to realize that neurologic symptoms in the pediatric oncology patient may result from a variety of conditions. These conditions may, or may not, be related to the cancer and its treatment. Table 34.1 illustrates a broad differential diagnosis of an altered mental status in the pediatric cancer patient.

Table 34.1 Etiology of acute alterations in consciousness in children with cancer

Tumor
Primary central nervous system tumor
Metastatic tumor
Leukemic meningitis
Hyperleukocytosis
Infection
Meningitis: bacterial, fungal
Viral encephalitis
Brain abscess
Septic shock
Cerebrovascular accident
Seizure/postictal state
Disseminated intravascular coagulation
Treatment
Cytotoxic chemotherapy
Methotexate
Cytosine arabinoside
Corticosteroids
Ifosfamide
5-Fluorouracil
Arabinofuranosyl guanine (Ara-G)
Supportive care
Opioids
Benzodiazepines
Antihistamines
Anticonvulsants
Tricyclic antidepressants
Leukoencephalopathy
Metabolic abnormality
Hyponatremia (Syndrome of inappropriate secretion of antidiuretic hormone)
Hypoglycemia/hyperglycemia
Hypomagnesemia
Uremia
Postradiation somnolence syndrome
Hypotension/hypertension
Dehydration
Hypoxia
Anemia
Hepatic failure
Depression

Adapted from Rheingold and Lange [1]. With permission from Wolters Kluwer Health

Brain Tumors

Incidence

Data suggest that over 3,000 children under the age of 20 years are diagnosed with a brain or spinal cord tumor each year in the United States with some estimates exceeding 4,000 children; approximately three quarters of these tumors are malignant [2–5]. Primary brain tumors are the most common solid tumor in the pediatric population, comprising 20–27 % of all childhood cancers, and are the second most common childhood malignancy overall [2–4, 6–9]. The incidence of central nervous system tumors is fairly stable through the first 7 years of age (36.2 cases per million during infancy and 35.2 per million at 7 years). However, between the ages of 7 and 10 years, a 40 % decrease in the incidence of these tumors has been reported (rates decreasing to 21.0 per million). This rate remains relatively steady through 18 years of age at which point there is another drop in the incidence to approximately 17 per million [2] (see Fig. 34.1).

The peak incidence of the various histological types of tumor also differs with age [2] (see Fig. 34.1). Astrocytomas have a bimodal incidence peaking at both 5 and 13 years of age. Medulloblastoma/primitive neuroectodermal tumor (PNET) incidence rates are fairly steady from birth through 3 years of age and decline steadily thereafter. The incidence of ependymoma is highest through the first 3 years of age with a peak incidence in the second year of life (see Fig. 34.1).

Although significant progress has been made in the diagnosis and treatment of childhood brain tumors, they are still responsible for the majority of cancer-related deaths in children [7–12]. Figure 34.2 depicts the most common brain tumors in children by histology [3]. Figure 34.3 depicts the most common pediatric brain tumors by location, an important consideration, as symptoms of brain tumors are frequently related to the location of the tumor [3]. Children with brain tumors frequently require pediatric critical care services for the management of increased intracranial pressure (ICP), post-operative care, and the treatment of other tumor or treatment-related morbidity.

Presenting Signs and Symptoms

The presenting signs and symptoms of brain tumors vary by the age of the child and by the location of the primary tumor.

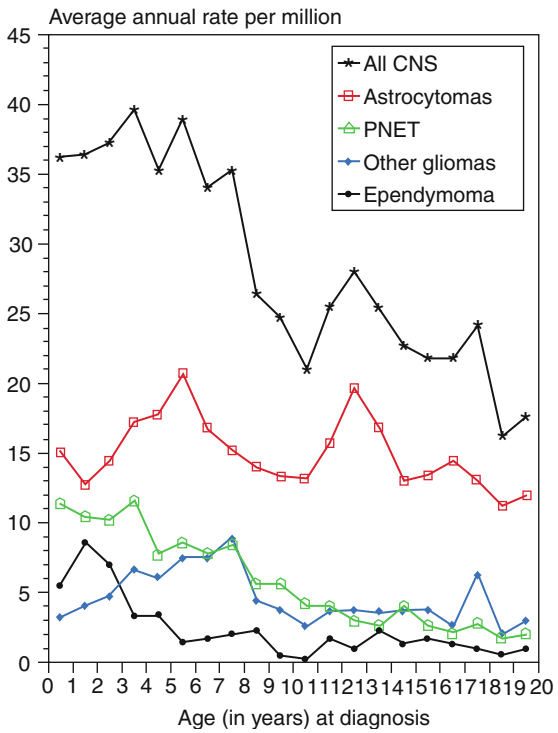


Fig. 34.1 Malignant central nervous system tumor age-specific incidence rates, all races, both sexes SEER, 1986–1994 (Reprinted from Gurney et al. [2], p. 54, Fig. III.3)

Tumors that present in infancy tend to be more insidious because of the non-specific nature of the clinical symptoms including vomiting, irritability, lethargy, macrocephaly, failure to thrive, and loss of or delay in attaining developmental milestones [8, 10]. In contrast, older children may better communicate specific neurologic deficits. Additionally, signs and symptoms related to increased ICP, including headache, nausea, and vomiting (particularly upon awakening in the morning) frequently occur in this age group [8, 10].

Supratentorial tumors produce signs and symptoms according to the area of the brain that is affected [8, 10]. For example, cerebral hemispheric lesions may present with focal neurologic findings or seizures, while tumors proximal to the optic chiasm and hypothalamus may produce vision loss, visual field defects, or endocrine abnormalities [10]. Cerebellar tumors, on the other hand, frequently result in ataxia, gait disturbances, and signs of increased ICP secondary to obstruction of the fourth ventricle (see Fig. 34.4) [8, 10]. Brain stem tumors present with cranial nerve abnormalities and/or upper motor neuron signs [8, 10]. Signs and symptoms associated with specific tumor types will be discussed in more detail in the following sections.

Gliomas

Tumors of glial origin constitute approximately 50 % of all primary central nervous system tumors in children (two thirds of the malignant tumors), and are grouped based on the histopathological appearance into low grade and high grade gliomas [3, 8, 10, 13, 14]. These tumors are found throughout the

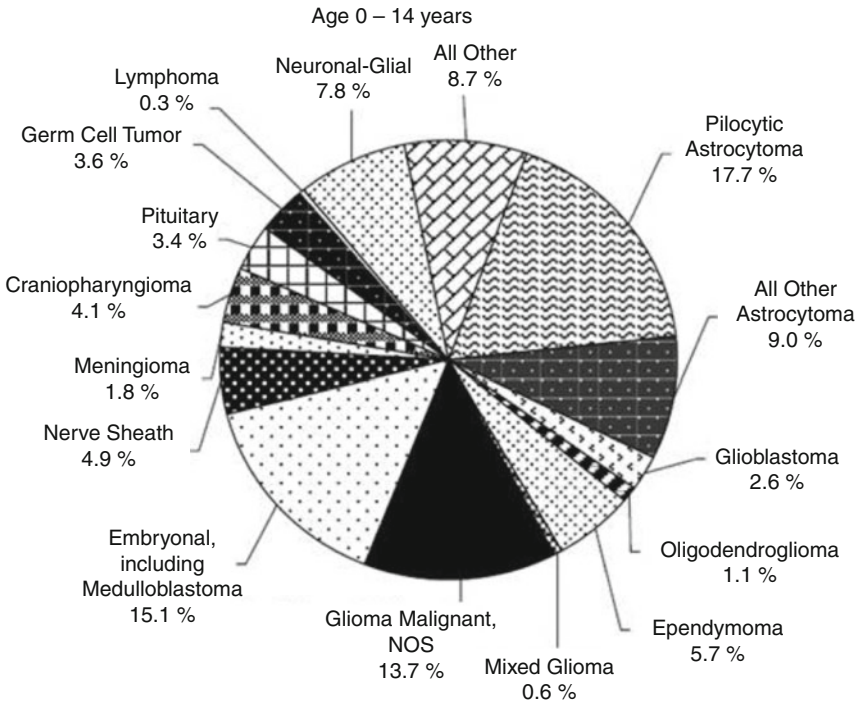


Fig. 34.2 Distribution of childhood primary brain and central nervous system tumors by histology. CBTRUS Statistical Report: NPCR and SEER Data from 2004 to 2008 (Reprinted from Central Brain Tumor Registry of the United States [3], p. 24, Fig. 15)

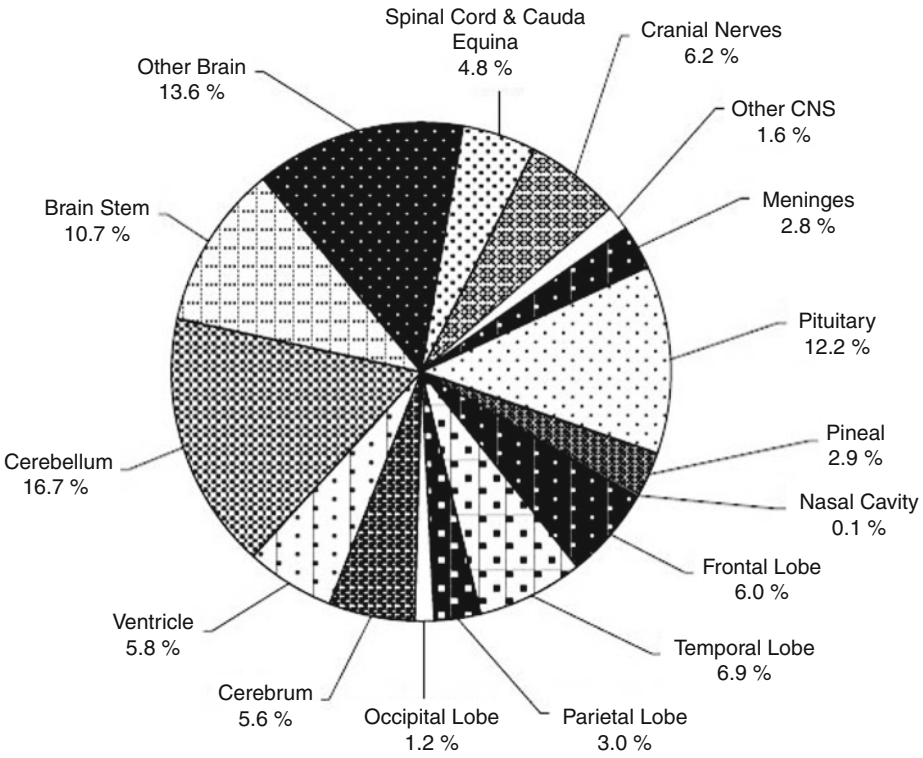


Fig. 34.3 Distribution of all childhood (ages 0–19 years) primary brain and central nervous system tumors by site. CBTRUS Statistical Report: NPCR and SEER Data from 2004 to 2008 CBTRUS (2012) (Reprinted from Central Brain Tumor Registry of the United States [3], p. 23, Fig. 14)

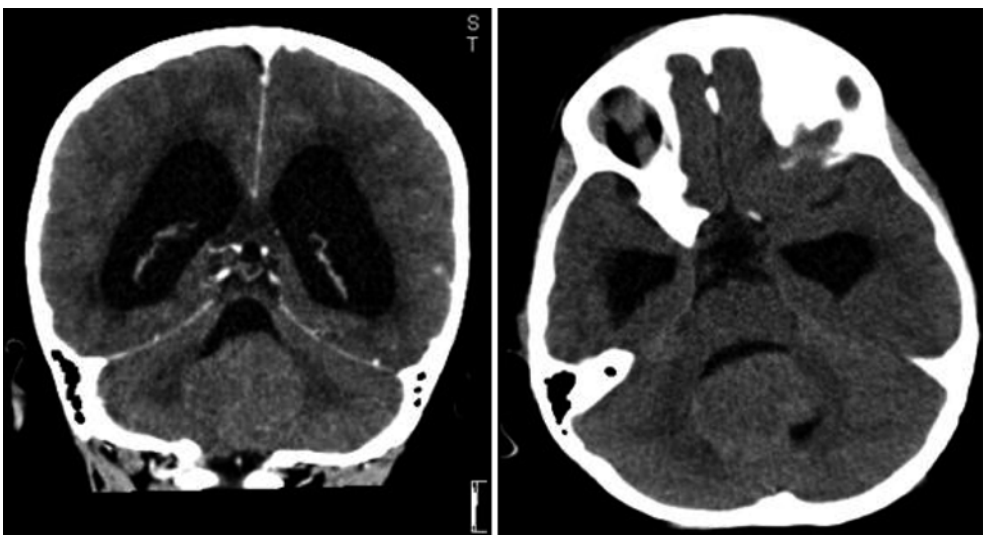


Fig. 34.4 Two views of computerized tomographic image illustrating a large medulloblastoma producing obstructive hydrocephalus (Courtesy of Melanie Comito and Robert Greiner)

CNS and location is an important prognostic factor as clearly the extent of the tumor resection has been associated with outcome [7, 11, 15]. Low-grade gliomas are a heterogeneous group of tumors with an overall long-term survival rate of greater than 80 % with appropriate treatment [7, 11, 16]. The most frequent low-grade gliomas are posterior fossa and cerebral hemisphere astrocytomas. Low-grade gliomas include many histopathological diagnoses: pilocytic astrocytoma and subependymal giant cell astrocytoma (generally categorized as World Health Organization (WHO) Grade I) and pilomyxoid or fibrillary astrocytoma (WHO Grade II) [7, 11].

Pilocytic astrocytomas occur primarily in young children with a median age of 4 years [7]. These tumors can occur at all levels of the neuraxis, but occur most frequently in the cerebellum and the optic pathways [17, 18]. On radiographic imaging, nearly all are brightly enhancing, well-circumscribed tumors that are clearly demarcated from surrounding brain tissue and have little surrounding edema; about half of them are cystic (see Fig. 34.5) [7, 17]. In contrast, Grade II astrocytomas occur at a median age of 10 years, infiltrate into the surrounding normal brain, do not enhance with contrast on diagnostic imaging, and



Fig. 34.5 Magnetic resonance sagittal image of a pilocytic astrocytoma (Courtesy of Melanie Comito and Robert Greiner)

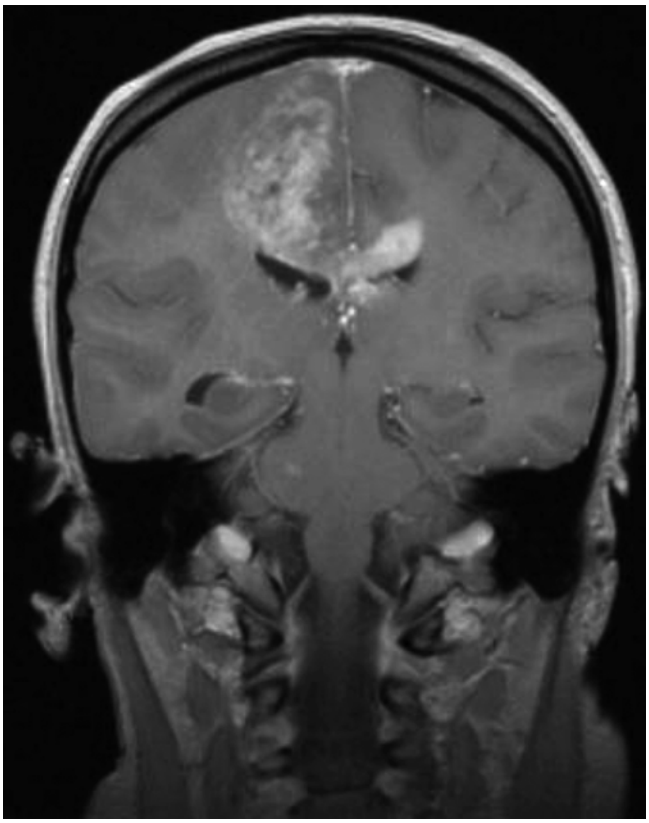


Fig. 34.6 Magnetic resonance image of supratentorial glioblastoma multiforme (Courtesy of Amar Gajjar)

mostly occur as cerebral hemisphere and intrinsic pontine tumors [7].

Pediatric high-grade gliomas are also a diverse group of tumors with different sites of origin and histological features that affect children of different ages [19]. They account for approximately 14 % of all childhood CNS tumors and consist of WHO grade III anaplastic astrocytomas, oligodendrogliomas, and oligoastrocytomas and grade IV glioblastoma multiforme and gliosarcomas [7, 11]. The overall incidence of high-grade gliomas in children less than 19 years of age is 6.3 per 1,000,000 person-years with a roughly equal distribution across age groups and gender [19]. These tumors can arise from any location in the CNS, but are most common in the supratentorial region and the brainstem (see Fig. 34.6). They rarely originate from the spinal cord or the cerebellum [19]. Regardless of location, these poorly circumscribed, highly infiltrative tumors are difficult to treat effectively, with long-term survival rates ranging from less than 10 % to 30 % for most supratentorial tumors and less than 10 % for diffuse brainstem gliomas [7, 19]. The prognosis seems to be better for patients with anaplastic astrocytomas than for those with glioblastoma multiforme although the degree of surgical resection is the most important clinical prognostic factor for children with supratentorial high-grade astrocytomas [7, 11, 19–24].

Supratentorial high-grade astrocytomas make up one-third of all pediatric high-grade gliomas and more commonly affect children during late adolescence (ages 15–19 years) [19]. These astrocytomas constitute 6–12 % of all primary pediatric brain tumors [25]. Children with supratentorial high-grade astrocytomas present with signs and symptoms attributable to the specific area of involved brain, as well as signs and symptoms of increased ICP and seizures [19].

Diffuse brainstem gliomas occur with an incidence of 1.8 per 1,000,000 person-years and constitute 3–9 % of all primary pediatric brain tumors [12, 19]. Children with diffuse brainstem high-grade gliomas classically present between 5 and 10 years of age with a brief history (<2–6 months) of pyramidal tract signs, cranial nerve deficits, and cerebellar signs and symptoms [19, 26]. This clinical picture differs from that of most pediatric posterior fossa tumors in which signs and symptoms of increased ICP dominate and focal deficits assume a secondary place [27]. Moreover, this clinical picture, in conjunction with typical magnetic resonance imaging (MRI) findings of an intrinsic, pontine-based infiltrative lesion that exerts significant mass effect on adjacent structures, including the basilar artery and the fourth ventricle, is highly specific for a diffuse brainstem glioma precluding the need for histological confirmation (see Fig. 34.7) [11, 19, 26]. Although improved MRI imaging has provided benefit in the form of identifying histologically low grade lesions that may be amenable to surgical intervention (e.g. dorsally exophytic brainstem gliomas and focal lesions of the

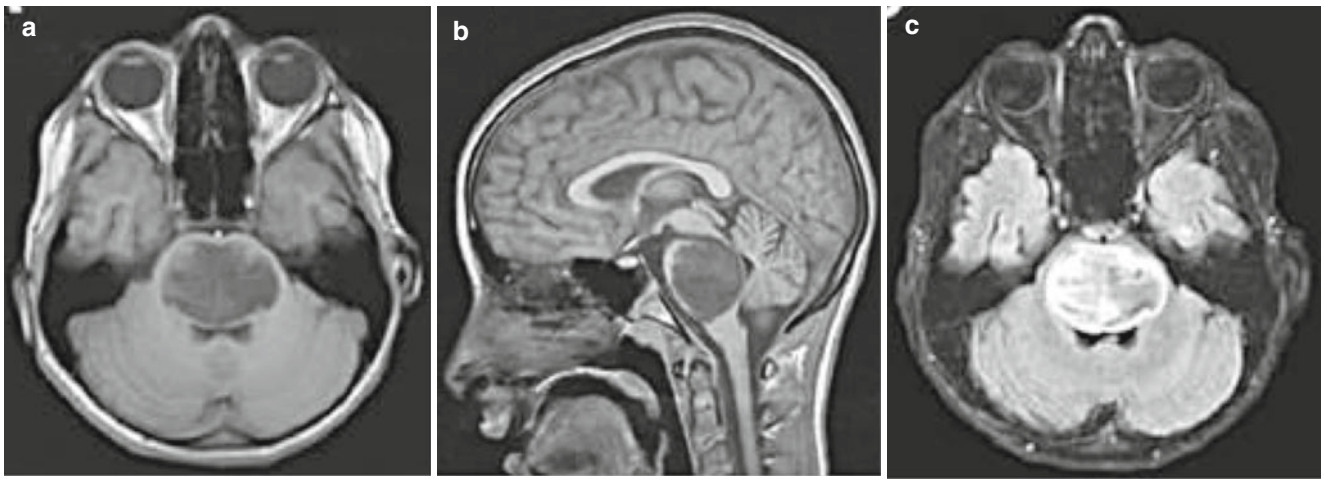


Fig. 34.7 Typical appearance of magnetic resonance imaging scans of a patient with a diffuse brainstem glioma. (**a** and **b**) T1-weighted axial and sagittal images without contrast. (**c**) Axial fluid-attenuated inversion recovery (FLAIR) image (Reprinted from Broniscer and Gajjar [19], p. 202. With permission from Alphamed Press)

midbrain and cervicomedullary junction), it has also resulted in a paucity of available tissue for molecular analysis [11]. The time between the onset of symptoms and diagnosis, as well as the degree of neurologic deficits, are important prognostic factors [25]. Although outcomes are generally poor for patients with diffuse intrinsic brainstem gliomas, those individuals with diffuse brainstem gliomas in association with neurofibromatosis type 1 tend to have better outcomes than anticipated [28, 29].

Medulloblastomas

Medulloblastoma is the most common malignant central nervous system tumor in children and the second most common pediatric brain neoplasm accounting for 12–25 % of all central nervous system tumors in children [3, 7, 30–32]. More than 90 % of medulloblastomas occur in the cerebellum, and medulloblastomas account for nearly 40 % of all pediatric posterior fossa tumors, the most common pediatric posterior fossa tumor overall (see Table 34.2) [30, 34]. Among children, the mean age at presentation is approximately 5–7 years and there is a slight male predilection [30, 31, 34, 35]. Clinical symptoms are usually brief (<3 months) reflecting the aggressive nature of the tumor, and commonly include headache and persistent vomiting [7, 30, 36, 37]. Since more than three fourths of medulloblastomas arise from the midline cerebellar vermis and involve the fourth ventricle, it is not uncommon for patients to present with obstructive hydrocephalus, at times requiring emergent placement of an external ventricular drain (EVD) (see Fig. 34.4) [7, 30, 34]. Macrocephaly, lethargy, and cerebellar signs such as ataxia and dysmetria may also be reported [7]. Truncal ataxia is the most common objective clinical sign and is frequently accompanied by spasticity [30, 36, 37]. Other clinical signs may include papilledema, nystagmus, and positive Babinski and Hoffmann signs [30, 36, 37]. Limb ataxia and dysdiadokokinesis suggest a laterally located mass within the cerebellar hemisphere [30, 36, 37]. Abducens nerve palsy results from compression of the nucleus of the sixth cranial nerve and suggests extraventricular tumor extension [30, 37].

Table 34.2 Relative incidence of common brain tumors in children by location

Supratentorial tumors (45–50 %)		Infratentorial tumors (50–55 %)	
Astrocytoma	23 %	Medulloblastoma	20 %
Malignant gliomas	6 %	Astrocytoma	15 %
Craniopharyngioma	6 %	Brainstem glioma	10 %
Embryonal tumors (PNET and others)	4 %	Ependymoma	6 %
Pineal region/ intracranial germ cell tumors	4 %		
Ependymoma	3 %		
Other	4 %		

Adapted from Halperin et al. [33]. With permission from Wolters Kluwer Health

Although histologically similar, gene expression analyses demonstrate that medulloblastoma is a tumor type distinct from supratentorial primitive neuroectodermal tumors (PNET) [7, 11, 38]. Recent data derived from gene expression analysis suggests that medulloblastoma is a heterogeneous disease that is comprised of at least four main subtypes of tumors [39]. The classic computerized tomagraphic (CT) appearance of a medulloblastoma is a hyperattenuated, well-defined vermian cerebellar mass with surrounding vasogenic edema, evidence of hydrocephalus, and homogeneous

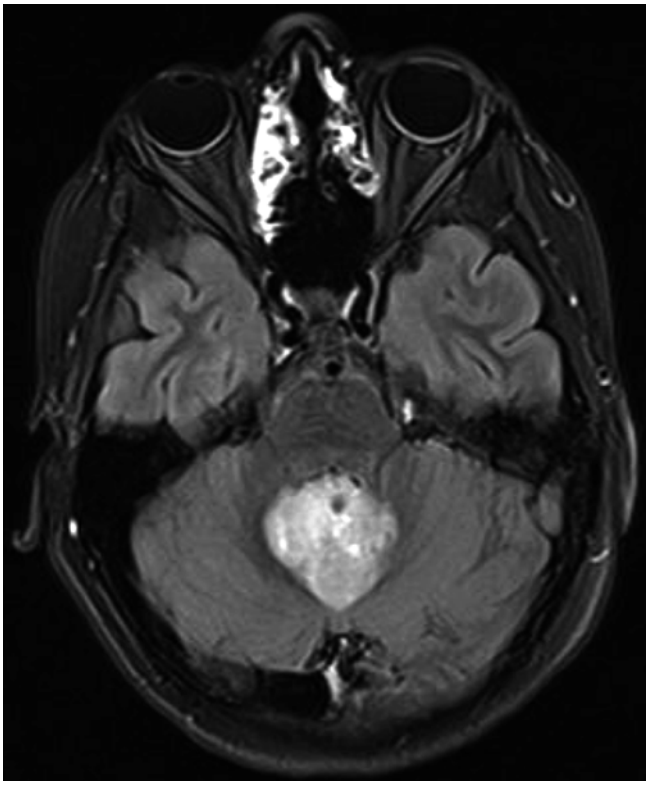


Fig. 34.8 Magnetic resonance T1 FLAIR image with contrast illustrating a medulloblastoma filling the fourth ventricle (Courtesy of Amar Gajjar)

enhancement on contrasted studies in a child less than 10 years of age [30]. MRI generally reveals a brightly enhancing posterior fossa mass with low T1-signal, and intermediate T2- and FLAIR-signals (see Fig. 34.8) [7].

Surgical resection to maximally reduce tumor burden and relieve obstructive hydrocephalus is the initial intervention [7]. A gross total resection is the goal, as this is associated with better long-term outcomes, but subtotal resection may be necessary in the setting of brainstem involvement [5, 7, 35, 40]. Post-operative mutism is not an uncommon complication of posterior fossa resections in children [7, 35, 41]. The incidence of cerebellar mutism syndrome (CMS) in patients with medulloblastoma is as high as 25 % [35]. A study of age- and risk-matched patients documented that those who have CMS after surgery demonstrate lower performance across several domains (i.e., processing speed, attention, working memory, executive processes, cognitive efficiency, reading, spelling, and math). These deficits are apparent as early as 12 months post diagnosis and necessitate careful follow-up with the recommendation of early, targeted intervention [42]. A recent study suggested that cerebellocerebral diaschisis caused by permanent surgical damage to the superior cerebellar peduncle is the mechanism underlying the neurocognitive manifestations of CMS [43] Other post-operative complications may include ataxia, hemiparesis, hydrocephalus, hematoma, aseptic meningitis, gastrointestinal hemorrhage, cervical instability and sixth cranial nerve palsy [7, 40]. Surgery is followed by adjuvant radiation, and chemotherapy based on the patient's risk stratification [5, 7, 35].

Long-term prognosis has improved dramatically in the recent past with 5-year survival rates between 50 % and 80 % now being reported [5, 30, 35, 44–47]. Adolescence, female gender, no tumor spread, and gross total surgical resection are all associated with a better prognosis [30, 34, 44, 46]. Patients with evidence of CSF spread have worse outcomes [47, 48]. Approximately 25 % of these tumors recur and recurrence is associated with a dismal prognosis [30].

Ependymomas

Ependymomas are the third most common pediatric brain tumor accounting for 6–15 % of brain tumors in children [7, 35, 49–51]. They tend to occur in younger children with a mean age at presentation of approximately 3 years and reported median ages ranging from 4 to 6 years [35, 49–51]. Although ependymomas may occur anywhere in the CNS, approximately two thirds of intracranial ependymomas are localized to the posterior fossa [35, 52]. Localization to the posterior fossa is, in fact, more common in children less than 3 years of age [7, 49]. A supratentorial location accounts for the remaining one-third of intracranial ependymomas and is more common in children over 3 years of age [49]. Posterior fossa ependymomas frequently present with symptoms related to obstructive hydrocephalus secondary to compression of the fourth ventricle including headache, nausea and vomiting [7, 49]. Tumor compression of posterior fossa structures may also result in ataxia, hemiparesis, neck pain, torticollis, nuchal rigidity, visual disturbances including nystagmus, papilledema, and cranial nerve palsies [49]. The duration of symptoms is usually less than 6 months at diagnosis [49]. In contrast, supratentorial tumors tend to present with signs and symptoms related to ventricular compression and midline shift including headache, nausea, vomiting, lethargy, papilledema, and cognitive decline or behavioral changes [49].

Ependymomas are usually well-demarcated and distinct from adjacent areas of unaffected brain (see Fig. 34.9) [7, 35]. They may have a large cystic component [35]. The World Health Organization classifies ependymomas as Grade I (myxopapillary), Grade II (cellular, papillary, clear cell and tanycytic) and Grade III (anaplastic); anaplastic ependymomas are less common in children [53].

Surgery is the major treatment modality and the degree of surgical resection appears to be a critical prognostic variable [7, 11, 35, 49–51, 54–58]. A gross total resection is associated

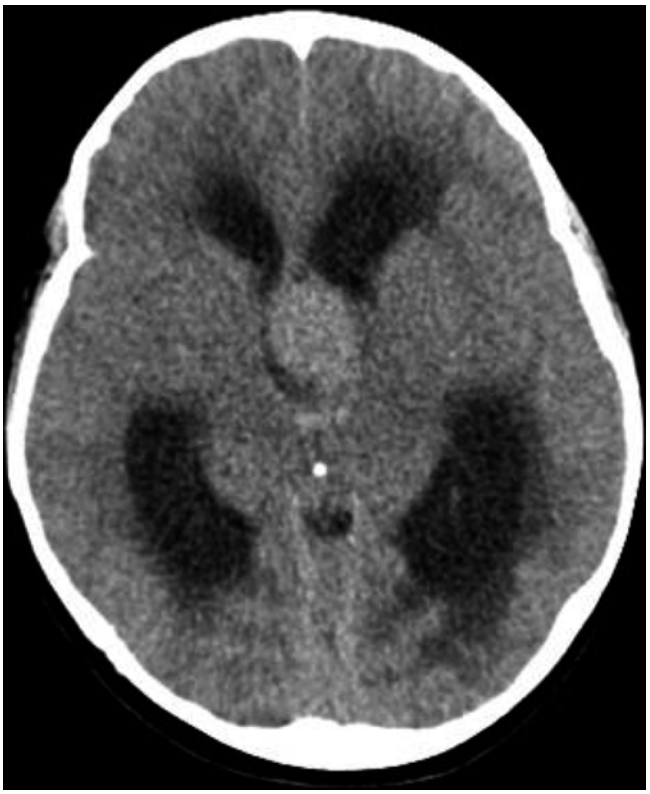


Fig. 34.9 Computerized tomography of a suprasellar ependymoma causing obstructive hydrocephalus (Courtesy of Melanie Comito and Robert Greiner)



Fig. 34.10 Magnetic resonance T1-weighted sagittal image with contrast of a large cystic craniopharyngioma (Courtesy of Amar Gajjar)

with a substantially greater 5-year progression-free survival as compared to a subtotal resection [7, 49–51, 54–58]. Centers that have achieved higher rates of gross total tumor resection in conjunction with well designed three dimensional conformal radiation are now reporting overall 7-year survival rates in excess of 80 % [11, 59, 60]. Younger age (≤3–5 years), metastatic disease, residual disease post surgery, and higher histologic grade are associated with worse outcomes [35, 49–52, 54–58, 61–64].

Craniopharyngiomas

Craniopharyngiomas are the most common tumor to affect the hypothalamic-pituitary region in children and account for approximately 4–10 % of all childhood intracranial tumors [3, 8, 65, 66]. Craniopharyngiomas are thought to arise from epithelial cell remnants of Rathke's pouch at the junction of the infundibular stalk and the pituitary gland, though one case report documents de novo tumor occurrence in a 55-year old woman [67]. The vast majority of these tumors have a cystic component with less than 20 % being totally solid [68]. Although the histology is benign and the overall survival rate is high, these tumors are associated with significant morbidity due to their proximity to the optic nerves and the hypothalamus [65, 68]. The median age of presentation is 8 years, and presenting symptoms are usually related to the location of the tumor including visual disturbances, headache, nausea and vomiting [68, 69]. Endocrine abnormalities and intellectual dysfunction are also common at presentation [68, 69]. The median duration of symptoms has been reported to be 8 months with a range of 1 week to 4 years; the wide range reflecting the nonspecific nature of the symptoms [69]. Neuroimaging is useful in determining the size, exact location, presence of calcification, and the cystic nature of the tumor as well as detecting the presence of hydrocephalus (seen in as many as 23 % of patients) (see Fig. 34.10) [68, 69].

Dr. Harvey Cushing once described the craniopharyngioma as "the most baffling problem which confronts the neuro-surgeon [70, 71]," and 80 years later, its optimal management remains controversial because of the attempt to balance the risks of a slowly progressive disease with the potential for high morbidity associated with treatment [68–70, 72, 73]. Some combination of surgical resection with radiation remains the mainstay of therapy. In the multicenter, European, prospective observational trial (KRANIOPHARYNGEOM), a complete surgical resection was associated with a substantially lower relapse rate and irradiation was associated with a significantly decreased progression rate [74–76]. Diabetes insipidus is a common complication in the immediate post-operative period and the pediatric critical care provider should be prepared for this

complication [69, 77]. In a report of 46 surgical resections for craniopharyngioma, diabetes insipidus was observed pre-operatively in 14 cases, intra-operatively in five others, and post-operatively within 18 h of surgery in 25 of the 27 remaining cases [77]. Long-term replacement of other hormones is almost always required.

Peri-operative Care of Brain Tumors

The pediatric intensivist plays a key role in the peri-operative care of children with brain tumors. For example, these children often present with increased ICP and require emergent attention. The initial management may include controlling the airway in a neuro-protective manner, facilitating transport to the imaging center, and consulting the neurosurgeon in a timely manner. Increased ICP is often secondary to obstructive hydrocephalus requiring emergent placement of an external ventricular drain [7, 35]. Among posterior fossa tumors with hydrocephalus, a generally accepted tenet is that about one third will require permanent CSF diversion pre-operatively, one third will require permanent CSF diversion post-operatively, and one third will not require any CSF diversion procedure [35]. For tumors with intraventricular extension and hydrocephalus, endoscopy is a neurosurgical technique that can both relieve the pressure and secure tissue for definitive histological diagnosis [78]. Shemie has described a series of seven children who had sudden unexpected death associated with acute hydrocephalus from a previously undiagnosed intracranial tumor, highlighting the need for a high index of suspicion and prompt intervention [79]. In addition to standard management of intracranial hypertension, intracranial tumors are often associated with local vasogenic edema and may benefit from the administration of corticosteroids. Corticosteroids have been used for brain tumors since the 1960s and a remarkable decline in peri-operative mortality rates coincided with their implementation [80–82]. Several mechanisms for the observed corticosteroid-induced reduction in edema in this setting have been suggested including reduced expression of the edema-producing factor vascular endothelial growth factor (VEGF) [80, 83, 84]. The edema-reducing effect of corticosteroids is rapid with decreased capillary permeability being noted 1 h after a single dose in an animal model [85]. In addition to decreasing edema around the tumor, corticosteroids have also been demonstrated to decrease the tumor volume itself [86, 87]. Dexamethasone appears to be the most commonly used corticosteroid in the neurosurgical literature.

In the operating room, the introduction of intra-operative MRI imaging has significantly enhanced the ability of the neurosurgeon to achieve gross total resection at the time of original surgical intervention, reduce hospitalization duration, and decrease the incidence of motor and sensory deficits [88–90]. Diffusion tensor imaging has recently been described as a neurosurgical technique to minimize potential neurologic injury and facilitate gross total resection [18]. The major drawback to the use of intra-operative MRI guidance is a longer surgical time, and therefore, a longer duration of anesthesia as well as the need for MRI compatible equipment [88, 89]. With the widespread availability of intra-operative MRI in academic pediatric neurosurgery centers, it is likely that neurosurgeons will be become increasingly reliant on the use of this technology. For the intensivist, there is the additional advantage of having imaging studies performed in the operating room available to assist in monitoring the post-operative course of these children.

In addition to emergent pre-operative management and meticulous operative technique, post-operative care may be critical for these patients as well. Intensive care monitoring has been recommended for ≥12–24 h to detect serious post-operative complications and facilitate rapid intervention, as well as to optimize the re-establishment of systemic and neurologic homeostasis [91]. Immediately upon admission to the PICU, a baseline neurologic assessment of the patient must be made so that any subsequent, subtle deterioration may be identified promptly. A clinical deterioration from baseline is an indication for emergent CT imaging. Early post-operative complications that may result in a prolonged PICU course include cerebrospinal fluid leaks, diabetes insipidus, lower cranial nerve palsies, pneumocephalus, intracranial hemorrhage, and significant post-operative edema [92]. In a study of 105 pediatric posterior fossa tumors resections, one-third of the patients were found to have an intra- or post-operative complication including hydrocephalus requiring shunt placement (n = 9), pseudomeningocele formation requiring additional treatment (n = 5), wound problems (n = 4), hematoma requiring craniotomy (n = 3), and gastrointestinal hemorrhage (n = 2) [93]. The association of gastrointestinal hemorrhage with intracranial pathology and posterior fossa resections has been long established [93–95]. Ross described three children with posterior fossa tumors who developed massive exsanguinating upper gastrointestinal hemorrhage within 7 days of their primary neurosurgical procedure and recommended stress ulcer prophylaxis for this patient population [94]. Cerebellar mutism has been reported to occur in approximately 10–30 % of patients undergoing posterior fossa tumor resection; most commonly in children with medulloblastoma and/or brainstem invasion [35, 96]. It occurs with an average onset of less than 2 days post-operatively, but its onset has been reported as to occur as late as 6 days after surgery. It is often the hallmark finding of the posterior fossa syndrome characterized by a number of other neurological abnormalities including ataxia, cranial nerve palsies, hemiparesis and emotional lability [96].

The monitoring of other parameters such as blood pressure, cerebral perfusion pressure, fluid balance, serum

sodium concentration (monitoring for central diabetes insipidus or cerebral salt wasting syndrome), and coagulation studies may be important in the post-operative care of these patients. The use of an arterial catheter may assist in blood pressure management. Although it is vital that an adequate cerebral perfusion pressure is maintained, it is also important to avoid potentially harmful hypertension. Consistent communication with the neurosurgeon and the oncologist will facilitate care. Post-operative imaging, which may provide important prognostic and therapeutic information, is best performed 24 and 48 h of surgery to avoid the effect of normal post-operative changes that may be mistaken for residual disease, and thus, is often the responsibility of the critical care team [8, 20].

Malignant Spinal Cord Compression

Acute spinal cord dysfunction is a neurological emergency and, in a pediatric patient with cancer, is most likely secondary to metastatic cord compression [97]. Acute metastatic spinal cord compression occurs in approximately 3 % of all children with cancer [97, 98] and in 5 % of those with solid tumors [99]. The most common tumors associated with malignant spinal cord compression in children include sarcomas, neuroblastomas, and leukemias/lymphomas [97–101]. Depending on the series, 8–12 % of patients with sarcoma, 7–8 % of patients with neuroblastoma and 2–4 % of patients with lymphoma will develop spinal cord disease [97, 99]. In one large series, 18 % of children with Ewing sarcoma developed this complication [99]. Primary spinal cord tumors are rare in childhood with a reported frequency of 1.9 per 1,000,000 person years [102].

Although often believed to be an end-stage problem, particularly in adults, as many as 33 % of cases in children occur at presentation of their malignant disease with an additional proportion occurring at the time of relapse [97, 101]. Moreover, children differ from adults in both the cause and mechanism of their spinal cord compression [97, 100, 101]. The mechanism of compression in the child is more often direct spread from a paravertebral tumor through the vertebral foramen that impinges upon on the spinal cord directly, without significant bony involvement. The mass compressing the lesion is lateral and spinal stability is usually not a factor [101]. This is in contrast to spinal cord compression in the adult, where metastasis more often invades the epidural space from a metastatic lesion in a vertebral body. This difference, and differences in tumor type (lung carcinoma, breast carcinoma, and prostate carcinomas being the most common causes in adults), suggest a need for a different approach to therapy in children [101]. In light of this, one report suggested that conclusions derived from the adult experience have led to recommendations that are inappropriate for children [99]. Moreover, there is data suggesting that children are more likely to have better outcomes than adults [99].

Pain is the most common symptom in the majority of reports, and may be the only symptom at presentation [97, 100–102]. Spinal tenderness and weakness are other common clinical findings [97, 100–103]. The weakness occurs predominantly in the lower extremities reflecting the most likely locations of the lesions; 6 % cervical, 59 % thoracic, and 35 % sacral [97, 100, 101, 103]. Loss of sphincter control and bowel/bladder dysfunction occurs in approximately 50 % of patients at presentation [97, 101]. Sensory deficits are often the least useful clinical finding as patients are frequently unaware of this finding and they are difficult to ascertain in younger children [97, 100, 101, 104].

The diagnosis of malignant spinal cord compression should be considered in any child with cancer (particularly those tumor types at highest risk, e.g. sarcomas) who presents with back pain, weakness, or sphincter disturbances. Although metastatic spinal cord compression is the most likely cause of spinal cord dysfunction in children with cancer, accounting for 88 % of the cases in one series, other conditions must be considered in the differential [97]. Infection or radiation-induced transverse myelitis, spinal cord stroke, intradural/extradural hematoma, or extradural abscess may all present with similar symptoms in this patient population. Cases may be misdiagnosed as Guillain Barre´ syndrome, sciatica, myopathy, plexopathy, or hip pain from bony metastasis. MRI is the diagnostic test of choice since it is non-invasive, provides high soft tissue resolution, can image several planes, and allows for reconstructed images (see Fig. 34.11) [100, 103]. Although plain radiographs and myelography are falling out of favor, CT imaging is still useful for implantation and instrumentation that may accompany surgery and dose planning for radiotherapy.

Treatment requires timely recognition and prompt intervention. The initial therapy for any child suspected of having malignant spinal cord compression is intravenous dexamethasone [97, 100, 104]. Emergent radiotherapy may be useful, however close proximity to the spinal cord limits the dose that may be administered, and tumor type influences radiosensitivity [99, 100]. Surgery is indicated when neurological dysfunction and an epidural mass are discovered in a child without a pre-existing diagnosis [97, 100]. Surgery may also be indicated if neurological function deteriorates during radiation therapy [97]. Two large pediatric studies have retrospectively assessed the role of surgical intervention in treating malignant spinal cord compression [99, 101]. In a series of 33 children, Raffel reported that a decompressive laminectomy resulted in better neurologic outcomes, both in terms of motor function and sphincter control, than radiation therapy alone [101]. In that series, all patients who were ambulatory prior to surgery remained so, and 5 of 13



Fig. 34.11 MRI picture of extradural malignant spinal cord compression at the T3–T4 level. The *arrows* depict both anterior and posterior compression of the spinal cord (Reprinted from Prasad and Schiff [100], p. 15. With permission from Elsevier)

patients who were not, became ambulatory after surgical intervention. Nine of 13 patients who were incontinent regained bladder control while 10 of 13 regained normal bowel function. Similar results were not observed in the children who received radiation alone. The authors of this study also reported immediate improvement in back pain, reported no surgical mortality or morbidity (although fusions were required in two patients), and recommended that radiation therapy and chemotherapy follow the surgery [101]. In another report of 112 children with malignant spinal cord compression, Klein recommended decompressive laminectomy for children with sarcomas (except for osteogenic sarcoma where it tends to be a late diagnosis and treatment may not be offered), but not for children with small cell tumors unless there was rapid neurologic deterioration or complete loss of motor function [99]. In that study, sarcoma patients treated surgically (n = 31) had a better improvement in neurological status post-treatment than those only medically treated (n = 21) despite no difference in pre-treatment neurologic status. Among the 40 patients with small cell tumors (neuroblastoma, germ cell tumors, Hodgkin lymphoma), there was no difference in outcome independent of treatment modality. However, independent of tumor type, among the 31 patients with a complete motor and sensory level, there was a significant difference in post-treatment neurological status between those treated with a decompressive laminectomy plus medical management (n = 18), and those treated with medical management alone (n = 13) [99]. In fact, 50 % of those treated with a laminectomy became ambulatory after the procedure. Because laminectomy and spinal radiation in children may ultimately result in anterior subluxation, scoliosis, and kyphosis, it appears best to use these therapies in those who will benefit most and to avoid these treatments and their complications whenever possible [99]. Recent studies suggest that in children undergoing surgical resection of a spinal cord tumor, instrumentation or performing a spinal fusion at the time of surgery results in significantly less post-operative spinal deformity [105].

The prognosis of malignant spinal cord compression is most related to the degree of disability at diagnosis, which is associated with the duration of symptoms and the time to diagnosis, emphasizing the need for early detection and intervention [97, 100, 106]. In one small series, 80 % of children who were paraplegic for <24 h regained function as compared to only 43 % of those who were paraplegic for >24 h [97]. Early and aggressive intervention can lead to improved neurological outcomes. Available data suggest that with appropriate and timely intervention, a majority of children who have loss of bowel or bladder function or who are unable to ambulate will regain these abilities [97, 99, 101]. As described above, as many as 50 % of children will regain the ability to ambulate even in cases of a complete motor and sensory level further underscoring the need for aggressive therapy [99].

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Intracranial Hypertension

35

Andrew C. Argent and Anthony Figaji

Abstract

Under both normal and abnormal circumstances intracranial pressure is the result of the interaction of multiple factors including blood pressure (and flow); cerebrospinal fluid dynamics; brain tissue and abnormal fluid or masses. Under pathological conditions these interactions are more complex than has previously been understood, but rational critical care for children with intracranial pathology requires an understanding of these interactions and their effects on brain metabolism. Intracranial pressure may be measured using a variety of techniques. Management of intracranial hypertension requires appropriate monitoring of multiple factors (relating both to parameters such as blood pressure, cardiac output and blood oxygen content and parameters such as the presence of seizure activity, brain oxygen content and brain metabolism); attention to basic parameters; optimization of blood pressure, cardiac output, blood oxygen content and pCO_2 as well as appropriate surgical intervention. It is essential to integrate the information from brain imaging, physiological measurements and responses to therapy in order to understand the optimal management strategy. Surgical interventions may include removal of abnormal mass lesions and appropriate drainage of cerebrospinal fluid, and in particular circumstances may extend to procedures such as decompressive craniotomy. It is likely that appropriate management of brain injury will be dependent on a more complex understanding of the potential interactions of all the factors that determine intracranial pressure and the consequences for the brain.

Keywords

Intracranial hypertension • Cerebrospinal fluid dynamics • Measurement of intracranial pressure • Management of intracranial pressure • Brain injury • Cerebral perfusion pressure Brain oxygen • Neurocritical care • Children

Introduction

Increased intracranial pressure (ICP) (called *intracranial hypertension*) is a common complication of acute brain injury and is known to cause secondary injury by brain shift and cerebral ischemia, leading to poor outcomes. It therefore would seem intuitive that knowing what the ICP is in an individual patient with acute brain injury, and by extension treating intracranial hypertension would be beneficial. However, in truth the relationship between ICP and outcomes is far more complex. Since the early reports of continuous monitoring [1] and management of intracranial hypertension,

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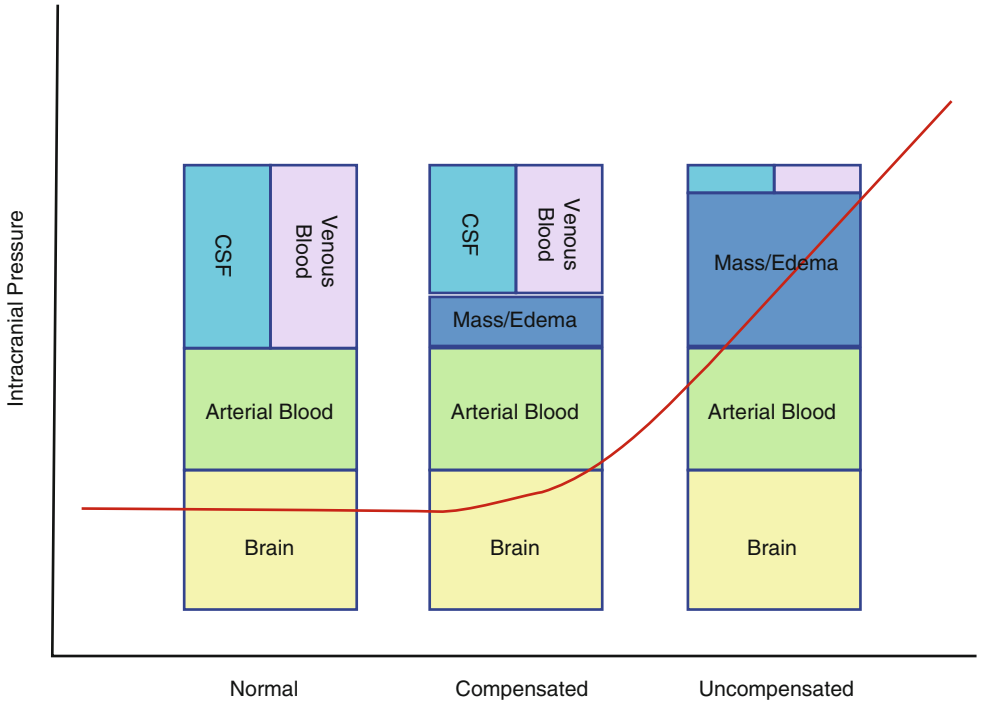


Fig. 35.1 The Monroe-Kellie doctrine

ICP management has become one of the cornerstones of neurocritical care, being used in a wide variety of conditions, including traumatic brain injury (TBI), hydrocephalus, cerebral edema from a myriad of causes (e.g., toxic-metabolic encephalopathy, infection, etc.) or hemorrhage. TBI is the condition most likely to be treated with ICP monitoring, and so serves as a useful template to discuss its merits and limitations. Despite recommendations for the use of ICP monitoring in TBI, largely based on reports that suggest benefit [2–4], there are still many centers that do not routinely use this modality – even when they direct therapy at the management of ICP [5]. Furthermore, and more disturbingly, there have been several reports in adult and pediatric studies that ICP monitoring is not associated with benefit to patients [6–11]. However, with the development of experience and newer technologies, it is becoming clear that the interpretation of ICP, and particularly intracranial hypertension, may be a complex process that has to be tailored very specifically to the context of the individual patient, which may in part explain the lack of stronger evidence for ICP monitoring and treatment, and the heterogeneity of outcomes in different series. Growing evidence now suggests that there may be several different pathophysiological reasons for an increase in ICP, and when ICP is increased, the corresponding changes in cerebral blood flow and tissue oxygenation are not easy to predict [12, 13]. The use of standard approaches in all patients based on a single ICP number regardless of the underlying physiology makes little physiological sense, given that the underlying cause of the increased ICP may not be addressed, and all ICP-lowering therapies have potential adverse consequences.

In this chapter we will first consider the various factors determining normal ICP in children. We will highlight the interaction of these factors that may occur in various pathological situations, and then consider the possible therapies that have been proposed and implemented. Although there are several causes of raised ICP in children – some acute, others chronic – this chapter largely concentrates on the acute causes of increased ICP in critically ill patients and its management.

Intracranial Pressure: The Outcome of Multiple Factors

The brain is surrounded by the cranium, which in adults is a rigid structure with no compliance. In contrast, during infancy there may be considerable compliance related to the fontanelles and sutures (however, acute, life-threatening ICP may develop even in infancy). The cranial space communicates with the lumbar-sacral sac, which is in turn surrounded by rigid structures, although there is more compliance in this region than there is within the intracranial space. The presence of vertebral foramina allows pressures generated within the thoracic and abdominal cavities to be transmitted through the cerebrospinal fluid (CSF) to both the lumbar space and the intracranial space.

The Monro-Kellie doctrine states that the volume within the cranial compartment is fixed; therefore, any increase in the volume of one of the principal components of that cranial space (brain, CSF, blood) must be offset by a change in one of the other components (Fig. 35.1). To understand

Table 35.1 Factors associated with changes in intracranial pressure

	Normally	Abnormal situations
Characteristics of the cranial vault	In adulthood and later childhood the vault is rigid. However in early infancy (particularly in premature infants) the vault may have considerable capacity to expand related to both sutures and open fontanelles	In children with craniosynostosis ICP may be raised depending on the particular sutures involved [15]
Volume of brain and meningeal tissue	this does not vary significantly under normal circumstances	may expand significantly when brain injury or inflammation is present, or when tumours are present
Blood volume present	this can vary substantially depending on arterial and venous pressures, and vascular tone	Under normal conditions the cerebral "autoregulation" controls the volume of blood in the cranium, but this may be lost in the context of injury
Volume of CSF present	CSF is produced, reabsorbed, but can also move through the foramen ovale into the spinal sac.	Obstruction to the flow or reabsorption of CSF will be associated with increased volume
Pressures superimposed on the baseline pressures by	arterial pressures; pressures transmitted through the intervertebral foramina from the intrathoracic and intra-abdominal spaces; venous pressures	
Additional tissues (tumours) and abnormal collection of fluid	Not applicable	Tumours may develop in various parts of the brain, and collections such as subdural blood or pus may also occur
Compensatory mechanisms	Fluids such as blood and cerebrospinal fluid can move out of the intracranial vault in response to increases in other volumes (within constraints)	Once the compensatory capacity has been exceeded, then the ICP will increase

this, one needs to appreciate some of the normal anatomy and physiology of the intracranial space, and how various pathophysiological mechanisms may disrupt this. In a typical adult skull brain tissue volume is about 1,400 ml, blood volume 75 ml and CSF volume 75 ml [14], i.e. blood volume is typically about 5 % of cranial contents. However, brain tissue has limited compressibility and cannot move between spaces, so most variations in the intracranial volume are from changes in venous blood or CSF volume. When this compensatory reserve, or compliance, is exhausted, ICP may rise precipitously. In practical terms, pressure within the cranial space is increased when volume is added due to a change in CSF dynamics, brain tissue (cellular and vasogenic edema), cerebral blood volume, or addition of a mass lesion. The accumulation of volume may be rapid or slow – depending on the underlying pathology – and when ICP rises, it has adverse implications for brain shift and reduction of cerebral blood flow. Regardless of the cause or speed of the ICP increase, the final decompensation may be rapid.

The pressure within the intracranial vault under normal circumstances depends on several factors (Table 35.1), which may change considerably from early infancy through adulthood. Normal ICP varies over several time scales. The pressures change through the cardiac cycle (providing an underlying pulsatility to ICP) from beat to beat; during respiration (and in response to interactions such as coughing or mechanical ventilation); in response to vasogenic waves; during changes in head and body position; during increases in intra-abdominal pressures (such as Valsalva maneuvers), all of which happen over very short time periods (from seconds to minutes). Other changes in ICP such as those related to the secretion, reabsorption, and circulation of CSF, may take place over hours. Likewise, changes in ICP related to the development of brain swelling are also likely to take place over a period of hours, but may be more rapid in some circumstances. Changes in ICP related to the interaction of the growing brain and surrounding skull may take place over weeks to months.

Cerebrospinal Fluid Dynamics

According to traditional teaching, CSF is produced in the choroid plexus. After circulation through the ventricular and subarachnoid systems, CSF is reabsorbed through the arachnoid granulations in the venous sinuses (although some may be reabsorbed through the brain). Recent studies have shown that although the bulk of CSF is produced in the choroid plexus (approximately 500 ml per 24 h in adults, with the total CSF volume of 120–150 ml), there is significant production of CSF from the brain capillaries, and there is mixing between fluid produced within the brain and the CSF. There is thus bulk flow of CSF from the choroid plexus through the ventricular system. In the subarachnoid system, there is flow of CSF related to both the fluid infusion from the ventricles and the pulsatility of the brain. CSF is reabsorbed into capillaries throughout the system. Thus the normal mean ICP is related to pressures within the intracranial venous and capillary systems.



Fig. 35.2 Diagrams showing the commonly accepted bulk flow model (**a**) and the two types of cerebrospinal fluid circulation related to the proposed concept of the circulation (**b** and **c**). (**b**) Shows pulsatile flow of CSF with a fast-velocity compartment in the brain stem–cord area and slow velocities at the upper and lower ends of the subarachnoid spaces. The amplitude and velocity are indicated by the length of the segments of the dashed line. This pulsative flow may be responsible for the rapid spread of tracers within the extraventricular cerebrospinal fluid spaces. Systolic and diastolic flows in the spinal canal follow one main channel, which is located toward the convexities showing a meandering S-shaped route caused by centrifugal forces and lower resistance in wider subarachnoid spaces. (**c**) Demonstrates the comparatively small bulk flow (**c**) of CSF which may be responsible for the washout of tracer in the ventricular system and basal cisterns. The thickness of the *arrows* is related to the magnitude of the bulk flow, which decreases in both directions from the foramen magnum. The cerebrospinal fluid is resorbed everywhere in the central nervous system by the circulating blood. The spinal nerves, including the cauda equina, are represented solely by one caudal root in this schematic drawing (Reprinted from Greitz and Hannerz [16]. With permission from the American Society of Neuroradiology)

Although CSF is moved through the ventricular system as a consequence of bulk flow, a significant proportion of CSF flow is related to the pulsations of the brain and the arterial system (Fig. 35.2). It is also likely that the CSF plays an important role in dissipating some of the pulsatile energy from the cardiovascular system [17, 18].

While considering intracranial hydrodynamics, it is also important to consider the compliance of the spinal sac [19]. It is only possible for fluid to move out of the intracranial compartment if there is compliance of the spinal sac. The pressure in (and compliance of) the spinal sac will also be related to the pressures transmitted into that space from the thoracic and intra-abdominal compartments via the vertebral foramina. As a result intracranial pressures are related to the pressures within the abdomen and the thorax [20].

Circulatory System

As alluded to above, a significant characteristic of intracranial pressure is its pulsatile nature, which is primarily related to the cardiac cycle and the transmission of pressure and flow waves through the vascular system into the intracranial space [21]. Blood is contained within the cerebral circulation. In the arterial circulation the pressure is normally significantly higher than the ICP. The volume of larger arteries is largely incompressible in this context and there is limited capacity of the arterial wall to vasoconstrict. The smaller arteries and arterioles have a significant muscular component to the wall and can thus reduce volume by vasoconstriction. The capillary and venous system is compressible and blood volume in this space could be reduced by external compression of the vessels.

The pulsatility of normal ICP is primarily related to the cardiac cycle. Pressures within the vascular system are transmitted into the intracranial space. However, there is considerable complexity related to these pressure waves [22]. The systolic pressure wave is immediately conducted throughout the brain (at a rate which is related to the compliance of the system). As the arterial tree is elastic, it enlarges during systole (thus dampening some of the pressure wave) and then contracts during diastole (the so-called *Windkessel effect*) which has the effect of maintaining diastolic capillary blood flow. As some of the arterial tree is extracerebral, the systolic pressure changes are transmitted directly to the CSF and may be responsible for flow of CSF into the spinal canal (the volume increase of the intracranial extracerebral arteries in adults is approximately 1.5 ml and is offset by similar volume decreases in the intracranial venous blood volume and CSF). After some delay (of millisecond duration) the systolic pressure changes within the brain occur (the volume change in adults is approximately 0.03 ml with systole). Thus the volume changes on the arterial side of the intracranial circulation during systole occur almost exclusively in the large extracerebral elastic arteries and the pressure changes within the intracerebral arteries are substantially damped.

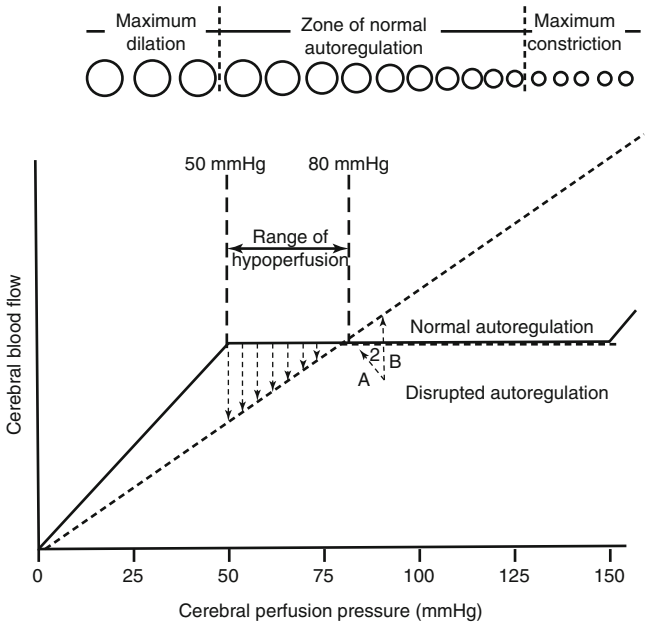


Fig. 35.3 Pressure auto-regulation (Reprinted from Lang and Chestnut [23]. With permission from Elsevier)

Under normal circumstances, changes in systemic arterial blood pressure are not translated into significant changes in cerebral blood flow, a phenomenon referred to as pressure autoregulation (Fig. 35.3). When pressure autoregulation is intact, an increase in blood pressure (within a range) leads to vasoconstriction of cerebral resistance vessels [24] with a decrease in cerebral blood volume. The reverse happens with a decrease in blood pressure, thereby maintaining relatively constant cerebral blood flow. Increased arterial pressure will be associated with an increase in the diameter (and thus volume) of elastic arteries, but if vasoconstriction occurs in the muscular arteries then the intravascular volume for these vessels will decreased at the same pressure (Fig. 35.4). When compliance is decreased, these changes in cerebral blood volume may be reflected in ICP changes. Generally the venous pressures will be lower than the intracranial pressures, but under abnormal conditions the venous back pressure may be significant, and may contribute to rises in ICP. This will relate to venous back pressure (with higher volume in the venous spaces); increased capillary pressure (with increased resistance to absorption of CSF).

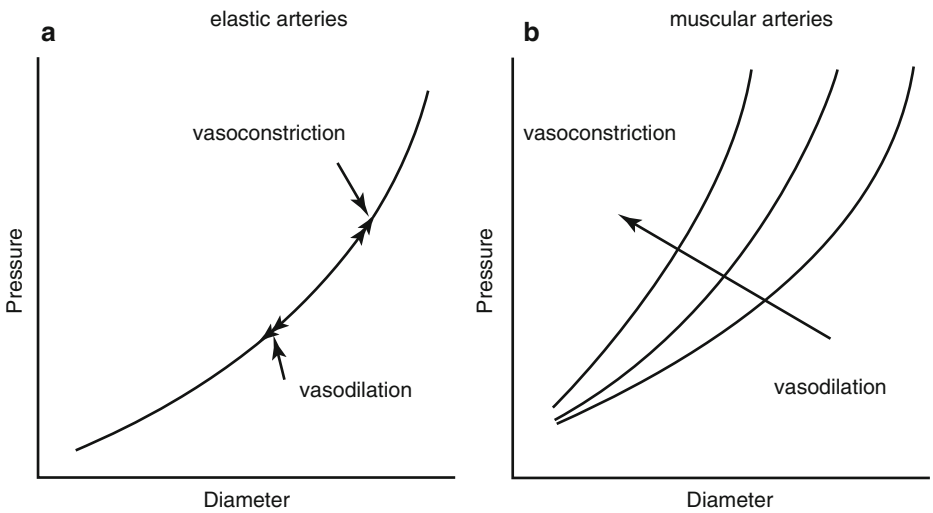


Fig. 35.4 The relationship between pressure and diameter for elastic (**a**) and muscular (**b**) arteries. Actual blood flow (and intravascular volume) is also affected by a number of other factors such as arterial CO_2 reactivity, where vascular tone is increased in response to a reduction in pCO_2. In addition "metabolic coupling" takes place, whereby the blood flow to a region of the brain is related to the activity in that area (Reprinted from Shahsavari et al. [25]. With permission from IEEE)

The Cranial Vault (the Significance of the Fontanelle)

The intracranial structures are contained within the skull, which in childhood and adulthood is a rigid structure with a limited number of openings, while in the neonatal period and infancy, there may be increased compliance of the cranial vault. This has some significance in relation to the risks of intracranial haemorrhage. With a closed skull, intravascular pressure changes related to changes in intrathoracic pressure (such as coughing or valsalva maneuvers) are balanced by changes in CSF pressure (transmitted via the intervertebral foramina, and the dural sac) with the result that transmural vascular pressures remain low. However, in small infants with compliant skulls, changes in intravascular pressures are not balanced by those pressures, and that may predispose to intracranial haemorrhage [26, 27]

Intracranial Pressure Under Abnormal Circumstances

Under abnormal circumstances ICP may rise. The two most important potential complications of this rise in ICP are brain herniation and ischemia [28, 29]. Herniation occurs as a consequence of pressure gradients between compartments within the intracranial space, typically subfalcine (medially beneath the falx), transtentorial (through the tentorial notch) or trans-foramen magnum (cerebellar tonsillar). These shifts occur secondary to either global increased ICP, or localized tissue pressure due to a mass lesion or regional brain swelling. Cerebral ischemia occurs when the rise in ICP causes a reduction in cerebral perfusion pressure below the lower limit of autoregulation, where cerebral blood flow progressively decreases, eventually to below that which is needed to sustain normal metabolism. Of importance in acute brain injury is the fact that the same process that causes an increase in ICP may also lead to impaired autoregulation, so in these circumstances cerebral blood flow may be passively dependant on cerebral perfusion pressure within the range that autoregulation should be functioning, and ischemia may occur at unpredictable perfusion pressure levels (see again, Fig. 35.3).

The relationship between intracranial volume and pressure is not linear (Fig. 35.5) [19]. Reduction of CSF and venous volume inside the cranium creates compliance so that the increased volume initially is not associated with increased ICP. When the compensatory reserve is exhausted however, any further small increase in volume may lead to a steep increase in ICP, which may be associated with clinical decompensation. At this point, release of relatively small volumes of accumulated fluid (blood, CSF, etc.) may be associated with very significant decrease in ICP. In addition,

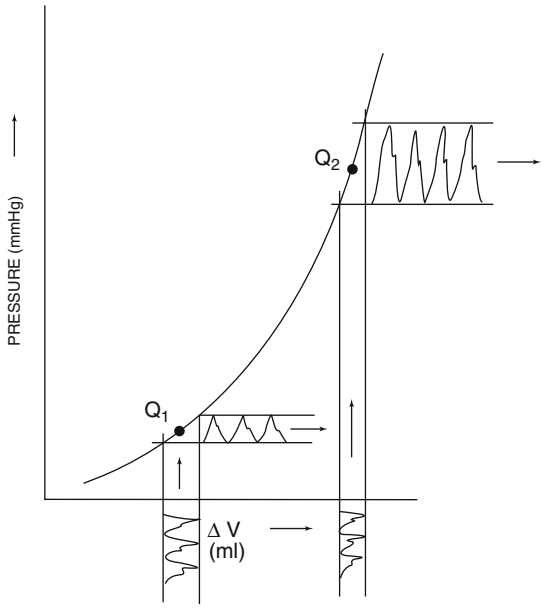


Fig. 35.5 As the relationship between volume and pressure within the skull is not linear, as the volume of structures within the intracranial space increases, the mean pressure rises dramatically (and can drop dramatically with relatively low changes in intracranial volume). The initial resting pressure level represents a stable point (Q1) positioned on the volume-pressure curve. The pressure change related to a pulse in volume is shown at that point. If the mean pressure rises (see point Q2), then a smaller volume pulsation will be associated with a larger pressure change (Reprinted from Marmarou et al. [19]. With permission from Rockwater, Inc.)

as the intracranial volume increases, there are substantial changes in the pulsatility related to the cardiovascular system and in the compliance of the brain (see again, Fig. 35.5). Considerable effort has been devoted to detailed analysis of pressures, pressure wave forms, and the timing of various pressures in a variety of abnormal situations.

Intracranial Pressure Waveforms

Various waves of ICP (Fig. 35.6) over time have been described, classically by Lundberg in 1960 [31]. From his original description, three types of waves are commonly observed. **A waves**, or plateau waves, are steep and sudden elevations of ICP from normal or near normal values to 40–50 mmHg or more. These typically persist for 5–20 min before a spontaneous reduction. They are thought to be related to the vasodilatory cascade – in some cases at least, they are preceded by a slight drop in blood pressure that sets up an autoregulation-based vasodilatory response that steeply increases ICP when compliance is poor. **B-waves** are smaller and sharper than A-waves, and rhythmically oscillate at a frequency of 1–2 min. They typically increase ICP to anything between 20–40 mmHg, and appear to be related

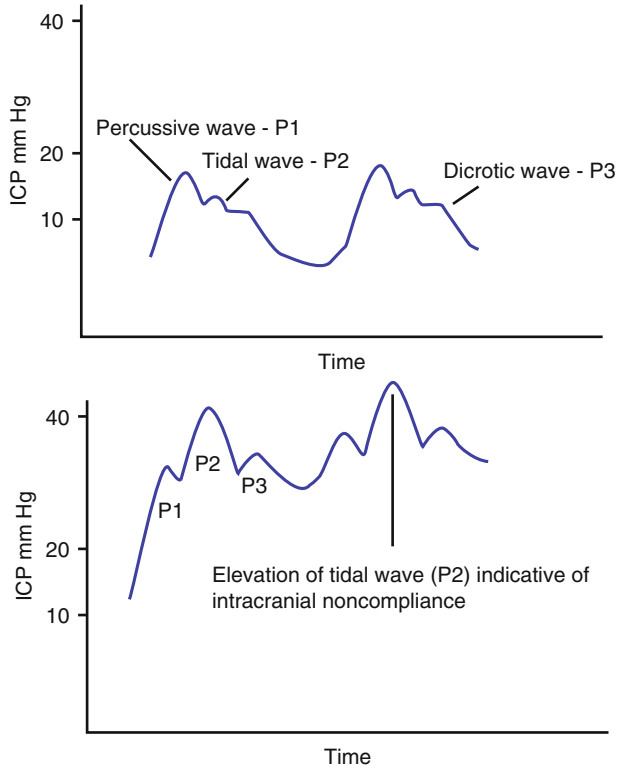


Fig. 35.6 Intracranial pressure waveforms. *Top panel* shows normal P1, P2, P3 relationship. *Bottom panel* shows P2 (tidal wave) as the most prominent peak indicating a state of reduced intracranial compliance (Reprinted from Scarlett et al. [30]. With permission from Springer-Verlag)

to changes in cerebrovascular tone and periodic breathing. **C-waves** are smaller waves (up to 20 mmHg) occurring at a higher frequency of 4–8/min. These appear to be related to rhythmic variations in blood pressure and probably do not have significant clinical implications.

"Normal" Intracranial Pressure

The absolute terms of reference for defining elevated ICP in children are not clear. It is well known that normal ICP in infants and young children is lower than in older children and adults, but the threshold at which this becomes pathological and requires treatment is less clear. There is an inherent bias in reporting ICP in patients who received ICP monitoring and treatment (for example TBI) because of the a priori decision to treat ICP at a specific threshold (usually 20 mmHg). The thresholds in these studies usually are reported in association with clinical outcome. These reports are also limited by their description of ICP either as mean or peak values only, and so less is known about individual tolerance for specific ICP values and the duration thereof. Although we have data for ICP in 'normal' children, their reliability can be criticized because these may be influenced by several factors, including the reason for the investigation (often lumbar pressure measurement) and whether the child was sedated for the investigation. Historical data suggest that the upper range of pressure for infants is 5–6 mmHg, and for children 6–7.5 mmHg. A recent study [32] suggested that the upper range of normal (90th percentile) for CSF opening pressure was 20.5 mmHg, although this was in a sample of patients aged 1–18 years old (60 % of patients older than 10 years) and may contain some bias due to the reason for performing the lumbar puncture (even though the authors tried to exclude conditions thought to be associated with increased ICP). Also, age was unexpectedly not an influencing factor. Current guidelines for pediatric TBI [4] recognize the insufficient data that we have to make strong recommendations, and suggest the treatment of ICP at 20 mmHg at the level of an option. It is generally agreed that brief episodes of ICP increases are tolerated, and that treatment should be reserved for sustained increases (≥5 min). Most clinicians feel that age should be a factor that determines this threshold and tend to treat ICP at a lower threshold for young children, especially given that 20 mmHg is the threshold also used in recommendations for adult patients (with more evidence). Exactly what this threshold should be for a given age though, is not yet determined.

Pressure Regulation

The relationship between ICP and blood pressure (BP) is complex. When ICP and BP are both increased, this may be a consequence of impaired pressure autoregulation (where the increased BP leads to the ICP increase), the Cushing's reflex (where the ICP increase primary), or a third factor that increases both. The autoregulatory phenomenon is probably most poorly understood. There are, in fact, several regulatory responses of importance in TBI: the vascular responses to changes in CO_2, metabolism, oxygen, and BP, the last of which is called pressure autoregulation, as discussed above. This is a physiological response in which cerebral blood vessels dilate or constrict inversely in response to BP to maintain a (relatively) constant cerebral blood flow. The BP range over which this dynamic response is active is known in adults, but is less clear in children. When autoregulation works, cerebral blood volume increases (and so ICP) as BP decreases, depending on intracranial compliance, and conversely, cerebral blood volume decreases when BP increases. Below and above the lower and upper thresholds of this phenomenon, cerebral blood flow and cerebral blood volume varies linearly with BP. When autoregulation is impaired however, the response of cerebrovascular dynamics to BP changes are less predictable, but broadly speaking, cerebral blood flow and cerebral blood volume (and therefore ICP)

tend to passively increase or decrease in concert with BP. Therefore, the cerebral blood volume and ICP response to BP changes is determined by the status of autoregulation. This has several important implications in TBI patients, including for ICP control, particularly given that most institutions do not attempt to measure autoregulatory capacity. Simple observation of BP and ICP values are insufficient because of the aforementioned complex nature of this relationship.

Metabolic Regulation

Metabolic regulation concerns the coupling between cerebral blood flow and metabolic demand, which is the basis for imaging studies that infer metabolic function in regions of the brain based on the pattern of cerebral blood flow. It is also the basis of pharmacological metabolic suppression, which not only decreases metabolic demand in the face of potential ischemia, but also decreases cerebral blood flow and therefore cerebral blood volume. In some cases of acute brain injury, this coupling between metabolism and cerebral blood flow is impaired, which has implications for the interpretation of the adequacy of absolute values for cerebral blood flow and the ensuing ICP changes that follow cerebral blood volume.

Carbon Dioxide Regulation

CO_2 reactivity is a potent response of cerebral arterioles to changes in arterial CO_2 tension via pH-dependent mechanisms (Fig. 35.7). It is generally a robust phenomenon that is usually retained even when the brain is severely injured. Hypocarbia causes cerebral vascoconstriction, and so cerebral blood volume and therefore, ICP, are also reduced. The vasodilatory response to hypercarbia, on the other hand, increases cerebral blood volume and ICP. Although this effect is compensated for over several hours, the immediate impact may be a dramatic change in cerebral perfusion and ICP. This is the basis for the practice of active lowering of CO_2 to reduce ICP that was common in the late 1980s (see below for more discussion).

Causes of Intracranial Hypertension

Cerebral Edema

Brain swelling occurs as a result of edema or increased cerebral blood volume. Brain edema may be vasogenic or cellular in origin (Table 35.2). *Vasogenic edema* occurs after mechanical microvascular tissue disruption, breakdown of the blood-brain barrier, and increased vessel permeability, which leads to water accumulation in the brain interstitium. This is mediated by various compounds such as bradykinin, arachdonic acid, histamine and free radicals. *Cellular edema* (also known as *cytotoxic edema*) is a different process that may or may not occur concurrently. Typically, it results

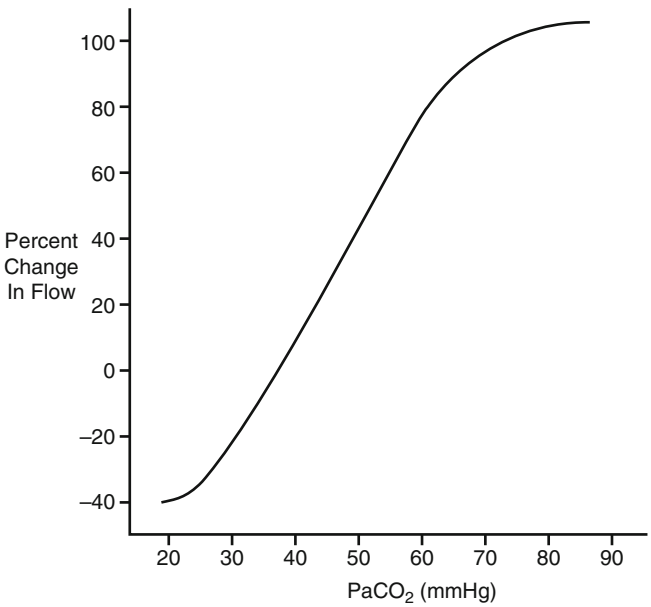


Fig. 35.7 The relationship between cerebral blood flow and arterial pCO_2 (Reprinted from Padayachy et al. [33]. With permission from Springer Science + Business Media)

Table 35.2 Classification of cerebral edema

Type	Location	Site	BBB integrity	Mechanism	Example
Vasogenic	Extracellular	White matter	Disrupted	Increased vascular permeability	Tumor Trauma Meningitis Abscess ICH
Cellular (cytotoxic)	Intracellular	Predominantly gray matter	Intact	Na+/K + pump failure	Anoxia Ischemia
Interstitial	Extracellular	White matter	Intact	Periventricular extravasation	Hydrocephalus

either from ischemic injury and the failure of cellular energy metabolism, or a neurotoxic pathway that occurs as a consequence of ionic disruption [34, 35]. This disrupts the extracellular-intracellular sodium gradient, and water leaks into the cells. It appears that in head injured adults, cellular edema is more prominent than vasogenic edema or vascular engorgement [36], but less is known in children.

Cerebral hyperemia causes engorgement of the vascular bed secondary to a vasoreactive event, the mechanisms for which are unclear. The current use of terminology is unclear, but most use the term to describe a situation where cerebral blood flow is increased in the setting of normal or depressed metabolism [37] leading to increased cerebral blood volume [38]. Usually cerebral blood flow is tightly coupled to regional metabolic demand, but this may be disrupted in head injury [39]. It is not always easy to make the diagnosis; hyperemic areas do not necessarily correlate with abnormal areas on MRI scans [37], and measures of increased cerebral blood flow that we have available in the clinical situation do not necessarily diagnose hyperemia unless there is some other evidence that flow is in excess of metabolic demand.

Because ICP is strongly influenced by cerebral venous sinus pressure, factors that influence intracranial venous pressure have a marked effect on ICP, including cerebrovenous thrombosis (or external compression of venous sinuses), obstruction of venous drainage in the neck, intrathoracic and intra-abdominal pressure, and position of the head relative to the body [40].

Mass Lesions

Intracranial mass lesions in trauma are less common in children than in adults. Typically these are hematomas in the epidural, subdural or parenchymal spaces. Epidural hematomas usually occur secondary to a fracture that lacerates a meningeal vessel or causes venous bleeding from the fracture edges (Fig. 35.8). Subdural hematomas typically are caused by a rupture of a bridging vein or decompression of a superficial lobar hematoma (Fig. 35.9). Intraparenchymal hematomas or contusions result from a rupture of perforator or pial vessels and may be small or large. Sometimes these may be mixed with parenchyma and are heterogenous in appearance, other times the hematoma is relatively discrete and ideal for surgical evacuation. Infections and infestations may also cause mass lesions – bacterial or fungal brain abscesses (Fig. 35.10), tuberculomas, cryptococcomas, toxoplasmosis, hydatid disease, neurocystercercosis, etc. Occasionally developmental lesions, such as arachnoid cysts, may present acutely with raised ICP. Brain tumours in children often present with raised ICP, most commonly due to hydrocephalus.

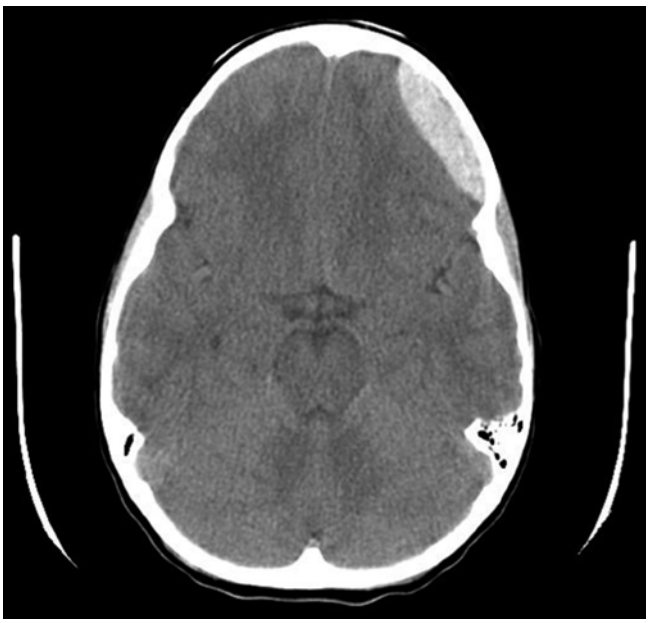


Fig. 35.8 CT appearance of an epidural hematoma

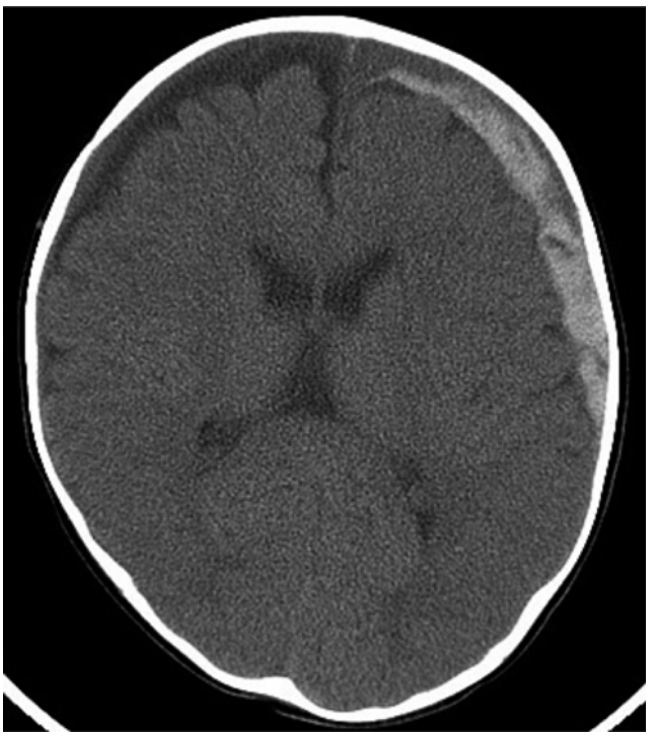


Fig. 35.9 CT appearance of a subdural hematoma

Hydrocephalus

Hydrocephalus is an acute disturbance of CSF pathways that results in accumulation of CSF under pressure in the ventricles. For practical purposes, all forms of hydrocephalus are



Fig. 35.10 CT appearance of a brain abscess

obstructive (excluding the very rare choroid plexus papilloma); the distinction occurs based on the level of obstruction. Either CSF is prevented from exiting the ventricular system (non-communicating, usually caused by a mass lesion or aqueduct stenosis) or CSF is obstructed distal to the ventricular system (in the subarachnoid space or venous sinuses). Posttraumatic hydrocephalus is relatively uncommon in children; postmeningitic and intraventricular hemorrhage secondary to prematurity are more common causes of communicating hydrocephalus in children.

Clinical Manifestations of Intracranial Hypertension

The clinical course of increased ICP is related to the underlying pathology, the time course of the increase in intracranial volume, and the compensatory capacity of the patient. In acute neurocritical care patients, the compensatory reserve is often rapidly exhausted and increased ICP may be an early, and even fatal, presenting feature. The most important clinical manifestation of increased ICP in this context is a decreased level of consciousness, particular in a deteriorating patient. Increased blood pressure and bradycardia may be a sign of the Cushing's response, which is a late response to severe intracranial hypertension with brainstem distortion or ischemia. In patients with meningitis, this can be mimicked by direct inflammation or ischemia of the brainstem. Focal clinical signs suggest a mass lesion, localized



Fig. 35.11 Papilledema

inflammation or ischemia of cranial nerves or brainstem, or a herniation syndrome. Chronically raised ICP usually presents with headache, which is typically worse in the morning. Vomiting is commonly associated with this, and the patient may have papilledema (Fig. 35.11). It is important to remember that papilledema is a reliable sign that intracranial hypertension is present, but generally takes a while to develop and the absence of papilledema should not be equated with the absence of raised ICP. Longstanding raised ICP may lead to loss of vision. Even though the cause of raised ICP is chronic in these patients, their deterioration may be acute when they can no longer compensate.

ICP Measurement

Since the first measurements of ICP in 1951 [1] and the 1960s, a range of techniques have developed. ICP can be measured using a wide variety of techniques of varying directness, invasiveness and accuracy. When considering ICP values, it is important to note the unit of measurement – fluid coupled methods for measuring or monitoring ICP (such as obtained via lumbar pressure measurement or ventricular measurement) are often reported in cmH_2O, while solid state devices report in mmHg; the conversion is 1 mmHg = 1.36 cmH_2O.

Indications for Monitoring

The full indications for monitoring ICP across the spectrum of pediatric neurocritical care are yet to be well defined. The most compelling data (and clinical experience) is in TBI, but even here, current guidelines [2, 4] concluded that

although they supported monitoring of ICP in children with severe TBI (GCS ≤ 8) there was no conclusive literature to support this. However, there is strong evidence to support the association between high ICP and poor neurological outcome, and monitoring and aggressive management of raised ICP has been associated with improved outcomes [41–46]. Importantly the presence of open fontanelles and sutures does not preclude the possibility of significant intracranial hypertension [47]. Still, the role of ICP monitoring in severe pediatric TBI (and adult TBI) is not without debate, and papers continue to be published questioning its role. However, these are not randomized studies; usually they are comparisons of outcome in patients who did and did not receive ICP monitoring. The common thread tends to be an inadequate control for the reason that the ICP monitor was placed. Most commonly it is the combination of severe TBI and an abnormal scan that initiates ICP monitoring. However, it is difficult to predict levels of ICP from CT scans [48] in the setting of TBI. ICP may be elevated despite widely patent basal cisterns. Therefore, our approach in TBI is to monitor all patients who require ventilation for a depressed level of consciousness after TBI, regardless of radiological findings, unless it is anticipated that the child is rapidly improving and due for extubation within 12 h of the injury.

Although ICP monitoring has been described mostly for TBI, several other conditions in pediatric practice present with acute coma for which ICP monitoring may be considered. These patients also often develop brain swelling and ischemia, but the role of ICP monitoring is less clear due to lack of data. These include meningitis, near-drowning, stroke, and metabolic encephalopathy. Given that the deaths of many of these patients are associated with increased ICP, it would seem logical that ICP monitoring, if it benefits TBI patients, may confer similar benefit in these patients. To date however, there are few studies that have examined this outside of limited case series [49–51], but the frequency of monitoring in these conditions appears to be increasing. It seems though that many neurosurgeons would be prepared to embark on such monitoring [52].

Invasive Measurement

A wide variety of devices have been used for invasive measurement of ICP with placement varying from epidural, subdural, intracerebral and intraventricular (Fig. 35.12). Most commonly, ICP is measured either using devices placed in the brain parenchyma, or catheters placed within the ventricular system of the brain [53]. Intraventricular catheters remain the gold standard for measuring ICP. These are a fluid-coupled devices comprising a catheter placed in the lateral ventricle connected to a drainage bag, which is zeroed at the level of the Foramen of Monro. It must be adjusted whenever the position of the head is changed vertically in relation to the body. It has the advantage of being able to drain CSF from the ventricles as an effective way of decreasing ICP. However, external ventricular drains have a higher complication profile [54] (see below under Drainage of CSF), with the risks in children possibly being fourfold higher with an external ventricular device compared to a parenchymal monitor [55]. It may be difficult to place ventricular catheters in the setting of brain swelling with effaced ventricles [56], and it is not possible to measure ICP while draining CSF – this may have the consequence that ICP crises may be missed [53]. If a ventricular drain is placed, the clinician may choose to allow constant drainage of CSF at a set pressure, or rather to leave the drain clamped so that ICP can be monitored, with intermittent opening of the catheter to drain when ICP is increased. We prefer the latter approach for several reasons, including the possibility that constant drainage may increase collapse of the ventricle, with apposition of the ependymal surfaces and greater likelihood of catheter obstruction.

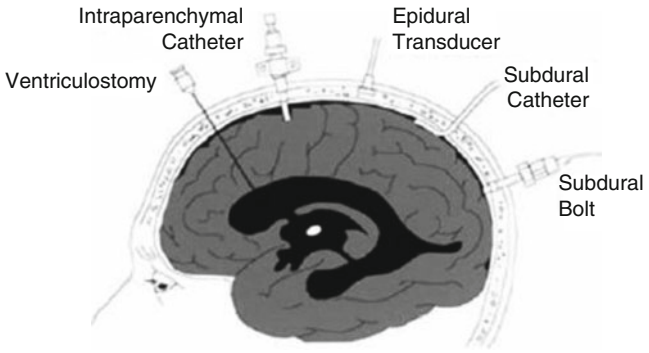


Fig. 35.12 ICP can be measured in a variety of locations

Fiberoptic and electronic strain gauge systems are being used more frequently. These are usually placed intraparenchymally; one can also place these in the subdural and extradural space, but this is much less reliable [57, 58]. Their disadvantages are that they are more expensive than ventricular catheters and cannot be recalibrated once placed (they are calibrated pre-insertion). On the other hand, the technology is robust, their calibration does not depend on the position of the head, the zero and sensitivity drift over time is relatively small, and the risks of causing a hematoma or an intracranial infection are low. The devices most commonly used include the Camino (Integra Neurosciences, Plansboro, NJ), Codman microsensor (Codman, Raynham, MA), the Spiegelberg ICP sensor and compliance device (Spiegelberg KG, Hamburg, Germany), and the new Raumedic ICP sensor and multiparameter probe (Raumedic AG, Germany). The first two devices listed are the most widely used in current practice.

Non-invasive Measurement

Several non-invasive methods have been tried over many years to measure ICP, including transcranial doppler (TCD), middle ear endolymph pressure estimation, visual evoked potentials and optic nerve sheath diameter. In many ways this is the holy grail of ICP monitoring as every clinician would like to be able to diagnose, and even monitor ICP, non-invasively. However, none of these methods has been widely adopted because they are not reliable enough [59, 60]. Although there are individual studies demonstrating their usefulness, and there usually is a relationship between the measured indices and increased ICP, none of these tools have sufficient sensitivity and specificity to reliably measure absolute ICP. There may be a role for these devices to assist screening patients who do not yet have a clear indication for ICP monitoring on other criteria; however, they should be used with caution as they could be misleading either way. As a typical example, it is worth considering one of the most commonly utilized methods, namely the transcranial doppler indices of ICP. One of the derived indices is the pulsatility index, which is based on the observation that under constant conditions of blood pressure and arterial carbon dioxide tension, pulsatility through the conductance vessel reflects distal cerebrovascular resistance. The Gosling index is the most common method for estimating this pulsatility [61]. Several studies have suggested usefulness of this index as a non-invasive estimate of ICP and CPP [62]; however, recent evidence demonstrates the lack of sufficient reliability of the method for clinical decisions.

Management of Intracranial Pressure

Setting Targets

Setting a target for treatment of ICP is more complex than one would think. Current recommendations, and largely also clinical practice in most units, suggest treatment at 20 mmHg, a value largely based on adult data. Most clinicians feel that age should be a factor when considering the threshold to initiate treatment, but there are very little age-based data to support specific recommendations. Furthermore, the way in which ICP is treated varies considerably. It is an individual institution-directed decision of whether to choose a standard stepwise approach to treating a particular ICP number, or a broader approach based on the contribution of data from other monitors to determine causes of increased ICP and its effect on physiology. Our preference is the latter. The decisions we make to treat ICP attempt to take into account the overall physiological status of the patient (cerebral and systemic), the course of the ICP increase, the likely etiology of the ICP increase, and its effect on cerebral perfusion or oxygenation. Not all second-tier therapies are applied at the level of 20 mmHg at our institution. For example, we tend to reserve decompressive craniectomy for ICP elevations well above that, and usually with an evident compromise of brain oxygenation. However, these are institutional preferences and there is no firm evidence to support widespread recommendations for a specific approach. Our rationale is that all ICP reduction therapies have potential adverse effects that may offset their benefits; therefore the decision to use them should be made with as much information and control as possible.

How Do You Approach an ICP Number?

ICP is a dynamic, fragile, and complex parameter to treat in childhood head injury, much more so than commonly appreciated. A starting point for the management of any rise in ICP is to understand the context and the cause, as these both influence the clinician's thinking about interventions. With regard to context, several questions may be asked: Is the patient well sedated? Is autoregulation impaired or intact? How high or low is the blood pressure? What is the arterial carbon dioxide level concentration? Is there underlying ischemia? Is there vasospasm? Is the patient hyperemic? In terms of specific causes, several factors may increase ICP: pain, suctioning and other nursing maneuvers, tightly applied surgical bandages (especially with progressive scalp swelling), high blood pressure (when autoregulation is impaired), subclinical seizures, surgical causes (hematoma, hydrocephalus), cerebral edema, hyponatremia, high CO_2, etc. Some of these factors can be difficult to identify with the conventional information we have available at the bedside, which include the head CT features, ICP number and trend, and clinical examination findings. The complexity of TBI has suggested the need for more information to make rational decisions in the management of these patients, which in turn has led to the development of ancillary investigations and monitors with which we may obtain more information to treat ICP more rationally. These include imaging based studies (such as Xenon perfusion, CT and MRI perfusion studies) and continuous or semi-continuous monitors at the bedside (brain tissue oxygen monitors, jugular venous saturation, near-infrared spectroscopy, transcranial Doppler, microdialysis). Additional information may avoid unnecessary or potentially harmful interventions. For example, increased ICP associated with subclinical seizures requires seizure treatment rather than mannitol. It is beyond the scope of this chapter to discuss the potential merits and limitations of all of these techniques. In summary though, it is worth noting that no single monitor gives all the information needed to make decisions at the bedside (which is the same for ICP monitoring); all have limitations and require expertise when used, and the best possible use of these monitors is to attempt to

integrate data we receive to obtain a better understanding of the individual pathophysiological disturbance rather than blindly targeting new thresholds for each new monitor.

Several studies have addressed the benefit of ICP monitoring and specific interventions for ICP control in adult and pediatric head injury, none of which have shown clear benefit. Of course, this does not mean that ICP monitoring and these specific interventions based on increased ICP are not useful. Arguably, the lack of demonstrable benefit may point more to the broad use of interventions in unselected patients regardless of the underlying physiology. Not all patients may require specific interventions, and the adverse effects of some interventions in specific patients do not necessarily render them ineffective and unsafe in others.

Basic Measures

To start, close attention should be paid to basic issues such as elevated and midline head position, removal of all items (such as ties around the neck) that may interfere with venous drainage, and the presence of constricting head bandages. These appear to be largely intuitive aspects of managing the head-injured patients, but there are important aspects of the role between ICP and venous physiology of the brain that are contained herein. Central venous pressure is a critical factor that influences ICP and defines our definition of CPP. The most important common use of this in the head-injured patient is the decision to elevate the head of the bed of the patient to use the influence of gravity on cerebral blood volume and CSF. In most circumstances this reduces ICP, but there is inter-patient variability and the degree of impact a particular elevation has is also influenced by the age (and therefore the length) of the patient, so perhaps the specific degree of elevation should be individualized [40, 63]. The patient should be adequately sedated both generally (restlessness, pain and distress often increase ICP) and specifically during procedures such as endotracheal suctioning, transport, physiotherapy, bronchoscopy, etc. Where procedures are planned, adequate sedation must precede these to avoid the ICP increase rather than treat the established ICP elevation. Much of the art of ICP control lies not only in treating elevated ICP, but anticipating the unstable patient who is likely to experience increased ICP, and where possible avoid the problem before it occurs.

Sedation and Analgesia

Analgesics and sedatives are used in neurocritical care to avoid and treat increases in ICP, especially when this is associated with pain and increased cerebral metabolism. These agents also facilitate the general care of ventilated patients for suctioning, performance of procedures, etc. Unfortunately, there is no ideal sedative or analgesic, which is reflected by the wide spectrum of practice for TBI patients. The most common adverse effect of sedation is hypotension.

Little data is available for children. Although opioids are used commonly for analgesia, a recent systematic review of sedation for adults with severe traumatic brain injury highlighted the observation that high bolus doses of opioid sedation were associated with an increase in ICP and reduced brain perfusion pressure [64].

Although ketamine was initially thought to increase ICP, a number of recent studies have demonstrated no increase in ICP in patients given ketamine infusions either together with other sedative agents [65–67], or alone [65, 68] and a recent review suggested that ketamine was not contra-indicated as an induction agent in patients with traumatic brain injury [69]. However a study of children with suspected viral meningo-encephalitis showed a rise in CSF opening pressure on lumbar puncture following ketamine administration [70]. Etomidate may have some ICP-lowering effects; however there is a risk of adrenal suppression [4]. Thiopental and Pentothal are discussed below. Propofol is used as a long term sedative in adult TBI, but not in the pediatric critical care unit because of the risks of propofol infusion syndrome. Neuromuscular blockade is sometimes also used, possibly reducing intrathoracic pressures and shivering. However, the risks of accidental extubation and consequent hypoxia are well known. Neuromuscular agents may also conceal seizures, increase respiratory infections, and lead to myopathy.

Drainage of CSF

Placement of an external ventricular drain (EVD) can be extremely effective in controlling ICP. Indeed, some units place EVDs almost routinely, and use these for both monitoring and treating ICP. EVDs have undeniable benefits. They are the gold standard for monitoring ICP and allow CSF drainage when ICP is elevated. The cranial pressure-volume relationship in children is such that when even small amounts of CSF are released there is usually a substantial decrease in ICP. However, EVD placement can be technically difficult when the ventricles are particularly small due to brain swelling. In this case, injury caused by several passes of the catheter to find the ventricle may outweigh the benefit [56]. Also, because it is a fluid-coupled device, there is a higher risk of causing a hematoma and developing meningitis [54, 55].

Removal of Mass Lesions

Initial head CT may reveal epidural, subdural, or intracerebral hematoms. The decision about whether these require surgical

evacuation is largely a neurosurgical one, but the general principle is that lesions causing mass effect should be removed, although some small lesions may on occasion be safely managed conservatively. When the hematoma is intracerebral, this decision is less clear. Hematomas that are relatively discrete and fairly close to the surface are more amenable to surgical evacuation. Some surgeons may leave the bone flap off if there is considerable swelling of the brain even after the hematoma is removed. The key principle is that, if a hematoma is to be removed, this should be done as soon as possible. It is also important to note that hematomas may take some time to develop, and may not be evident on the initial head CT, or may be of smaller volume. This is a particular risk when the head CT is obtained within the first hour or two after injury. Therefore, a low threshold should be maintained for obtaining repeat imaging. Keep in mind though that transport to the scanner is not without adverse consequences. Portable head CT may have some advantage in this scenario.

Hyperventilation

Hyperventilation was practiced almost routinely in the late 1980s, often on the assumption of the presence of hyperemia in the diffusely swollen brain after TBI. The ICP-lowering effects of hyperventilation are well known, and CO_2 reactivity is a well-maintained mechanism even when the brain is severely injured (see above). As a technique for controlling ICP though, this practice has largely been abandoned in the neurosurgical/neurointensivist community because of concern about causing vasoconstriction-induced ischemia, especially after the publication of a randomized controlled trial that showed worse outcomes in patients treated with hyperventilation. However, this study examined only *prolonged, severe* hyperventilation, so it can be argued that moderate hyperventilation, intermittent use (to break ICP plateau waves), and hyperventilation under some form of brain oxygen monitoring control, may be have some benefit, but this kind of management strategy has not as yet been evaluated properly. Given that lowering CO_2 acutely may paradoxically lead to increased oxygenation in selected cases (if ICP is substantially increased and is causing a brain ischemia due to pressure effects), hyperventilation as a technique perhaps should not be completely abandoned quite yet, but if performed should only be done in a controlled context. This is in keeping with the current recommendations in children [4].

Osmotherapy

The transport of water and solutes across the endothelium of brain capillaries is determined by several factors: (1) hydrostatic forces, (2) osmotic pressure (created by the concentration gradient of solutes), and (3) the reflection co-efficient of the endothelium for various substances (the higher the co-efficient, the less likely substances will pass across the endothelium) [71]. When the blood brain barrier is impaired, solutes pass freely across the endothelium and the primary driving force is hydrostatic pressure. These physiological (and pathophysiological) principles must be considered when interpreting the role of the agents most commonly used to treat brain edema. Various substances have been used over the years, but only two are in common use currently, namely mannitol and hypertonic saline (HTS). The primary action of these agents is to draw fluid from the brain across an intact blood brain barrier by increasing the osmotic gradient across the endothelium. In addition to its osmotic effects, mannitol also improves blood rheology and cardiac output, and may decrease CSF production. On the other hand, it may also lead to hyperosmolality, osmotic diuresis (and consequent systemic hypotension), renal impairment, and possible intracerebral accumulation with resultant rebound effects on ICP. HTS also exerts its primary effect via a changed osmotic gradient, but also improves rheology, circulating blood volume and cardiac output, and may have neuroprotective properties [72]. It has a slightly higher reflection co-efficient and so is less likely to move across the endothelium. When using HTS, hypernatremia is a risk, and rapid changes in the serum sodium level in particular should be avoided.

In general terms it would appear that older clinicians tend to prefer mannitol because of their familiarity with the agent, while younger clinicians tend to prefer HTS, a more recent addition. Although mannitol may still be used more frequently, the argument for HTS seems to be growing [73–75], and its use increasing [76]. In treating brain edema, hypertonic saline is at least as effective, and possibly better than mannitol in reducing ICP and improving brain oxygenation [77, 78]. The evaluation of the benefits and risks of HTS are complicated by the different formulations that are used, and whether it is given as a bolus or as a continuous infusion.

Treatment Directed as Cerebral Perfusion Pressures

Cerebral perfusion pressure (CPP) is usually considered to be the difference between mean arterial pressure (MAP) and ICP, i.e. CPP = MAP-ICP, when ICP is greater than central venous pressure. Much has been written about how CPP should be calculated when the head of the bed is raised – the central issue is that MAP is usually referenced at the level of the right atrium, which may introduce error in the calculation of true CPP when the point of interest, i.e. the head, is vertically higher than the reference point. However, we are familiar with the MAP references in children as conventionally measured, and some argue by the siphon theory of the inlet

and outlet pressures of the cerebral circulation, that in a closed loop system it is the starting (MAP) and ending point (central venous pressure) of the circulation that best define the CPP, and which are uninfluenced by the vertical height of the loop in between [79].

The issue of what CPP target is appropriate for both adults and children has generated much debate over the last two decades. It is also debated whether ICP-targeted treatment or CPP-targeted treatment is better. The association between low CPP and poor outcome is often reported, but may reflect the association with elevated ICP in the calculation of CPP, or with increased severity of injury and low blood pressure in polytrauma patients. Conversely, low CPP may represent a true secondary insult and some may even argue that absolute ICP values are of lesser importance if an adequate CPP can be preserved. Whether active modulation of CPP may improve outcome is much less certain. If the latter is true, the question remains: what is the optimal CPP for patients?

Some have proposed higher CPP targets in adult TBI, that on the basis of presumed intact autoregulation this would lead to better ICP control (by avoiding the vasodilatory cascade at the lower breakpoint of autoregulation) and lead to fewer ischemic episodes. However, this may be problematic for several reasons: autoregulation is commonly impaired after TBI, higher CPP may increase microcirculatory dysfunction and exacerbate tissue oedema [80, 81], and higher CPP may increase systemic adverse effects [82]. Others have argued for lower CPP thresholds to be targeted, using principles of brain volume regulation by aiming to limit oedema formation; [83] however, this approach has also not been without controversy [84]. A middle approach suggests that CPP should be individualized to the patient, i.e. a single CPP may not be appropriate for all patients. However, the endpoint that should be targeted is not clear and there are several possibilities, all of which have potential limitations. These include optimal CPP based on maximal autoregulatory capacity, brain tissue oxygenation, jugular venous saturation, and microdialysis measures.

In pediatric TBI, the issue is further complicated by changing BP and ICP norms with age, and so what constitutes an appropriate CPP for age, or even the definition of hypotension in a TBI patient, is unclear. Jones et al. considered a CPP threshold of 50 mmHg for children under 13 years old to be appropriate [85]. Chambers et al. [43] used a novel pressure-time index to evaluate secondary insults in children, and found critical CPP thresholds of 48, 54 and 58 for age-groups 2–6, 7–10 and 11–15 years respectively. In an earlier paper, the same group [44] used receiver-operating curves in the determination of outcome, finding 45 mmHg to be the minimum CPP threshold for outcome prediction in children. Downard et al. [86] on the other hand found that CPP elevation beyond 50 mmHg was not associated with improved survival, arguing that CPP management may simply be acting as a proxy for the avoidance of hypotension. Yet Hackbarth et al. [87] found that maintenance of an adequate CPP was the single most important factor for survival in paediatric TBI. More recently, Mehta et al. [88] found that low CPP (less than 45 mmHg) discriminated between good and bad outcome better than ICP in children less than 2 years old. Current recommendations recognize the paucity of clear evidence, but support the avoidance of CPP < 40 mmHg in all children, considering targeting a CPP threshold of 40–50 mmHg, and the concept that an age-related approach may be optimal [4]; however, these are still at the level of an option

Barbiturate Therapy

Barbiturates reduce ICP by metabolic suppression (assuming flow-metabolism coupling is intact) and changing vascular tone. There is also some suggestion that they may have some neuroprotective effects, but this can be difficult to separate from their overall metabolic and ICP effects. The goal of barbiturate therapy is to achieve burst suppression on EEG, at which point its effects are maximal. Pentobarbital and thiopental have been used in children, though there is no clear evidence to choose between the two. Very few studies have evaluated barbiturates in children, all as cases series [89, 90]. There is no clear evidence that barbiturate therapy benefits patients as yet. The major limitations of barbiturate therapy are their potential adverse effects – hypotension, decreased cardiac output, immune modulation, and prolonged sedation after terminating therapy. Patients on barbiturate therapy usually require inotropic support to avoid hypotension.

Decompressive Craniectomy

Decompressive craniectomy (DC) for TBI remains a controversial topic. Several uncontrolled studies suggest that craniectomy may benefit children with refractory intracranial hypertension [91–94]. The rationale for the surgery is simple. ICP is increased because of increased volume within a closed skull compartment. The purpose of a DC is to remove a large part of the cranium to increase the volume available for cerebral swelling, preferably with dural augmentation as the dura similarly limits the volume. Several studies have demonstrated the clear and usually dramatic reduction in ICP that can be achieved. A small pilot trial of DC versus ongoing medical management in pediatric TBI suggested benefit of the intervention, but the sample size was small [95]. A recent randomized controlled trial in adult TBI suggested that DC decreased ICP and hospital stay, but despite this it was associated with worse functional outcomes. A major criticism of this study was the low ICP level at

which bifrontal DC was applied (20 mmHg) and the fact that the median value of ICP before randomization was not particularly high, suggesting that many patients were subjected to DC who may have been able to manage without it – most surgeons reserve DC for more substantial increases in ICP. Furthermore, no other monitoring was done in the patients of this study, so there was no evidence that the ICP values were causing perfusion or metabolic abnormalities.

If DC is to be done, the expertise with which it is done is of paramount importance, and may make the difference between the operation being effective or not, and between a successful operation and one that can rapidly lead to an uncontrolled swollen brain that herniates through the defect. Patients should be well selected, and an early decision for DC must be made rather than subject the patient to prolonged refractory ICP. However, it should also be clear that a surgical procedure is needed, rather than intervene at a level that may respond to medical therapy. The most important aspect of the bone removal is that it should be large, either bifrontal or unilateral (hemicraniectomy). The choice between the two is personal. If there is any laterality to the injury, or midline shift, we prefer a unilateral craniectomy on the side of maximal swelling. Bifrontal craniectomy potentially has the disadvantage of subjecting both frontal lobes to the procedure and may explain some of the poor performance in executive function in the adult randomized study discussed above. The surgeon must make every effort to control brain swelling before the dura is opened. Although this may be seem contradictory (i.e. the DC is required for refractory increased ICP), it is often possible to control the ICP at least temporarily by co-ordinating several maneuvers to be maximally effective at the time of dural opening. These include timed doses of hypertonic saline and/or mannitol before surgery, controlling the blood pressure, lowering the CO_2 (while on a high FiO_2), raising the head of the bed, giving a bolus of thiopental, etc. If the brain swelling can be temporarily lessened for 15–20 min, the dural graft should be ready (pericranium is optimal) and the dura should be opened and grafted quickly. If the brain swelling cannot be controlled, it is usually too hazardous to open the dura because of the risk of uncontrolled herniation of the swollen brain through the dural defect. After surgery, it is very important to avoid hypertension, as this may increase edema in the decompressed brain because of the changed arterial-tissue pressure gradient and possibly impaired blood brain barrier.

Hypothermia

Hypothermia is neuroprotective in laboratory studies, improving survival and neurologic outcome. Much attention has been focused recently on moderate hypothermia (32–33 °C) in adult and pediatric TBI based on the expected reduction of secondary injury, including raised ICP. However, despite some preliminary encouraging data [96], the most recent data are less optimistic. A trial of 225 children with TBI randomized patients to hypothermia or normothermia within 8 h of injury, and found there were more deaths in the treatment arm. However, there was also more hypotension in the treatment arm and the limitations of the trial have been extensively discussed (cooling only for 24 h, slower rewarming possible). However, a recent Phase 3 trial that addressed some of these limitations was stopped prematurely due to a likelihood of not being able to prove its primary objective that hypothermia is beneficial. It may be that hypothermia still is beneficial in TBI, but the selection of patients and control for complications requires better elucidation. The evidence in hypoxic ischemic encephalopathy and cardiac arrest is more encouraging but less is known in these clinical scenarios of its effect on ICP.

Future Directions

ICP remains poorly understood. As much as it is clear that increased ICP causes secondary injury that aggravates poor outcome, how we should respond to this to improve outcome is much less clear. What is clear though, is that all therapies that we use to decrease ICP may in fact harm patients, and perhaps in some circumstances knowing what the ICP is and inadequately or inappropriately treating it may be worse for the patient than not monitoring ICP at all. The key is a better understanding of ICP, the etiology of raised ICP in individual cases, a broader appreciation of the underlying pathophysiology, and controlled methods for monitoring the effectiveness or risks of our chosen therapy.

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Stroke

36

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Abstract

Stroke in infants and children is a neurological emergency. Prompt diagnosis and treatment are essential to the prevention of further brain injury. There are three major categories of stroke - ischemic stroke, hemorrhagic stroke, and neonatal stroke. Arterial ischemic stroke is most commonly due to vasculopathy, thrombotic state, or metabolic disease. Vasculopathies include focal cerebral arteriopathy, arterial dissection, Moya moya syndrome, and genetic disorders causing vascular abnormalities. Thrombotic stroke is due to an underlying hypercoagulable state or thromboembolic disease. Metabolic diseases causing stroke include mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes, Fabry Disease, urea cycle disorders, and organic acidurias. Hemorrhagic stroke is almost always due to a pre-existing vascular malformation. Various diagnostic modalities are used to diagnose stroke. Computed tomography is rapid but exposes children to radiation. Magnetic resonance imaging is the modality of choice, though its use can be limited if sedation is required. Evaluation for underlying cause of stroke is guided by the stroke subtype, though in pediatric stroke, genetic causes of stroke should be carefully considered. Treatment of stroke is based largely upon adult practice, even though the etiology of stroke in childhood is not the same. Acute treatment is largely supportive and focused on secondary prevention. Multicenter studies of neonatal and childhood stroke are underway, and evidence-based diagnostic and treatment strategies are on the horizon. A comprehensive and systematic approach to pediatric stroke is a necessary component of pediatric intensive care.

Keywords

Stroke • Ischemia • Arteriopathy • Hemorrhage • Subarachnoid

Introduction

Stroke is a neurological emergency affecting infants and children. Unlike other organs, the brain is exquisitely sensitive to injury, unable to heal itself and unable to be replaced - even with the most advanced medical technologies. Given our inability to repair or replace damaged brain, early recognition of stroke and initiation of protective measures to prevent further brain injury are imperative. Following significant advances in diagnosis and treatment of adult stroke in the late twentieth century, advances are currently being made in pediatric stroke. We now know that stroke in children has historically been dramatically under-recognized. The first large, multi-center publications are describing

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the natural history of stroke in children, and international treatment trials are ongoing. Pediatric intensive care units will care for an increasing number of children with acute stroke and have new diagnostic and treatment modalities to offer. This chapter provides an overview of all causes of pediatric stroke, with a focus on arterial ischemic stroke.

Epidemiology

Cerebrovascular disease is now one of the top ten causes of death in children [1]. Stroke occurs in 2–3/100,000 children per year [2], which is on par with the incidence of all pediatric brain tumors combined. The identification of risk factors for childhood stroke remains an area of active research. Early reports indicate there may be an racial/ethnic risk for childhood stroke, even after accounting for sickle cell disease. There appears to be a slight male predominance in childhood ischemic stroke, which remains unexplained. Trauma and infection also likely increase the risk of stroke in children. Traditional adult stroke risk factors such as hyperlipidemia, diabetes, or carotid artery disease play little if any role in stroke in children.

Etiology

In broad terms, stroke is caused by either *ischemic* or *hemorrhagic* injury to the brain parenchyma. Causes of ischemic stroke can be grouped into two etiologies – (1) abnormalities inside the blood vessels and (2) abnormalities intrinsic to the blood vessels themselves. Metabolic stroke is acute ischemia due to a defect in cellular energy metabolism. This subtype of ischemic stroke is of stronger consideration in stroke evaluation in children versus adults, and has unique clinical findings. Hemorrhagic stroke is almost always due to intrinsic abnormalities or malformations of the blood vessels, but the etiology and treatment differ significantly from ischemic stroke. Finally, as in most classification schema there are special considerations. Neonatal stroke is generally considered a different entity than stroke in older children and is discussed independently here. Brain ischemia due to cerebral sinovenous thrombosis shares some features with thrombotic stroke, however the clinical presentation is distinct and also merits unique discussion here. A clear understanding of stroke etiology has significant implications for diagnosis and treatment.

Arterial Ischemic Stroke (AIS)

Vascular Causes

Focal cerebral arteriopathy is an increasingly recognized cause of acute ischemic stroke in children. Non-progressive arteriopathy describes a focal stenosis of a cerebral artery. Typically this is unilateral and involves a vessel in the anterior circulation such as the supraclinoid carotid or the middle cerebral artery. The course can be transient or progressive. In transient cerebral arteriopathy, stroke is often in the basal ganglia and recurs only about 20 % of the time [3]. Preceding varicella zoster virus exposure has been associated with transient cerebral arteriopathy. The mechanism may be direct virus invasion of the vessel or an extension of meningeal inflammation into the vessel walls. Based on this specific virus association with childhood stroke and observational studies showing preceding upper respiratory infection is common in childhood stroke, current studies are systematically investigating infection as a cause of stroke [4]. Results may offer further insight into pathogenesis and eventually disease-specific treatment for focal cerebral arteriopathy. The current treatment of focal cerebral arteriopathy varies from center to center. Aspirin is often used; anticoagulation is also used, especially if there is question of an arterial dissection. As above, current studies may indicate whether anti-inflammatory or immunosuppressive therapy would be of theoretic benefit. These are not routinely used at present.

Arterial dissection causes up to 20 % of arteriopathy and AIS in children [5]. These are typically extracranial dissections of the carotid or vertebral arteries, although dissections can occur or extend intracranially. Arterial dissection exposes inner layers of arterial vessel walls, which are highly thrombogenic. If a thrombus embolizes, it can cause an occlusion of a distal vessel. This vessel occlusion causes an acute stroke. An incidental injury to the head or neck, such as a fall from a low height, tumbling run, roller coaster ride, or mild athletic injury is often identified preceding the onset of stroke symptoms by hours or days. It is unclear why such modest head or neck injury can cause arterial dissection. Collagen or other vascular anomalies may play a role. Dull, aching posterior head or neck pain immediately after an incidental injury is particularly suggestive of a vertebral artery dissection. In conjunction with an acute neurological deficit, this history is highly suggestive of dissection and stroke. Diagnosis is made based on brain imaging, finding both the acute ischemia and the arterial dissection (see Diagnostic Imaging below). Acute treatment is comprised of anticoagulation and systemic support. Beyond the acute phase, treatment of extracranial arterial dissection is often with aspirin or anticoagulation. Pediatric providers treating children with stroke should be aware of ongoing adult stroke trials comparing these two treatments for adults with extracranial dissection. Currently it is not clear even in adults whether aspirin or anticoagulation is better for secondary stroke prevention in cases of arterial dissection. It is likely that the data from these adult trials will be extrapolated to pediatric cases until pediatric stroke treatment data is available. Duration of treatment is unclear as well. If anticoagulation is started, it is often continued for 3 months and/or until follow up vascular imaging shows resolution of abnormal findings. Aspirin has

lower potential risks and cost and is often continued longer. Treatment of intracranial arterial dissection should be approached with caution, due to the risks of intramural hematoma and intracranial hemorrhage.

Moya moya disease is an idiopathic, progressive occlusion of large to medium-sized vessels around the Circle of Willis, most commonly one or both internal carotid arteries and their branches. With occlusion of these vessels the basal ganglia is at high risk for ischemia. Chronic brain ischemia promotes formation of collateral blood vessels. The formation of these small anastomotic blood vessels is called Moya moya vasculopathy. On angiography, these vessels are so small and prolific that their territories are indistinct. Injected contrast appears as a diffuse haziness - thus the Japanese name, 'moya moya' (Fig. 36.1). Moya Moya syndrome refers to this vasculopathy occurring in clinical situations with a known risk factor. Risk factors for Moya moya syndrome include Trisomy 21, Sickle Cell Disease, cranial radiation and Neurofibromatosis type 1, for example. In children, Moya moya vasculopathy causes ischemic stroke, typically of the basal ganglia or cerebral watershed zones. In contrast, adults with Moya moya vasculopathy tend to have hemorrhagic strokes. The ischemic strokes can occur in the setting of decreased brain perfusion such as dehydration or increased metabolic demand such as fever. They can also be unprovoked. The only successful treatment of Moya moya disease is surgical revascularization. In Moya moya syndrome due to Sickle Cell Disease, prophylactic blood transfusion with a goal of 30 % or less sickle hemoglobin prevents ischemic stroke and is the standard of care for these patients [6].

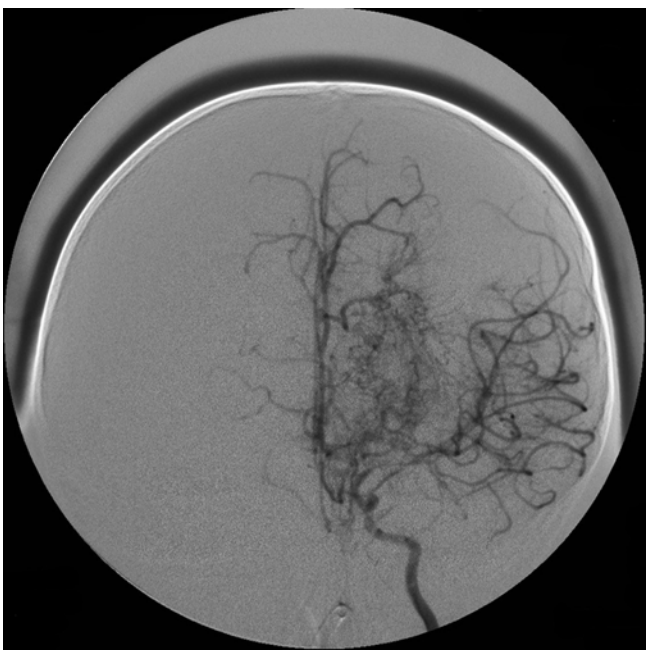


Fig. 36.1 Moya moya vasculopathy. Cerebral angiogram, coronal view, showing moya moya vasculopathy in the region between the anterior cerebral artery and the middle cerebral artery. Note the narrowed caliber of the proximal middle cerebral artery

Vasculitis, systemic or isolated to the central nervous system (CNS), can cause stroke. These strokes are typically unilateral, multifocal and affecting the basal ganglia. Systemic lupus erythematosis is a well-known cause of cerebral vasculitis, but theoretically any systemic vasculitis can involve blood vessels in the brain. Isolated CNS vasculitis is difficult to diagnose clinically because by definition only the brain is involved. Childhood CNS vasculitis presents clinically with cognitive dysfunction, chronic headache, and focal neurological deficits [7]. Imaging typically shows unilateral strokes in the basal ganglia [8]. While cerebral angiography can confirm a vasculitic appearance of blood vessels, brain biopsy is still the definitive diagnostic tool. Treatment of CNS vasculitis is difficult and usually involves steroids and steroid-sparing immunosuppression.

Genetic syndromes causing abnormal cerebral vasculature can cause stroke as well.

Neurofibromatosis type 1 is associated with Moya moya syndrome, aneurysms, and other vasculopathies affecting intracerebral vessels. PHACES, a neurocutaneous syndrome of *p*osterior fossa malformation, facial *h*emangioma, *a*rterial cerebrovascular abnormalities, *c*ardiovascular abnormalities and *e*ye abnormalities, is associated with ischemic stroke due to the cerebrovascular abnormalities. Incontinentia pigmenti and Menkes disease have both been associated with stroke in infants, possibly through a vascular mechanism. Fibromuscular dysplasia most commonly affects the renal arteries but can affect the carotid and intracranial arteries, and thereby cause stroke.

Thrombotic Causes

A *hypercoagulable state* is a risk factor for both arterial and venous thrombi, either of which can cause acute brain ischemia or stroke. An underlying hypercoagulable state can be found in up to 50 % of cases of childhood acute ischemic stroke [9]. Case series and case control studies in childhood stroke have shown an association between several hypercoagulable states and stroke. Since stroke can be the presenting symptom of one of these disorders, evaluation for these is undertaken in almost all cases (Table 36.1). Treatment of an underlying hypercoagulable state should involve consultation with a hematologist or rheumatologist. Depending on the disorder, aspirin or anticoagulation are the most common treatments.

Thromboembolic stroke occurs when a thrombus formed elsewhere in the body embolizes through the arterial system and causes a stroke in the brain. The most common source of emboli is the heart. Risk factors for forming cardiac emboli include low motion of the atrial or ventricular wall, as in atrial fibrillation or very low ejection fraction from any cause. Another major cause for cardioembolic stroke is an

Table 36.1 Hypercoagulable state testing

Condition	Test
Factor V Leiden mutation	Factor V Leiden mutation (PCR)
Prothrombin mutation	Prothrombin mutation (PCR)
Antithrombin III deficiency	Antithrombin III enzyme activity
Protein C or S deficiency	Serum protein C and S levels
Hyperhomocysteinemia	Serum homocysteine
Elevated lipoprotein (a)	Serum lipoprotein
Antiphosphoplipid syndrome	Serum lupus anticoagulant and anticardiolipin antibodies

abnormal right to left shunt through the heart. This can happen intraoperatively or can be due to congenital heart disease. Single ventricle physiology, atrial and ventricular septal defects with right to left flow can allow a thrombus to pass from the venous system into the arterial system and then into the brain. Patent foramen ovale (PFO) is a common finding in up to a third of adults and is also seen in children [10, 11]. In theory, a thrombus could pass through and cause a stroke. However, this appears to only happen very rarely based on the prevalence of PFO in asymptomatic adults. Current studies in adult stroke literature are attempting to determine the contribution of PFO to stroke risk, and the optimal treatment if this occurs. There is no firm data yet regarding PFO and childhood AIS.

Evaluation of thromboembolic stroke focuses on finding the source of the thrombus. Cardiac etiologies should be investigated in every case; if a PFO is identified and no other likely source found, then evaluation for lower extremity deep venous thrombosis (DVT) can be undertaken. In the setting of an embolic appearing stroke, presence of a PFO and no other cause found, the finding of a DVT would be a reason to start anticoagulation. In rare diseases like Hereditary Hemorrhagic Telangiectasia (HHT), arteriovenous malformations (AVMs) in the lungs or liver can allow paradoxical emboli to the brain. HHT is suggested by an autosomal dominant family history of AVMs and the presence of telangiectasias in older children.

Treatment of thromboembolic stroke is directed at the source of the embolus. Anticoagulation is often initiated when a thrombus is identified in the heart or elsewhere. In rare cases such as patients with congenital heart disease, surgical thrombectomy can be attempted. Acute treatment of intracranial thrombus in children is discussed below.

Metabolic Causes

In addition to vascular and thrombotic stroke, a third subcategory of ischemic stroke is metabolic stroke. In these cases an underlying metabolic defect directly or indirectly causes acute brain ischemia.

Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) is the sentinel disease causing metabolic stroke. In MELAS, presentation of stroke-like episodes is very similar to AIS, with an acute focal neurological deficit. However brain imaging shows an unusual, non-arterial distribution of ischemia, typically in the parietal and occipital areas (Fig. 36.2). Symmetric lesions, particularly in the basal ganglia, can be a clue to metabolic stroke. Vascular imaging is normal. Diagnosis is suggested by the non-vascular distribution of acute ischemia on imaging, in conjunction with the clinical elements of short stature, developmental delay, sensorineural hearing loss, seizures and cardiac arrhythmias such as Wolf-Parkinson-White. A family history of diabetes, migraines and MELAS phenotypes distributed in a maternal inheritance pattern is highly suggestive for the diagnosis. Confirmation is by mitochondrial DNA sequencing. Treatment of MELAS is with a 'mitochondrial cocktail' and is best managed by an expert in mitochondrial disorders.

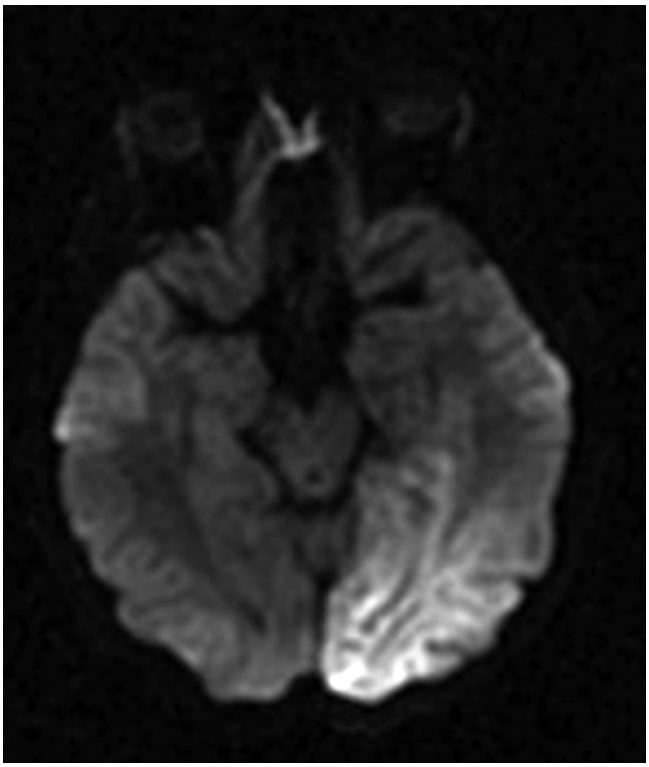


Fig. 36.2 MELAS. MRI, axial view, diffusion weighted imaging, showing acute ischemia in a left parietal and occipital distribution. This stroke-like episode presented with seizure and homonymous hemianopsia; MELAS was confirmed with genetic testing

Fabry disease is an X-linked lysosomal storage disorder. Early symptoms of Fabry disease include acroparesthesias, abdominal pain, and angiokeratomas. Corneal deposits and renal insufficiency can occur. Later, cardiac manifestations can include ventricular hypertrophy, cardiac arrhythmias and coronary artery disease. Stroke in patients with Fabry disease can be secondary to the cardiac abnormalities or due to cerebral arteriopathy from the accumulation of

globotriaosylceramide due to the disease. Although stroke in Fabry disease typically does not occur until adulthood, recognition and treatment of Fabry disease in childhood could help prevent disease progression. Enzyme replacement is available and is recommended for stroke prevention in Fabry disease.

Homocystinuria is an autosomal recessive disease causing elevated serum homocystine. Diagnosis is suggested by elevated serum homocysteine, homocystine and methionine, with elevated urine homocystine, and can be confirmed with genetic testing. Clinical manifestations include tall, thin body habitus, lens dislocation, cognitive impairment, hypopigmentation and stroke. Stroke is due to cerebral arteriopathy or thromboembolism. Lowering homocysteine levels reduces stroke risk in patients with this disease. This is typically accomplished with vitamin supplementation including folate, B vitamins, cysteine and avoidance of dietary methionine.

Other metabolic disorders, such as glutaric aciduria, organic acidurias, and urea cycle disorders have been associated with ischemic or hemorrhagic stroke. The pathophysiology of stroke in these rare disorders is unknown. Treatment is directed at correcting the underlying disease. Medications for secondary stroke prevention, such as aspirin, should be discussed with a metabolic geneticist prior to initiation.



Fig. 36.3 Cerebellar stroke causing obstructive hydrocephalus. CT, axial view, showing acute right cerebellar hemisphere ischemia. Note the compression and displacement of the fourth ventricle by the expanding stroke, and the dilation of the third ventricle and temporal horns of the lateral ventricles, all indicating obstructive hydrocephalus

Treatment of AIS

Acute treatment of a child with an ischemic stroke is first and foremost supportive. Low risk neuroprotective measures used in adults are often used in children, including maintenance of normothermia and normoglycemia, although firm supportive data is lacking. Blood pressure should be monitored carefully, and most experts recommend moderate permissive hypertension. Ischemic brain parenchyma swells for up to 3 days after the initial ischemic event. In a fixed volume space, this swelling can cause increased intracranial pressure. Strokes affecting large areas of brain parenchyma, such as an MCA distribution stroke causing hemispheric ischemia, can result in brain herniation. Strokes in the posterior fossa merit particular attention, as they can rapidly swell, block CSF outflow and cause obstructive hydrocephalus leading to highly morbid cerebellar herniation (Fig. 36.3). As intracranial pressure is increased, compensatory systemic hypertension develops. These higher than normal systemic blood pressures are necessary to promote cerebral perfusion pressure; clinical acumen is needed to determine when cautious antihypertensive agents may be necessary. In some cases, neurosurgical intervention with craniectomy can allow brain expansion without further ischemic injury, although again supportive data are lacking [12].

Medical treatment for pediatric AIS is not supported yet by data. Nonetheless, aspirin 3–5 mg/kg/day is often started in the acute setting for secondary stroke prevention based on efficacy in adults with stroke [13]. The unknown benefit must be weighed against the small risk of Reye syndrome in children. Optimal duration of aspirin treatment for secondary stroke prevention is unknown. For a visualized intracranial thrombus, extracranial arterial dissection, or thromboembolic stroke, anticoagulation is commonly initiated. Following adult stroke data, anticoagulation should not be used in the absence of a known abnormality. If anticoagulation is started, it is often continued for 3–6 months and/or until follow up vascular imaging shows resolution of abnormal findings. Thrombolytics or mechanical clot retrieval devices have not been studied in pediatric stroke. Dosing, safety and efficacy are unknown. Case reports describe their use; however publication bias may result in over-representation of good outcomes [14].

Outcome from AIS

Mortality is less than 10 % following AIS in recent studies; however morbidity is high with 74 % of survivors having neurological deficits [13, 15]. In survivors, long term

outcome depends largely on the underlying etiology. Current data show a 20 % recurrence risk for childhood AIS [16]. Recurrence risk is increased with the identification of vascular abnormalities, total occlusion of blood vessels and untreated underlying disorders. Whether aspirin or other secondary prevention measures are effective in childhood stroke is as yet unstudied and unknown.

Hemorrhagic Stroke

Intracerebral hemorrhage results from blood vessel rupture, and depending on the size and location of the vessel(s), can result in silent microbleeds or catastrophic hemorrhage. Hemorrhagic stroke (HS) is virtually always a secondary result of a distinct primary problem: intracranial vascular malformation, hematologic abnormality, aneurysm, tumor, infection, or intrinsic vasculopathy (Table 36.2). Rarely, hyperacute extreme hypertension or vascular spasm can precipitate intracranial hemorrhage in otherwise normal vessels, particularly in the setting of exertion or illicit drug use. Most hemorrhagic stroke in children involves parenchymal injury, and the terms intraparenchymal hemorrhage (IPH), intracerebral hemorrhage (ICH), cerebral hemorrhage (CH), and hemorrhagic stroke are often used interchangeably. Traumatic intracranial bleeding, subdural and epidural hematomas, and secondary hemorrhagic transformation of arterial ischemic stroke are not considered hemorrhagic strokes.

Symptoms of hemorrhagic stroke are identical to arterial ischemic stroke, and for all practical purposes cannot be distinguished clinically from other types of stroke. Heralding headache and prominent emesis can be a clue, but are not distinct presenting features. The appropriate diagnostic imaging evaluation of children with hemorrhagic stroke has not been established. Low-dose non-contrast head CT is often performed in the emergency department for the rapid identification of intracranial blood (Fig. 36.4). MRI/MRA is the study of choice if available, and for follow-up study. CTA is not preferred given large radiation doses, and it has not been shown to be superior to MRA. Direct catheter angiography is informative in many clinical settings.

Table 36.2 Causes of hemorrhagic stroke

Cause	% Contribution
Arteriovenous malformation	30
Cavernous malformation	25
Hematologic abnormalities[a]	25
Tumor	10
Other	10

[a]Including liver failure, thrombocytopenia, hemophilia, disseminated intravascular coagulation

Notably, there are not consensus guidelines for treatment of pediatric hemorrhagic stroke, despite its accounting for roughly half of all stroke in children [2]. Although not validated in the pediatric population, classification schemes based on the location and volume of hemorrhage are sometimes employed for treatment decision-making. Substantial hematomas (midline shift, herniation, large volume) and those presumed due to aneurysmal rupture require prompt consultation with neurosurgeons and interventional neuroradiologists. In stable patients, emergent surgical treatment can be deferred to allow blood products to resorb, providing an opportunity for more detailed assessment of underlying lesions. Diagnostic cerebral angiography should be obtained if aneurysm or other vascular malformation is suspected. Prognosis is highly variable, depending on severity of initial bleed, resulting injury, as well as clinical course. Long-term treatment is directed toward the underlying primary abnormality, and can include surgical lesionectomy, radiotherapy, or intra-arterial embolization. Recurrence rate also depends on etiology. Some meta-analyses suggest cumulative risk of 10 %, although follow-up times vary, and risks of 2 % per year are often cited for untreated arteriovenous malformations [17].

Subarachnoid hemorrhage (SAH), a distinct hemorrhagic stroke subtype, is a well-defined clinical entity with characteristic clinical history, readily identifiable signs and



Fig. 36.4 Intraparenchymal hemorrhage. CT, axial view, showing a right hemisphere IPH, in a patient on anticoagulation for vasculitis, who presented with acute mental status change

symptoms, and specialized treatment approaches. In general, SAH associated with other types of intracranial hemorrhage (e.g. subdural or epidural hematomas from trauma) does not represent a primary mechanism and thus is usually not considered hemorrhagic stroke. However, SAH is commonly seen in the context of other types of HS. As a primary entity, it is uncommon in children, comprising approximately 10 % of all hemorrhagic stroke [18]. Ruptured aneurysm is the most common cause of primary SAH in children. Presenting symptoms include acute severe headache, meningismus, and often syncope or altered mental status. Often a less severe headache can precede aneurysmal rupture by hours or days. Retinal findings such as flame hemorrhages strongly support this diagnosis and are nearly pathognomonic in this clinical setting. CT has notoriously limited sensitivity for early, small, or occult (e.g. posterior fossa) SAH, and if clinically suspected, lumbar puncture for xanthrochromia is crucial. If detected, SAH treatment is obligatory, and cerebral angiography should be performed promptly. MRI/MRA should be performed emergently, if available. CTA is advised in the absence of MRA. Initial treatment typically is comprised of urgent intervention to secure the bleeding lesion, followed by hydration, blood pressure control, and monitoring for signs of additional bleeding or vasospasm. Prophylaxis for vasospasm in all but the smallest SAH is prudent; 21 days duration is typical. Repeat angiography with direct injection of calcium-channel blockers or balloon angioplasty is typically offered for clinical or radiographic signs of vasospasm. Definitive surgical treatment depends on type, location, and nature of the hemorrhagic source.

Neonatal Stroke

Cerebrovascular events occurring between roughly 20 weeks of gestation and 28 postnatal days of life share etiologic overlap with entities described above. However, neonatal physiology is distinct from later childhood, and thus neonatal stroke deserves particular attention in diagnosis, prognosis, and treatment. Thromboembolic stroke can involve transient physiologic 'coagulopathies' in the first days, as well as placental pathology. Cerebral sinovenous thrombosis results from relative dehydration, venous stasis, and transient physiologic coagulopathy. Intracerebral hemorrhage results from transient though sometimes dramatic swings in blood pressure, oxygen saturation, and vasoreactivity, and some cerebral vessels particularly at risk for hemorrhage exist only for short periods of time in mid-gestation. Vulnerable brain regions are those that tend to be most metabolically active; basal ganglia, thalamus, cerebellum, and subcortical gray matter. Clinical signs and symptoms can be subtle, and include a rapid drop in hematocrit, persistent unexplained oxygen desaturations or vital sign instability, and bulging fontanelle. Focal seizures, unusual in neonates, should be considered stroke until proven otherwise. Ultrasound is a quick, non-invasive, readily available screening tool to evaluate for intracranial hemorrhage and secondary signs of ischemia. Neonatal MRI is commonly performed for definitive diagnosis at most large pediatric medical centers. Treatment, in the absence of a fixed lesion, is largely supportive. Recovery encompasses an extremely broad spectrum, even in cases that appear catastrophic.

Cerebral Sinovenous Thrombosis (CSVT)

CSVT results from thrombosis and occlusion within one or more dural venous sinuses, which drain deoxygenated blood from the brain. This entity is unusual in that it can result in ischemia, hemorrhage, or both. Thus, mixed clinical signs and symptoms can occur. Classically, patients present with subacute diffuse headache that may be positional, a modest degree of visual disturbance which may be intermittent and ill-described or subtle altered mental status. Remaining clinical features depend on regional involvement, and unlike AIS are often bilateral. Typically, a thorough clinical history will reveal one or more risk factors, including dehydration, anemia, known coagulopathy, concurrent infection (otitis media, sinusitis), sepsis, oral contraceptive use, or oncogenic process. Pregnancy should be given careful attention. Pathophysiology involves dural venous stasis, thrombosis formation, resultant venous hypertension, "upstream ischemia", and ultimately hemorrhage. Imaging (MRI with DWI and GRE-based sequences and MR venography is the study of choice) may reveal a non-arterial ischemic pattern juxtaposed to a major venous sinus, with or without associated hemorrhage (Fig. 36.5). If clinically suspected, MR venography should be performed for definitive evaluation. Prompt anticoagulation and aggressive hydration is imperative for acute or progressing CSVT. Anticoagulation should be considered even in hemorrhagic CSVT, as the thrombosis is the causative agent of the hemorrhage [19]. A more conservative "watchful waiting" approach is appropriate for some cases, provided close follow-up and clear care plans.

Diagnostic Imaging in Stroke

Rapid advances in clinical neuroimaging have provided an array of utilities to aid in stroke evaluation. MRI in particular has seen remarkable advances in recent years. Each institution should utilize a process model or protocol for imaging evaluation of suspected stoke in children.

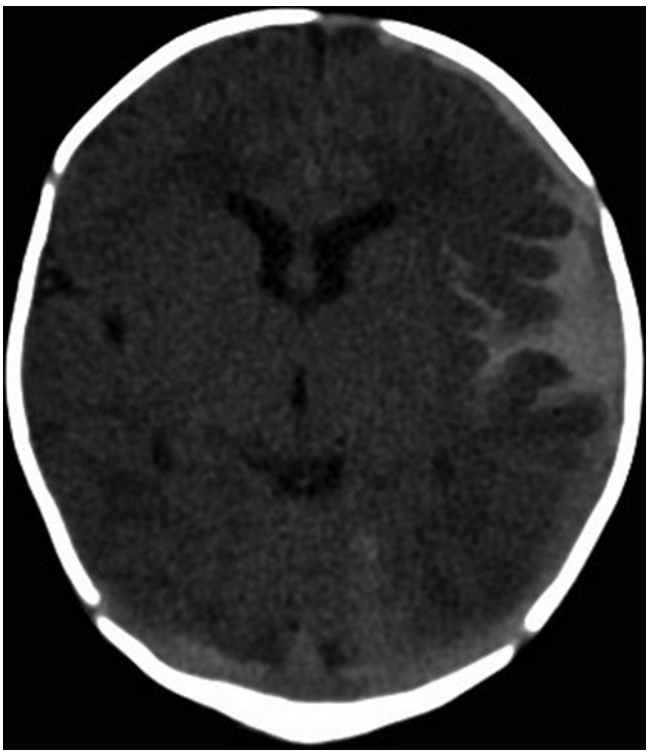


Fig. 36.5 CSVT with hemorrhage. CT, axial view, showing left sided subdural hemorrhage (SDH) and CSVT in the sagittal sinus and bilateral transverse sinuses. Note the slight difference in density between the SDH and CSVT

Magnetic Resonance Imaging (MRI)

MRI is the imaging modality of choice for evaluation of acute stroke in children. The sensitivity and specificity are very high for virtually all pathologic entities in the differential diagnosis at initial presentation, and the combined yield in both stroke and non-stroke entities is vastly superior to other modalities. MRI can be obtained rapidly, and if prioritized appropriately, key studies can be obtained in minutes. Unlike X-ray-based computed tomography (CT), MRI does not employ ionizing radiation, sparing children from the unnecessary risk of future cancer and other morbidity.

There are four major types, or sequences, of MRI scans that have high utility in evaluation of acute stroke. Diffusion-weighted imaging (DWI) relies on the measurement of random Brownian water motion and any 'restriction' of this movement due to the presence of a space-occupying lesion, proteinaceous content, or cytotoxic edema, as in the case of acute stroke. Diffusion restriction appears bright on DWI within minutes of stroke onset. The apparent diffusion coefficient (ADC) is a derived value calculated to remove technical artifacts that might make illusory bright spots on DWI. ADC is dark in acute stroke. DWI and ADC changes, which occur essentially at stroke onset, are extremely sensitive; suspected acute stroke with normal DWI/ADC imaging demands further evaluation for non-ischemic etiology. These sequences can be obtained in 5–10 min. Inversion recovery (FLAIR) sequences are essentially T2-weighted images with CSF signal suppression, and are useful in dating stroke onset, identifying hemorrhagic stroke including SAH, as well as for evaluating stroke mimics. Gradient recalled sequences (GRE) are based on detection of hemolyzed blood products, and have excellent sensitivity for intracerebral hemorrhage.

3D time-of-flight MRA is an extremely useful technique in initial evaluation of pediatric stroke. Blood is 'labeled' as it transits thorough an acquisition volume, giving rise to a maximum intensity projection of head and neck vessels without the need for contrast. However, it is important to recognize that this flow-dependent signal is both a benefit as well as a limitation of MRA; often turbulent flow or modest relative stenosis will cause focal loss of signal in an otherwise normal vessel. Thus, vascular narrowing tends to be overestimated, particularly in regions of slow flow. Contrast can assist in improved visualization of suspicious vessels, as can conventional angiography. If dissection is suspected, axial T1 fat-saturated images through the vessels in question should be obtained. MR venography (MRV) is the preferred study for evaluation of cerebral venous sinus thrombosis. Perfusion MRI is not widely used for evaluation of acute stroke in children at present. However, this technique shows promise in differentiating infarcted tissue from tissue at risk that is potentially salvageable if appropriate intervention is instituted promptly.

Computed Tomography (CT)

Non-contrast head CT remains in wide clinical use for the purpose of rapid diagnosis of intracranial blood. Rapid, low dose CT scans limit potentially harmful doses of ionizing radiation without loss of diagnostic accuracy for intracranial blood or hydrocephalus [20]. Outside of this setting, clinical use of CT scanning in acute pediatric neurological disease is of limited value, unless MRI is unavailable. In this situation, CT and CTA are imperative for evaluation of suspected dissection, HS and SAH. CT in the setting of acute ischemic stroke has virtually no utility beyond screening for intracranial blood or assessing vascular integrity.

Cerebral Angiography

Conventional angiography is likely underutilized in pediatric stroke. It is particularly useful for clinical situations in which vessel injury is likely or suspected (i.e. to identify thombogenic sources), to further characterize abnormalities on MRA/CTA, to identify aneurysms and vascular malformations, and to identify bleeding source in most cases of hemorrhagic stroke. Most experts recommend diagnostic catheter angiography in

cases of cryptogenic AIS to screen for occult vascular abnormalities, and in our experience the yield of detecting distal as well as subtle abnormalities is substantial.

Cardiac Imaging

Echocardiogram is a non-invasive, useful tool to investigate structural abnormalities of the heart that may predispose to thromboembolic stroke. These include valvular lesions or vegetations, wall motion abnormalities and in situ thrombus. Very low ejection fraction also predisposes to intracardiac thrombus formation. Intravenous contrast or agitated saline is needed for detection of intracardiac shunt, especially a PFO. Transcranial Doppler (TCD) with contrast is a non-invasive test that can enhance detection of cerebral emboli, including those due to systemic right to left shunt. While echocardiogram is sufficient for structural imaging of the valves and ventricles, evaluation for right to left shunt is also needed. In children, transthoracic echocardiogram (TTE) with agitated saline ("bubble" study) is 88 % sensitive in detecting a PFO, compared to the gold standard of transesophageal echocardiogram (TEE) [21]. TCD has not been systematically studied for detection of emboli in children, but in adults it appears to be as sensitive has contrasted TEE [22]. Thus, contrasted TTE with TCD may be the least invasive, most sensitive imaging for paradoxical embolus.

Conclusion

Stroke in childhood has many etiologies. In the absence of known pathology, workup should include evaluation for rare causes of stroke including metabolic and hematologic disease. Detailed history and exam can be of invaluable import here, since these disease states typically have systemic signs and symptoms. Risk factors for adult stroke, such as hypertension, hyperlipidemia, diabetes, atherosclerosis, atrial fibrillation, and sedentary lifestyle are acquired over a lifetime and generally do not play a role in childhood stroke. Cryptogenic stroke, in which no cause is found despite extensive evaluation, remains prevalent. Hemorrhagic stroke is almost always due to a vascular abnormality, and may require neurosurgical or interventional radiological treatment. Neonatal stroke is not well understood, and treatment is largely supportive. Cerebral sinovenous thrombosis can cause acute brain ischemia, hemorrhage, or both, and is best treated with anticoagulation or supportive care.

Pediatric intensivists should employ a comprehensive and systematic approach to patients with an acute neurological deficit. Almost always multiple subspecialists will be involved, with the intensivist directing care. In addition to a foundation of knowledge in pediatric stroke, intensivists should look for emerging publications and evidence-based medicine regarding the evaluation and treatment of children with stroke. Current recommendations are based largely on expert opinion [19]. These will likely be supplanted as ongoing research yields more information about risk factors for stroke, and risks and benefits of treatments [23]. The following is a framework for an approach to suspected stroke; this framework should be amended as appropriate for available clinical resources, individual cases and as new information is published.

Approach to a Patient with a Suspected Stroke

The first step is to establish a diagnosis of stroke. (Table 36.3) Acute focal neurological deficits in a child can be due to various non-stroke causes (Table 36.4). Stroke in neonates presents with non-specific signs such as encephalopathy, apnea and bradycardia, or seizure, and the threshold to pursue diagnostic testing must be low. Stroke in infants is likely to present with seizure and encephalopathy, whereas stroke in older children is more likely to present with significant hemiparesis. A brief history should be obtained, focused on identifying comorbidities suggestive of stroke, and baseline vital signs, especially blood pressure, and neurological exam should be well-documented. The initial exam will be the baseline for clinical decision-making throughout the acute treatment course. When acute stroke remains in the differential, the next step is to determine optimal imaging. Both the brain and the blood vessels may need to be imaged. Options may include CT, MRI, or angiography as discussed above. Imaging is essential both to make the diagnosis of acute stroke and to evaluate for mimics of acute stroke.

Table 36.3 Summary approach to suspected stroke

Establish the diagnosis	Evaluate for causes of stroke and stroke mimics
	Determine optimal imaging
Initiate supportive care	Maintain cerebral perfusion pressure
	Neurosurgical consult for hemorrhagic stroke
	Intensive care unit admission for close monitoring
Investigate for cause	Further vessel imaging
	Cardiac imaging
	Hypercoagulable labs
	Evaluate for infection, including varicella
Consider treatment options	Aspirin 3–5 mg/kg/day for secondary prevention
	Anticoagulation for identified thrombus or dissection
Stroke rehabilitation	Physical therapy
	Occupational therapy
	Speech therapy
	Physiatrist consult

Table 36.4 Stroke mimics

Normal imaging	Abnormal imaging
Migraine	Posterior reversible encephalopathy syndrome
Seizure	Acute disseminated encephalomyelitis
Hypoglycemia	Multiple sclerosis
Hypocalcemia	Meningoencephalitis
	Cerebral abscess
	Subdural or epidural hematoma
	Tumor

Table 36.5 Causes of acute ischemia in a non-arterial distribution

Venous ischemia	Cerebral sinovenous thrombosis
	Venous hypertension
Metabolic	MELAS[a]
	Glutaric aciduria
Demyelination	Acute disseminated encephalomyelitis
	Multiple sclerosis
Other	Tumor
	Abscess

[a]Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes

The second step, after diagnosis of stroke, is to initiate supportive care. Maintaining appropriate cerebral perfusion pressure is critical. Hemorrhagic stroke may need urgent neurosurgical intervention. Neuroprotective measures should also be in place as soon as possible.

The third step is to find the cause of the stroke. Multimodal imaging may be required to determine the cause. Most ischemic strokes occur in an arterial distribution; if non-arterial distribution ischemia is found, the differential diagnosis may change (Table 36.5). In focal cerebral arteriopathy, one should consider infectious causes including varicella zoster. In thromboembolic appearing stroke, prompt investigation for a source should ensue. Early treatment of the source may prevent stroke recurrence. In thrombotic stroke, consider evaluation for hypercoagulable state. Vasculopathies, including arterial dissection and Moya moya vasculopathy have distinct treatments. Finally, in pediatric stroke, consideration of genetic and metabolic causes of stroke is particularly important.

Secondary stroke prevention should be considered in all cases. If an underlying, treatable cause of stroke is identified, then determining secondary prevention is straightforward. In cases of acute ischemic stroke with no cause found, many clinicians consider empiric aspirin 3–5 mg/kg/day. These measures should all be initiated within the first 24 h after a stroke, and thus will take place in the pediatric intensive care unit. Additional considerations are anticonvulsants if the patient has seizures, nutritional support with enteral feeds if necessary, and deep venous thrombosis prophylaxis. As the patient is stabilized, efforts towards stroke rehabilitation start. Physical, occupational and speech therapists are closely involved especially in the hospital setting. Many children with stroke develop behavioral and learning disorders requiring the help of psychologists, psychiatrists and educational specialists.

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Inflammatory Brain Diseases

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Marinka Twilt, Dragos A. Nita, and Susanne M. Benseler

Abstract

Inflammatory brain diseases in childhood are underrecognized and lead to devastating, yet potentially reversible deficits. New onset neurological or psychiatric deficits in previously healthy children mandate an evaluation for an underlying inflammatory brain disease. Distinct disease entities have been described in childhood. Clinical symptoms, initial laboratory test and neuroimaging studies help to differentiate between different causes. However more invasive tests, such as lumbar puncture (neuronal antibody tests), conventional angiography, and/or brain biopsy are usually necessary before start of treatment. This Chapter will focus on the differential diagnosis of inflammatory brain diseases which can be encountered when taking care of children on an intensive care unit.

Keywords

Vasculitis • Neuroinflammation • Anti-neuronal antibodies • Infection • Demyelination • Rheumatic diseases • Hemophagocytic lymohohistiocytosis HLH • Inflammatory brain disease • Rasmussen encephalitis • MRI • Angiography • Brain biopsy • Treatment • Immunosuppression

Introduction

Inflammation is an increasingly recognized underlying pathology in children presenting with severe acquired neurological deficits. All the individual components of the central nervous system (CNS) and peripheral nervous system (PNS) can be targets of a dysregulated innate or adaptive immune system [1, 2]. The interaction between the target structure and the specific antibodies or cellular response will determine the clinical phenotype of the disease, including mode of onset, severity, and long term evolution. A typical clinical presentation if inflammatory brain disease in children is subacute, often multifocal, with a fluctuating but rapid progressive course, either idiopathic or less frequently in the context of a systemic illness or paraneoplastic process [3–6].

Inflammatory conditions of the CNS are also known as inflammatory brain disease. Children with inflammatory brain disease can present with devastating neurological deficits requiring admission to the pediatric intensive care unit (PICU) for seizure control, mechanical ventilation, and other supportive intensive care therapy. Early recognition and diagnosis of inflammatory brain disease is critical, since the reversibility of acquired deficits is closely linked to rapid initiation of therapy and prevention of secondary brain tissue damage (for example, due to prolonged seizures).

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Primary inflammatory brain diseases solely affect the brain and/or spinal cord and encompass vasculitis and non-vasculitic inflammatory brain diseases, such as demyelinating diseases, neuronal antibody mediated inflammatory brain disease, T-cell mediated inflammatory brain disease, and granulomatous inflammatory brain disease (Table 37.1) [3, 6, 7]. Secondary inflammatory brain diseases correspond to brain inflammation in the context to a systemic disease, such as infections, rheumatic diseases, systemic inflammatory diseases and other systemic illness or exposures [4, 8–29].

The diagnosis of inflammatory brain disease is based on a thorough clinical evaluation, including features of systemic inflammatory illnesses, blood and CSF analysis, neuroimaging studies, supportive testing such as electromyography / nerve conduction studies and targeted tests such as specific antibodies or brain biopsies (Fig. 37.1). Muscle and nerve biopsies can have great utility, but their sensitivity is altered due to the fact that immune disorders often have a patchy involvement of these organs. For antibody-mediated diseases, there are commercial and experimental laboratory tests available. Brain biopsies should be considered in specific patient populations, such as refractory seizure status early in the course of immunosuppressive therapy [30].

Every child with a newly acquired neurological deficit (focal or systemic) should be investigated for an underlying inflammatory etiology. The differential diagnosis for neuroinflammatory conditions is very wide and rapidly expanding. This chapter focuses on the common inflammatory brain diseases that are encountered in the PICU and discusses the extensive differential diagnoses, as well as the common therapeutic approaches.

Vasculitic Inflammatory Brain Diseases

Primary CNS Vasculitis

Primary Angiitis of the central nervous system (PACNS) is the most common cause of severe, acquired neurological deficits in previously healthy children [15, 31, 32]. PACNS was first described in adults in 1959 [33]. Initial cases were almost exclusively diagnosed at autopsy, demonstrating granulomatous inflammation of the cerebral arteries [34]. In 1988 Calabrese et al [31] described 8 new cases and summarized the available literature of PACNS in adults. He coined the term PACNS and proposed diagnostic criteria for adults. These criteria mandate (a) a newly acquired neurological deficit, (b) angiographic and/or histological evidence of CNS vasculitis, and (c) the absence of a systemic condition that could explain these findings [31]. The Calabrese criteria were adopted and modified for childhood PACNS (cPACNS), requiring a newly acquired neurological deficit and/or psychiatric symptom in a patient $\leq$ 18 years of age [15]. In our tertiary care center, cPACNS was the most frequently diagnosed inflammatory brain disease over the past last 5 years. The current classification of cPACNS is based on affected cerebral vessel size and disease course [15, 35]. Three subtypes are recognized; (1) Non-progressive (NP) large-medium vessel cPACNS (angiography positive), (2) Progressive (P), large-medium vessel cPACNS (angiography positive) and (3) small vessel (SV) cPACNS (angiography negative, biopsy positive) [15, 35]. The three subtypes display distinct presenting symptoms, laboratory findings, disease course and treatment outcome [15, 35].

Angiography-Positive Nonprogressive cPACNS (NP-cPACNS)

Children with NP-cPACNS present with sudden onset focal neurological deficits and are frequently diagnosed with arterial ischemic stroke [15]. This subtype affects boys more commonly than girls, corresponding to the gender predilection in stroke overall [36]. Focal deficits can include hemiparesis, hemifacial weakness, hemisensory loss, and fine motor skill loss [15]. Approximately 10 % of children present with additional diffuse focal deficits such as decreased cognition or behavior change. Overall headaches are present in 40 % of the children with NP-cPACNS [15]. Inflammatory markers including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are frequently normal. The endothelial cell marker von Willebrand Factor (vWF) antigen remains to be studied systematically, in this population. The evaluation of potential prothrombotic abnormalities is mandatory. In NP-cPACNS, less than 50 % of the patients have an elevated protein level or evidence of leukocytosis on cerebrospinal fluid (CSF) analysis [15, 37]. The role of the opening pressure remains uncertain.

Magnetic resonance imaging (MRI) and angiography studies are mandatory and should include T1, T2, Fluid attenuated inversion recovery (FLAIR), diffusion weighted imaging (DWI), and apparent diffusion coefficient (ADC) sequences for parenchymal lesions [38]. MRI studies in NP-cPACNS patients reveal unilateral ischemic lesions large vessel distributions, most commonly the basal ganglia are affected [39]. Vasculitis is best confirmed on angiography demonstrating unilateral stenoses and dilatations of the proximal segments of the anterior and/or middle cerebral arteries [15]. Beading and irregularity of stenoses can be seen. Gadolinium contrast studies of the affected vascular wall segment should also be requested [40]. In NP-cPACNS these reveal wall thickening and contrast enhancement due to wall inflammation.

Children with NP-cPACNS require initiation of antithrombotic therapy, with regimens varying between centers. Frequently heparin is started in children with high degree of vascular stenosis followed by long-term, low-dose acetylsalicylic acid for secondary stroke prevention [41]. Adjunctive therapy with corticosteroids for 3 months remains controversial [37]. Non-progression is confirmed on the repeat imaging at 3 months, establishing no evidence

Table 37.1 Differential diagnosis for inflammatory brain diseases in children

Vasculitic inflammatory brain disease	
Primary CNS vasculitis (cPACNS)	Angiography positive, large-medium vessel cPACNS
	Progressive
	Non-progressive
	Angiography negative, small vessel cPACNS
Secondary CNS vasculitis	Infection associated
	Viral (CMV, EBV, HIV)
	Bacterial (mycobacterium tuberculosis, mycoplasma pneumonia, streptococcus pneumonia, others)
	Fungal (candida albicans, aspergillus, actinomyces, others)
	Spirochaete (*Borrelia burgdorferi*)
	Post-infectious
	VZV – post-varicella angiopathy
	Systemic vasculitis
	ANCA-associated vasculitis, polyarteritis nodosa, takayasu arteritis,
	Systemic rheumatic disease
	SLE, systemic vasculitis, scleroderma, dermatomyositis, others
	Systemic inflammatory disease
	Hemophagocytic lymphohistiocytosis, Kawasaki disease, inflammatory bowel disease, celiac disease, graft versus host disease
	Exposures
	Radiation
	Drugs (cocaine, amphetamines)
Non-vasculitic inflammatory brain disease	
Demyelinating disease	Acute demyelinating encephalomyelitis (ADEM)
	Multiple sclerosis
	Transverse myelitis (when demyelinating)
Antibody mediated inflammatory brain disease	Anti-NMDAR encephalitis
	Antibody-mediated limbic encephalitis
	Neuromyelitis optica
	Hashimoto encephalitis
T-cell mediated inflammatory brain disease	Rasmussen's encephalitis
Granulomatous inflammatory brain disease	Neurosarcoidosis
	Blau syndrome
others	Febrile infection-related epilepsy syndrome (FIRES)
Non-inflammatory brain diseases (mimics)	
Vascular	Posterior reversible encephalopathy syndrome (PRES)
	MoyaMoya disease
	Arterial dissection
	Thromboembolic disorders
	Fibromuscular dysplasia
	Collagen vascular disorders (Marfan syndrome, Ehlers Danlos syndrome)
Hematologic	Hemoglobinopathies (Sickle cell anemia, others)
Metabolic	Mitochondrial, encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)
	Rolandic mitochondrial encephalomyelopathy (ROME)
	Polymerase gamma deficiency (POLG)
Genetic	Neurofibromatosis type 1
	Down syndrome
	Posterior fossa malformations, hemangiomas, arterial anomalies, cardiac defects, eye abnormalities, and sterna or ventral defects (PHACES)
	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
	Fabry disease
	Homocysteinuria
Neoplastic	CNS lymphoma

of involvement of new vascular beds and resolution of contrast enhancement in the vascular wall in steroid treated patients. Recurrent ischemic events are observed in 30–60 % of children [37]. The long-term outcome remains to be systematically studied, it appears to be closely related to the location and extent of the ischemic lesion, stroke recurrence and possibly the use of corticosteroids. Early, comprehensive rehabilitation, as practiced in adult stroke care models, has not been systematically performed or studied in this population, however it appears to have striking benefits.

Angiography-Positive Progressive cPACNS (P-cPACNS)

Children with P-cPACNS can commonly present with both focal and diffuse neurological deficits [15, 42]. Interestingly, both angiography positive CNS vasculitis subtypes, NP-cPACNS (discussed above) and P-cPACNS, predominately affect boys. Children with P-cPACNS are commonly diagnosed when they develop focal deficits, including hemisensory loss or fine motor skill deficits [15]. In addition, difficulty in concentration, cognitive dysfunction, and mood and personality changes are present in these patients [15]. These diffuse deficits develop insidiously. Correspondingly, the time from onset of any symptoms to diagnosis is frequently longer in P-cPACNS compared to NP-cPACNS patients. Headaches are the leading clinical symptom and present in 95 % of P-cPACNS patients [15]. Systemic underlying conditions have to be carefully looked for and excluded, since the clinical and imaging pattern of P-cPACNS is frequently found in angiography-positive, secondary CNS vasculitis of childhood (see below).

Children with P-cPACNS may have raised mild-moderately raised inflammatory markers; however inflammatory markers and CSF analysis are not discriminative [15]. A normal CSF cell count or a normal ESR does not exclude an angiography-positive CNS vasculitis. Required MRI sequences are identical to those performed in suspected NP-cPACNS. In p-cPACNS parenchymal lesions on MRI can be ischemic and/or inflammatory and are commonly present in more than one vascular territory. One in four children has bilateral MRI lesions, which are more frequently asymmetric in appearance [39]. The angiography characteristically demonstrates vasculitis of proximal and distal segments of the cerebral arteries, typically involving multiple vascular beds [39]. Different degrees of gadolinium contrast enhancement can be found in affected vessel wall segments. The anterior circulation is more commonly affected; isolated posterior circulation vasculitis is less common. Conventional angiography provides additional information about the length and degree of stenosis potentially impacting in antithrombotic treatment choices [43]. It also visualizes collateral blood flow into the affected brain tissue identifying additional brain at risk.

Children with P-cPACNS require combination immunosuppressive therapy in addition to antithrombotic therapy. At time of diagnosis once daily intravenous methylprednisolone pulses (30 mg/kg/day) are given at many centers for a duration of 3–7 days. Subsequently corticosteroid therapy is switched to daily oral prednisone (2 mg/kg/day, max 60–80 mg) with significant variation between centers. Barron et al [44] first documented the efficacy of cyclophosphamide in cPACNS. In 2001, Gallagher et al [42] reported cyclophosphamide efficacy in five children with P-cPACNS. Intravenous monthly cyclophosphamide pulses are commonly prescribed for 6 months, followed by oral maintenance immunosuppression while tapering the child off corticosteroids. The long-term outcome of children with P-cPACNS has not been systematically studied. Residual focal neurological deficits are often seen in this subtype [15].

Angiography-Negative, Small Vessel cPACNS (SV-cPACNS)

Small vessel cPACNS is increasingly recognized in PICUs around the world. Children present with severe encephalopathy, extensive focal deficits and/or seizure status and require a rapid, invasive evaluation including an elective brain biopsy. The differential diagnosis is equally challenging and includes demyelinating disease, neuronal antibody mediated inflammatory brain disease, and other less common conditions (Table 37.1). In contrast to angiography positive disease, SV-cPACNS has a female predominance [35, 45]. The mode of onset varies significantly from child to child. Some patients develop significant cognitive deficits over weeks and months, complain of constant headaches, or are diagnosed with focal seizures [45]. Inflammation associated cognitive decline is particularly difficult to detect in children with an underlying learning disability or autism. In contrast, some children have a rapidly progressive disease onset and present with a meningitis-like illness. Systemic features including fever and fatigue can be present [45]. Seizures are common at diagnosis of SV-cPACNS. All seizure types are seen. Status epilepticus or refractory status epilepticus in previously healthy children mandates an evaluation for an underlying inflammatory brain disease, in particular for SV-cPACNS. In 1990, Matsell et al. [46], was the first to report a case of a child with refractory status epilepticus, in whom the diagnosis of cPACNS was made, unfortunately only on autopsy.

Inflammatory markers are frequently abnormal in children with SV-cPACNS, however the degree of abnormality varies between patients. Hutchinson et al. [45] documented that three out of four children with SV-cPACNS had at least one abnormal inflammatory marker in the blood at diagnosis. More importantly >90 % had an abnormal CSF analysis including increased CSF protein and/or cell count [45]. Mild to moderate CSF lymphocytosis is most commonly seen.

MRI abnormalities are present in the vast majority of SV-cPACNS patients at diagnosis [39]. Serial studies may be required. MRI lesions are best viewed on T2/FLAIR sequences. Ischemic lesions are very uncommon. Lesional gadolinium contrast enhancement is present in less than 50 % of children with active disease at diagnosis. Meningeal contrast enhancement is equally infrequently seen; however it is one of the few specific MRI finding of SV-cPACNS after infectious meningitis is excluded [39]. Notably, meningeal contrast enhancement on MRI is not present in other inflammatory brain diseases, including demyelinating diseases [47]. Inflammatory lesions are most commonly found in the subcortical white matter and cortical grey matter [45], though any MRI pattern can be seen in SV-cPACNS due to the ubiquitous presence of small blood vessels in the brain and spinal cord. Autopsies have established the generalized character of small vessel vasculitis, in contrast to the focal nature of disease suggested by detectable MRI lesions. Children presenting in status epilepticus may even have repeatedly normal MRI studies and brain biopsy evidence of SV-cPACNS (unpublished data).

By definition, all patients with SV-cPACNS have normal MRA and conventional angiography studies. Other neuroimaging techniques have so far not provided additional diagnostic certainty in SV-cPACNS.

The next step in the diagnostic evaluation is an elective brain biopsy, which should be completed within 10 days from starting immunosuppressive therapy. The brain biopsy should preferably target lesions identified on MRI [48]. However, these may either not be accessible or in functionally important areas. In these children, non-lesional biopsies should be performed targeting the non-dominant frontal lobe. The diagnostic yield of elective brain biopsies performed for suspected inflammatory brain disease and other treatable conditions other than tumors in children was found to be 69 % (1996–2003) [30, 34]. The yield is therefore significantly higher than in adults [30, 34]. The review of brain biopsies in children with SV-cPACNS reveals intramural, inflammatory infiltrates consisting predominantly of lymphocytes. These can also be detected in the perivascular space (Fig. 37.1) [35, 45, 48–50]. Childhood CNS vasculitis is a lymphocytic vasculitis which is therefore histologically not characterized by vessel wall destruction, fibrinoid necroses or evidence of necrosis or granulomas as seen in other types of vasculitis. Granulomatous infiltrates, which are frequently described in adult PACNS, have so far not been reported in children with cPACNS [32, 35, 45, 49].

Children with SV-cPACNS require combination immunosuppressive therapy in addition to the mandatory treatment

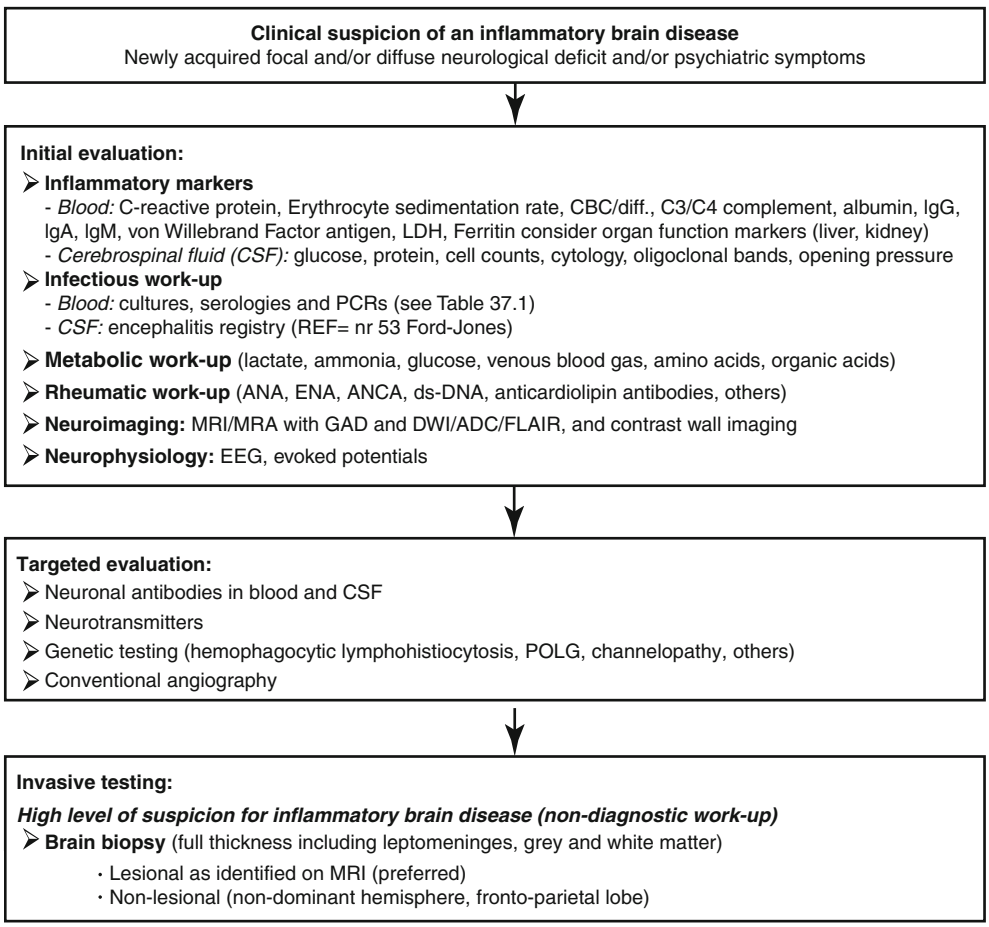


Fig. 37.1 Diagnostic algorithm for children with suspected inflammatory brain diseases

of seizures, abnormal movements, or psychiatric symptoms. Treatment should be initiated rapidly in order to control the devastating brain inflammation and the resulting clinical features and prevent disease-related damage. Hutchinson et al [45] reported an open-label treatment study of children with SV-cPACNS receiving a 6 month induction protocol consistent of corticosteroids (initial methylprednisolone pulses 30 mg/kg/day, max 1,000 mg for 3–5 days followed by oral prednisone 2 mg/kg, max 60 mg/day with defined monthly taper) plus monthly intravenously cyclophosphamide pulses (500–750 mg/m [2], plus MESNA and hyperhydration). After 6 months children were switched to maintenance treatment with initially azathioprine, but more recently mycophenolate mofetil (MMF). The treatment was found to be effective and safe. After 24 months, 70 % of the children had no evidence of any functional neurological deficit as measured by the pediatric stroke outcome measure (PSOM) [45]. Case series from other centers supported the efficacy of cyclophosphamide and MMF [51, 52]. Most series document good recovery of neurological deficits. At many centers, children continue the anti-convulsive medication beyond 24 months.

Secondary CNS Vasculitis

Infection-Associated Secondary CNS Vasculitis

The most common etiology for a secondary inflammatory brain disease is infection [53]. Infections can cause a true infectious CNS vasculitis with bacteria infecting the vessel wall, as seen in for example patients with streptococcus pneumonia or mycobacterium tuberculosis meningitis. Infections can also lead to a post-infectious inflammatory vasculitis. Finally, infections can cause MRI lesions mimicking those seen with vasculitis. A comprehensive infectious work-up is mandatory in all children with suspected vasculitic or non-vasculitic inflammatory brain disease. Standardized approaches such as encephalitis registries are helpful [53]. Most infections can be identified in cultures and/or by polymerase chain reaction (PCR) of serum and CSF [53]. However specific circumstances including travel history has to be considered when testing.

Varicella zoster virus (VZV) can infect a wide variety of cell types in the central and peripheral nervous system and cause a severe infective encephalitis [19]. VZV infection can lead to latency of virus in the nerve root ganglia, including the trigeminal nerve which is located in close proximity to the branching of the major cerebral blood vessels [19, 54]. Reactivation of VZV and axonal migration causes a focal, unilateral inflammation of the vascular wall of the adjacent proximal segments of the large CNS vessels virtually indistinguishable from NP-cPACNS, apart from evidence of VZV infection [19, 54, 55]. This condition is referred to as post-Varicella angiopathy (PVA) or Transient Cerebral Angiopathy (TCA). The proposed treatment regime includes antiviral therapy plus immunosuppression with high-dose corticosteroids. Many physicians consider the different diseases PVA, TCA and NP-cPACNS to be widely overlapping, and primarily inflammatory in nature.

Human Immunodeficiency virus (HIV) can cause a secondary CNS vasculitis in children and adults, which closely resembles P-cPACNS [56]. Initiation of antiviral therapy frequently causes an immune reconstitution inflammatory syndrome with worsening vascular disease. Immunosuppressive therapy has to be considered. Many other viruses, bacteria and fungal infections can cause secondary CNS vasculitis (Table 37.1).

Secondary CNS Vasculitis in Rheumatic and Systemic Inflammatory Diseases

Secondary CNS vasculitis can be the presenting symptom in childhood rheumatic diseases or develop in the course of illness [57]. CNS vasculitis is seen in children with systemic lupus erythematosus (SLE), ANCA- associated systemic vasculitis, including granulomatosis with polyangiitis (GPA, previously known as Wegener's granulomatosis) and microscopic polyangitis (MPA), in polyarteritis nodosa (PAN) and Takayasu arteritis [23, 26, 28, 57, 58]. The treatment of secondary CNS vasculitis in rheumatic diseases commonly includes high-dose corticosteroids and cyclophosphamide. Inflammatory conditions such as hemophagocytic lymphohistiocytosis (HLH), Kawasaki disease, and inflammatory bowel disease can also be complicated with secondary CNS vasculitis [59, 60].

HLH is a rare, potentially fatal disease of activated histiocytes and macrophages clinically presenting as fever, hepatosplenomegaly, pancytopenia, low fibrinogen level, organ dysfunction, elevation of liver enzymes, Ferritin and LDH, and hypertriglyceridemia [61]. Pathology relates to the dysfuntion of activated CD8+ T lymphocytes and NK cell and their inability to kill targets such as virus infected cells. Subsequently, macrophages are activated and hemophagocytosis is present in multiple organs causing organ dysfunction. CNS involvement is frequently present. The neuropathological hallmarks of HLH consist of a diffuse infiltration by monocytes and activated lymphocytes of leptomeninges and brain parenchyma along penetrating vessels. Infiltration is associated with focal and confluent areas of myelin pallor, as well as neuronal loss, tissue necrosis, and cavitation [8, 62]. The presenting symptoms reflect the CNS localization of the lesions. They can be present only in the white matter of the cortex and cerebellum, but often involve the cortical structures or the brainstem. Moshous et al. [60] describe a 4 year old girl with CNS vasculitis and perforin deficiency without classical laboratory or clinical signs of active HLH at the time of her CNS manifestations. Therefore, a new neurologic deficit in children with systemic inflammatory diseases

should lead to prompt further investigations such as MRI, MRA, angiography and if required a brain biopsy. The primary form, the familial HLH (FHLH), typically seen during infancy and early childhood, is thought to be fatal, with a median survival without therapy of 2 months after onset, if not rescued by bone marrow transplantation [8, 63]. The known genetic causes involve genes that regulate proteins that are important in the secretory cytolytic pathway: perforin (*PRF*) in FHLH2, adaptor protein-3 β1 subunit (*AP3B1*) in Hermansky-Pudlak type 2, the lysosomal trafficking regulator (*LYST*) in Chediak-Higashi syndrome, Rab27z (*RAB27A*) in Griscelli type 2, Munc13-4 (*UNC13D*) in FHLH3 and Stx-11 (*STX11*) in FHLH4 [63]. Macrophage activation and hemophagocytosis also occur in association with severe infections, malignancies or rheumatologic diseases. The Histiocyte Society in 1994 developed a common treatment protocol (HLH-94) in which immunotherapy with CSA is combined with CS and VP-16. Intrathecal MTX is added in selected patients. The aim is first to achieve a clinically stable resolution and ultimately to cure by bone-marrow transplantation.

Kawasaki disease is a systemic vasculitis, mainly involving the coronary arteries. However, it can be complicated by a secondary CNS vasculitis [10]. Although MRI scans do not reveal abnormalities in the acute stage of the disease, in some patients single-photon emission computed tomography (SPECT) imaging demonstrated localized cerebral hypoperfusion [64] and postmortem brain examinations may reveal leptomeningeal thickening, endarteritis, and periarteritis [10]. A different pathophysiological mechanism of CNS injury in Kawasaki is related to the macrophage activation syndrome (MAS). The clinical and laboratory similarities between HLH and MAS have led to the general acceptance of MAS as a form of secondary HLH [65, 66].

Secondary CNS Vasculitis in Other Systemic Diseases/Exposures

Secondary CNS vasculitis has been described in patients after radiation therapy [11]. Graft versus host disease can also cause CNS vasculitis in children who were treated for malignancies. Drugs, such as cocaine and amphetamines can cause a secondary CNS vasculitis, but are also capable of mimicking CNS vasculitis without an inflammatory component but a vasoconstrictive component [67].

Non-vasculitic Inflammatory Brain Diseases

Demyelinating Diseases

Inflammatory demyelinating diseases include clinical entities of Acute Disseminated Encephalomyelitis (ADEM), Multiple Sclerosis (MS) and Transverse Myelitis (TM), and can mimic CNS vasculitis [6]. Most of these conditions are thought to be caused by immune system dysregulation triggered by an infectious or other environmental agent in a genetically susceptible host. Neuromyelitis Optica (NMO) will be discussed separately as data suggest that NMO is part of a spectrum of CNS inflammatory disorders associated with NMO-IgG autoantibodies and aquaporin-4 autoimmunity.

ADEM is generally a monophasic, immune mediated, demyelinating disease of the CNS, that presents with polyfocal neurological deficits accompanied by encephalopathy [68, 69]. A clinical presentation consistent with ADEM can also be the first manifestation of MS, particularly in children. MRI lesions are evident and usually diffuse and bilateral [70]. The total lesion number does not help in differentiating ADEM from MS, but the absence of a diffuse bilateral lesion pattern, the presence of black holes, and the presence of two or more periventricular lesions may distinguish MS from monophasic ADEM [70]. Symptoms are determined by the location of the lesions and the severity of the damage in the affected areas. Besides encephalopathy and neurological deficits, fever and seizures can be seen in children with ADEM [71]. There is no specific diagnostic test. Infectious and metabolic etiologies have to be excluded. Patients may have elevated CSF cell counts and protein levels. New deficits occurring within 3 months of onset are considered to be part of the same episode [71, 72]. Treatment of ADEM consists of intravenous corticosteroids 20–30 mg/kg/day (maximum 1 g) for 3–5 days. In cases of incomplete symptom resolution after intravenous corticosteroid a short course of oral prednisone 1 mg/kg/day tapered over 14–21 days is indicated [73]. Intravenous immunoglobulins are used in children, who fail to respond to corticosteroids [74].

MS most commonly presents as a polyphasic, immune-mediated demyelinating disease of the CNS. It is seen mostly in adult patients, though 3–10 % of patients will have an onset before the age of 18 years [75]. Early childhood onset MS does not show the female predominance seen in adult MS, but an equal distribution between boys and girls [75, 76]. Family history is positive for MS in 6–8 % of children with childhood onset MS and 20 % in adult onset MS [76]. As in ADEM, acute symptoms are determined by the location of the lesions and the severity of the damage in the lesions. In many cases, chronic deficits accumulate over time. A recent review identified polyfocal presentation in 50–70 % of patients and a monofocal presentation in 30–50 % of patients [76]. Most frequent presenting symptoms included motor dysfunction (30 %), sensory dysfunction (15–30 %), brainstem function (25 %), optic neuritis (10–22 %), and ataxia (5–15 %) [76]. There is no specific laboratory test for MS. MRI findings, supportive laboratory studies, and the clinical course are used to make the diagnosis. Initial specific images of MS on MRI (100 % specific of MS) consist of well-defined lesions and the presence of lesions perpendicular to

corpus callosum [47, 77]. Current management is focused on treating the acute presentation and preventing recurrent relapses. The usual treatment is a short course of high dose glucocorticoids. More severe relapses that fail to respond to glucocorticoids are often treated with plasma-exchange in adults. In children plasma exchange or IVIG are used [76]. Chronic management is focused on preventing relapses. "Disease-modifying therapy" includes glatiramer acetate, interferon beta- 1a and beta-1b. Because of its favorable side effect profile, rituximab is gaining acceptance in this disease particularly in refractory pediatric cases [76]. Given the variety of proven disease-modifying therapies, azathioprine, methotrexate, cyclosporine A, and mycophenolate mofetil are only used for progressive forms of MS [76]. Cyclophosphamide is being used for severe and/or refractory cases [76].

Transverse myelitis (TM) is an acute, severe, monophasic illness clinically presenting as an acute spinal cord dysfunction. It can occur in the context of infectious, inflammatory or rheumatic diseases or can represent a manifestation of primary CNS vasculitis, MS or NMO [78]. TM has multiple inflammatory pathologies including antibody mediated cytotoxicity, small vessel vasculits, occlusive or embolic vasculopathy and demyelination. Many cases of idiopathic TM have a presumed postinfectious etiology, although a specific pathogen is rarely identified. Consensus criteria for TM diagnosis include sensory, motor, or bladder and bowel dysfunction attributable to the spinal cord, with progression to nadir in less than 21 days from onset [78]. Diagnosis is based on clinical examination, CSF studies (typically showing pleiocytosis), and MRI that may reveal focal or extensive inflammatory lesions [78]. TM remains a devastating illness in at least 20 % of affected children, 40 % will not be ambulatory, and 50 % will have chronic bladder dysfunction [79]. Poor prognosis for motor or bladder function is associated with the presence of longitudinally extensive transverse myelitis in the context of monophasic idiopathic transverse myelitis. Treatment regimens include glucocorticoids plus additional IVIG, plasma exchange, or cyclophosphamide [78].

Neuronal Antibody Mediated Inflammatory Brain Diseases

Inflammatory brain diseases caused by antibodies directly targeting brain structures including receptors, channels, synaptic or secreted proteins have been increasingly recognized. These antibodies were thought to be solely paraneoplastic. Neurological symptoms preceded the identification of a cancer in the majority of patients. The most commonly associated neoplasms in children are neuroblastoma, Hodgkin's lymphoma, Ovarian teratomas, seminoma and thymoma. In adults paraneoplastic syndromes with neuronal antibodies can also be related to small-cell lung carcinoma (see Table 37.2). More recently neuronal antibodies have been recognized independent of malignancies in children with severe acquired deficits admitted to the PICU, including limbic encephalitis and intractable seizures, severe movement disorders, or optic neuritis. Neuronal antibodies are frequently divided into either targeting neuronal/ glial nuclear and/or cytoplasmic antigens or neuronal cell surface antigens. Over the last few years antibodies targeting extracellular epitopes of synaptic receptors and components of transsynaptic protein complexes have also been identified in several forms of autoimmune encephalitis or epilepsy [4, 13, 80, 81] (Table 37.2).

Anti-NMDAR encephalitis is an important, newly recognized inflammatory brain disease [4, 82]. Typically children and adults may present with a clinical continuum of psychosis, seizures, movement disorders, decreased level of consciousness, and/or life threatening autonomic instability. Atypical presentations such as optic neuritis [83], isolated hemidystonia [84] and nonconvulsive status epilepticus [85] have been reported. Dalmau et al. [4] first described anti-NMDAR encephalitis and recognized a strong female predominance [86]. In adult patients the disease is frequently associated with ovarian teratomas [4], while this is less commonly observed in children [4, 81]. The clinical course can vary between patients, rapid clinical deterioration may occur [4, 81]. The diagnosis is confirmed by a positive anti-NMDAR antibody test of CSF and/or serum, with CSF testing being more sensitive [81]. Treatment with corticosteroids, IVIG and rituximab seems to be succesfull [81]. Plasmapheresis and/or cyclophosphamide are reported to be effective in severe clinical presentations.

Encephalitis associated with antibodies against α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), and γ-amino-butyric acid-B receptor (GABAB-R) were reported in adults but not yet in children [87]. Autoimmunity to AMPAR or GABAB-R may occur in association with antibodies against intracellular antigens, such as thyroid peroxidase (TPO), glutamic acid decarboxylase 65 (GAD 65), SOX1, ANA, but also against cell surface antigens such as N-type voltage-gated calcium channels. Recent studies have shown that the target antigens of antibodies attributed to voltage-gated potassium channels are in fact proteins that are components of transsynaptic complexes or cell adhesion molecules, including leucine rich glioma inactivate 1 (LGI1) and contactin-associated protein-like 2 (Caspr2) [13, 88, 89].

NMO is an inflammatory brain disease characterized by antibodies directed against aquaporin 4 (NMO-IgG) [90]. The clinical phenotype of includes optic neuritis, transverse myelitis, encephalopathy, seizures, intractable vomiting and brain-stem mediated hiccups [9, 91]. In adults, the outcome is reported to be poor with marked visual loss and/or paralysis

Table 37.2 Neuronal antibodies, associated conditions and clinical phenotype in children presenting with inflammatory brain diseases

Anti neuronal nuclear antibodies		
ANNA-1	SCLC, thymoma; children: neuroblastoma or no detectable tumor	Neuropathies (mainly sensory), limbic encephalitis
ANNA-2	Lung and breast	Brainstem syndrome, cerebellar syndrome, neuropathies
ANNA-3	SCLC	Neuropathies, ataxia, limbic encephalitis
Zic4	SCLC	Cerebellar syndrome
Anti-Ma (anti-PNMA1 and 2)	Breast, lung, germ cell, renal	Brainstem syndrome, cerebellar syndromes, limbic encephalitis, polyneuropathies
Anti-Ta (anti-PNMA2)	Testicular, extragonadal germ cell	Limbic encephalitis, brainstem syndrome, cerebellar syndrome, polyneuropathies
Anti neuronal/glial nuclear antibodies		
AGNA (SOX1)	SCLC	Lambert-Eaton, cerebellar syndrome, limbic encephalitis
Anti neuronal/glial/muscle cytoplasmic antibodies		
Amphiphysin	SCLC, breast	Neuropathy, encephalopathy
CRMP-5	SCLC, thymoma, thyroid, renal	Neuropathy, ataxia
Anti-Yo (PCA-1)	Ovarian, fallopian tubal, breast adenocarcinoma	Ataxia
PCA-2	SCLC	Brainstem and limbic encephalitis, ataxia
PCA-Tr	Hodgkin's lymphoma	Ataxia
Striational	SCLC, thymoma	Neuropathies, ataxia
Anti channel/receptor antibodies		
VGCC (P/Q type)	VGCC (P/Q type)	Lambert-Eaton syndrome
VGCC (N type)	Lung, ovarian, breast	Lambert-Eaton syndrome
VGKC complex	SCLC, thymoma, prostate, breast	Encephalopathy, limbic encephalitis
AChR (muscle)	Thymoma, SCLC	Myasthenia Gravis, Lambert-Eaton syndrome
AChR (ganglionic)	Adenocarcinoma, renal, thymoma, thyroid carcinoma, ovarian	Dysautonomia, encephalopathies
NMDA-R	Ovarian teratoma	Limbic encephalitis, neuropsychiatric, dysinesia, dystonia, seizures
AMPA-R	Thymoma, breast, lung	Limbic encephalitis, seizures
GABA-B	Lung, thymoma	Limbic encephalitis, seizures

AChR acetylcholine receptor, *AGNA* anti-glial nuclear antibody, *AMPA-R* α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, *ANNA* anti-neuronal nuclear autoantibody, *CASPR2* contactinassociated protein-2, *CRMP* collapsin response-mediator protein, *GABA-B* gamma-aminobutyric acid, class B, *GAD65* glutamic acid decarboxylase (65 kDa isoform), *NMDA-R* N-methyl D-aspartate receptor, *NMO-IgG* neuromyelitis optica immunoglobulin G, *PCA* Purkinje cell cytoplasmic autoantibody, *PNMA1* paraneoplastic antigen Ma1, *SCLC* small cell lung carcinoma, *VGCC* neuronal voltage-gated calcium channel, *VGKC* neuronal voltage-gated potassium channel

in 60 % [29, 90, 92, 93]. The typical MRI pattern includes optic nerve enhancement and periventricular and/or peri-aquaductal lesions. Extensive longitudinally spinal cord lesions are also typical. Clinical and MRI features may overlap with other inflammatory brain diseases. Disease recognition and rapid start of B-cell targeting therapies including glucocorticoids, IVIG, rituximab and plasma exchange is required.

Other antibodies associated inflammatory brain disease include Hashimoto encephalitis, acute cerebellar ataxia, pediatric autoinflammatory neuropsychiatric disease associated with streptococcus (PANDAS), and celiac disease associated encephalitis [17, 18, 94–96]. Children with Hashimoto encephalopathy commonly present acutely or subacutely with encephalopathy, seizures, movement disorders, and psychosis. Some patients have associated thyroid dysfunction. Antithyroid antibodies support the diagnosis. CSF protein levels are frequently elevated; MRI and electroencephalography can show nonspecific abnormalities. The reported treatment approaches include glucocorticoids alone or in combined with methotrexate, azathioprine, cyclophosphamide, IVIG, or plasma exchange. Acute cerebellar ataxia, PANDAS, and celiac disease associated encephalitis are rarely seen in the PICU [17, 18, 95].

T-cell Mediated Inflammatory Brain Diseases; Rasmussen Encephalitis

Rasmussen encephalitis is a rare, progressive, unilateral neurological disorder in previously normal healthy children. Intractable focal seizures are the first sign of the disease [97–99]. As the disease progresses, the patient progressively loses function of the hemisphere and develops a hemiparesis.

The duration of intellectual and functional deterioration can range from months to years [98, 99]. Multiple studies have confirmed the central role of cytotoxic T-lymphocytes and neuroglial cells in the process of immune-mediated neuronal damage [24, 100]. The definite treatment option for Rasmussen's encephalitis at this moment is hemispherectomy, however immunosuppressive treatments are available and may stop disease progress in an earlier stage in some patients [101, 102]. Thilo et al. [103], report the case of an adult patient with Rasmussen encephalitis successfully treated with rituximab.

Granulomatous Inflammatory Brain Diseases

Granulomatous inflammatory brain diseases in children comprise neurosarcoid and pediatric sarcoidosis which includes Blau Syndrome (BS) and Early Onset Sarcoidosis (EOS), the latter are familial and sporadic diseases characterized by a triad of polyarthritis, uveitis and rash [104–106]. Pediatric epidemiologic data is scarce. A Danish national registry reported an overall incidence of pediatric sarcoidosis of 0.29/100.000/year [14, 20]. In 2005 an international registry for Pediatric Sarcoidosis was established, which demonstarted gender difference or geographic predominance. Most pediatric patients with the classic triad presented before the age of 5 years [107]. Genetic studies revealed evidence of NOD2 mutations in pediatric patients with BS or EOS [108]. Pediatric sarcoidosis is distinctly different from the well-known adult form of sarcoidosis. Lung involvement, multi-organ disease, CNS granulomatous inflammation and/or eye involvement were found to be associated with a worse outcome [22]. Evidence based treatment protocols are not available. Usually daily corticosteroid treatment in addition to Methotrexate (10–15 mg/kg/once weekly) are used to control uveitis and joint disease [109]. Limited information is available for the use of TNF-alfa blockers and anti-Il-1 therapy [110, 111]. In childhood, granulomatous cPACNS has not been described, in contrast with the adult population, where 58 % of patients had a granulomatous, intramural infiltrate on brain biopsy [32, 35, 48].

Febrile Infection-Related Epilepsy Syndrome (FIRES)

FIRES is a newly recognized inflammatory brain diseases presenting as a catastrophic epilepsy syndrome in school aged children. Currently the terminology FIRES is used in North America and Europe, while the term Acute Encephalitis with Refractory, Repetitive Partial Seizures (AERRPS) is preferred in Japan [112, 113]. Children characteristically present with a preceding febrile infection with no evidence of an infectious agent [113]. The mean duration of the fever before onset of seizures is 4 days [27]. The median age of onset is 8 years (range 2–17) [27]. The pathology of this devastating disease remains controversial. It was suggested to reflect an immune dysregulation [113, 114], a potential genetic predisposition, and a primary inflammatory disease [115]. Seizures are mainly partial complex with facial myoclonia or secondary generalized at onset of the disease [112, 116]. Within days of onset of seizures, children develop a status epilepticus or even refractory status epilepticus [27]. Cerebrospinal fluid analysis shows pleiocytosis in 60 % of patients; the extensive infectious work-up remains negative. The initial MRI is normal in 55 % of patients [27]. Treatment strategies include antiepileptic drugs and burst suppression coma, intravenous immunoglobulin and steroids. Outcome of FIRES is poor: the mortality is reported to be 10 %; 93 % of surviving patients have refractory epilepsy. Poor cognitive outcome is seen in the majority of patients, especially in patients with a young age at onset [27].

Non-inflammatory Brain Disease Mimics

In both adults and children non-inflammatory vasculopathies can mimic CNS vasculitis. In adults, the most frequent mimic is arteriosclerosis. In children, non-inflammatory mimics include MoyaMoya disease, dissection, thromboembolic disorders, fibromuscular dysplasia, hemoglobin disorders, metabolic and genetic disorders [12, 21]. Some of these disorders can be excluded based on thorough examination or with simple non-invasive test, however frequently advanced studies including MRA contrast wall imaging or conventional angiographies are required.

Posterior Reversible Encephalopathy Syndrome

The posterior reversible encephalopathy syndrome (PRES), also known as the reversible posterior leukoencephalopathy syndrome (RPLS), is an important mimic of CNS vasculitis and inflammatory brain diseases [117]. It is a clinic-radiological syndrome with heterogeneous etiologies characterized by clinical findings of headaches, altered level of consciousness, visual disturbances and seizures and neuroimaging findings of symmetrical white matter areas of edema in the posterior cerebral hemispheres, particularly the parieto-occipital regions [118]. While patients with PRES may have typical signal abnormality of ischemia, MRI lesions more likely represent transient vasogenic edema. Classically MRI lesions resolve within days or weeks [16, 119]. The pathogenesis remains unclear, impaired cerebral autoregulation and endothelial dysfunction have been

postulated [119]. Multiple medical conditions have been associated with PRES including hypertension, acute or chronic renal disease, thrombotic thrombocytopenic purpura, hemolytic and uremic syndrome, contrast media exposure and immunosuppressive and chemotherapeutic agents (cyclosporine A, tacrolimus, sirolimus, cisplatin as well as interferon) [119]. The suggested treatment includes tight blood pressure control and seizure prophylaxis.

Diagnostic Approach to Inflammatory Brain Diseases

Laboratory Testing

An inflammatory brain disease should be considered in every child with a newly acquired neurological deficit and/or psychiatric symptom. A thorough clinical and laboratory work-up is mandatory to exclude infection, systemic illnesses and malignancies. Laboratory testing should include blood samples and CSF samples. Blood tests should include inflammatory markers, organ function parameters and autoantibodies (Fig. 37.1). CSF analysis should include opening pressure, cell counts, glucose and protein levels, oligoclonal banding, a thorough infectious work-up and neuronal antibody testing, if applicable.

Neuroimaging

All patients with suspected inflammatory brain diseases require high sensitivity brain imaging. A CT scan may be indicated for specific suspicions, such as a cerebral hemorrhage or a cerebral vein thrombosis. Inflammatory parenchymal lesions are frequently missed on CT-scans and mandate MRI [39, 120]. MRI studies should include T1 and T2 sequences, fluid-attenuated inversion recovery (FLAIR), gradient-echo T2 weighted sequences, diffusion-weighted images and gadolinium contrast-enhanced T1–T2 sequences [38]. Recently studies towards the use of apparent diffusion coefficient (ADC), a technique to measures the integrity of structures in the brain and vessel wall contrast enhancement are used to define active cerebral vasculitis [40, 121]. Dedicated vessel wall imaging is equally mandatory and of great importance as demonstrated in a large cohort study: 82 % of PACNS patients had evidence of vessel wall contrast enhancement, vessel wall thickening was present in 92 % [40].

Conventional angiography is considered the gold standard for specific indications, but remains an invasive modality. The complication rate (stroke) of conventional angiography in adults has been estimated at 0.25 % [122]. Studies comparing MRA and conventional angiography in CNS vasculitis in children and adults determined that MRA is a sensitive imaging modality [32, 43, 123, 124], it appears to have limited sensitivity in young children and when detecting distal vessel lesions or those affecting the posterior circulation. A negative MRA in children with suspected cPACNS mandates a conventional angiography [123, 124].

Brain Biopsy

An elective brain biopsy should be considered in patients with a suspected small vessel cPACNS. The diagnostic algorithm captures the diagnostic path, including evidence of inflammatory markers, inflammatory MRI lesions, no evidence of MRA or conventional angiogram abnormalities consistent with large-medium vessel cPACNS, and exclusion of other inflammatory brain diseases or their mimics. Preferably, new inflammatory lesions identified on MRI should be biopsied. In patients with inaccessible lesions or even normal MRI scans in the context of high clinical suspicion, non-lesional biopsy should be performed (non-dominant frontal lobe, full thickness leptomeninges, cortex and white matter) [48]. In the past characteristic findings of CNS vasculitis were derived from autopsies. The diagnostic yield for PACNS on brain biopsies in adults is low: Alrawi et al. [125] was able to confirm the diagnosis in only 36 % of 61 adults with suspected PACNS. In contrast, a recent single-center study of brain biopsies obtained from 66 children presenting with newly acquired, devastating neurological symptoms demonstrated an overall diagnostic yield of 68.8 % between 1996 and 2001 [30]. Brain biopsies are not only required to confirm a diagnosis of CNS vasculitis, but also to exclude other disease, such as Rasmussen's encephalitis, malignancies, rare infections and demyelination. Complications are rare and may include transiently increased seizure activity and cellulitis [30]. Brain tissue should be processed including, (a) hematoxylin and eosin and other staining to define the anatomy and integrity of CNS structures, (b) targeted testing for infections including viral inclusion and TB, if indicated, (c) immunohistochemistry staining to characterize the inflammatory infiltrated, and (d) electron microscopy to determine the presence of endothelial cell activation and tubular-reticular inclusions.

Management of Inflammatory Brain Diseases

Corticosteroids (CS) are a first line, cost effective, therapeutic option for many inflammatory brain diseases. The typical initial pulse treatment dose for acute, severe CNS inflammation is methylprednisolone 15–30 mg/kg of body weight given once daily intravenously. After 3–5 days of therapy, patients are commonly switched to prednisone at a dose of

1–2 mg/kg either IV or orally. The subsequent taper varies widely between diseases and their severity. Abrupt withdrawal should be avoided after long term therapy and suppression of endogenous cortisol production. Side-effects for acute administration include hypertension, impaired glucose tolerance, bradycardia, gastrointestinal upset, increased irritability, sleep disturbance, psychosis, weight gain and with long term use cataracts, osteopenia and bone fragility and avascular necrosis.

Intravenous immunoglobulin (IVIG) is a frequently used immunosuppressive treatment particularly in (neuronal) antibody-mediated inflammatory brain disease. IVIG is made up of purified antibodies collected from healthy blood donors and is administered intravenously. It has shown utility against nearly all autoimmune disorders of the central and peripheral nervous systems [126]. IVIG can be used acutely because of their rapid onset of action, but also as part of long-term therapy. The typical acute treatment dose is a total of 2 g/kg of body weight (max 70 g) either as a single dose or divided over 2–5 days.

Plasma exchange or plamapheresis is used in acute life- or organ threatening inflammatory disease, in particularly when an antibody-mediated process is suspected. The treatment requires large-bore intravenous access and special expertise, as many electrolytes, soluble factors, coagulation and complement proteins, and cytokines are trafficked during this process. Some prefer plasma exchange followed by IVIG although there is no published evidence that this is more efficacious then either alone [127]. A typical treatment course is 5–10 cycles over 5–14 days.

Rituximab is the best B-cell targeted therapy available to date. It is a chimeric monoclonal antibody that binds to the CD20 surface antigen on B-cells. Long term immunological memory is commonly maintained. The circulating B-cell population reconstitutes from memory B-cell pools and nascent B cells. The typical dose is either 375 mg/m^2 weekly for 4 consecutive weeks or 500 mg/m^2 weekly for two doses. Side effects may include those typically seen with infusions such as hypotension, flushing, rigor, headache, pruritus, fever, nausea, and fatigue [128]. Rare cases of progressive multifocal leukoencephalopathy have been reported in adults [129].

Disease Modifying Drugs

This group of medications is initially used in addition to corticosteroids and maintained while the patient is tapered of corticosteroids providing a steroid-sparing effect. Methotrexate is an inhibitor of dihydrofolate reductase and other enzymes in purine metabolism, impairing lymphocyte proliferation. The starting dose is 10–15 mg/m^2 given orally or subcutaneously once weekly. Folic acid 1 mg orally per day is typically given simultaneously to limit its toxicity. Side effects may include nausea, diarrhea, elevated liver enzymes, and in rare cases bone marrow suppression [128].

Azathioprine is a purine analogue and also interferes with lymphocyte activation. The oral or intravenous starting dose is 1 mg/kg/day, the target dose is 2–3 mg/kg/day. Side effects may include nausea, anorexia, elevated liver enzymes, and bone marrow suppression. Approximately 20 % of patients have low endogenous metabolism rates for this drug.

Cyclosporine A, a cyclic nonribozomal peptide, and FK506, a macrolide immune suppressor, act through similar mechanisms by calcineurin inhibition, that prevent T-lymphocyte activation. They are often considered interchangeable, but patients with side effects on one can often be switched to the other with good effect. Side effects may include hypertension, renal/hepatic toxicity, tremor, and gastrointestinal complaints.

Mycophenolate mofetil is a reversible inhibitor of inosine monophosphate dehydrogenase, in the purine metabolism. It reduces B- and T-lymphocyte proliferation. The dose is titrated up to 600 mg/m2 given orally twice a day with a maximum daily dose of 2 g. Side effects may include diarrhea, headache, elevated liver transaminases, and bone marrow suppression. Rare cases of PML have been reported with this medication in adults and children [130].

Cyclophosphamide is an alkylating agent that causes DNA interstrand crosslinkage and reduces lymphocyte proliferation. It is highly effective in CNS vasculitis and refractory demyelinating diseases. The dose is 500–750 gr/m^2 for 7 intravenous monthly pulse. Side effects may include nausea and other gastrointestinal symptoms. In high diseases alopecia and bone marrow suppression can occur. MESNA and pre-hydration are mandatory to prevent side effects.

Glatiramer acetate and interferons (beta-1a or beta-1b) are used almost exclusively for multiple sclerosis (MS). Dosing rates and schedule depend on the individual drug. These medications are only available for subcutaneous use. They are still being actively studied in children. A review of these agents for children is detailed elsewhere [73].

Novel Biologic Therapies

Humanized monoclonal antibody therapies include natalizumab, daclizumab, and alemtuzumab. They also are used almost exclusively for MS and administered intravenously. Natalizumab blocks entry of lymphocytes and monocytes into the central nervous system. Rare cases of PML have been reported with natalizumab. Alemtuzumab and daclizumab cause varying degrees of T-cell/B-cell depletion or decreased activation, respectively.

Conclusion

Children with primary or secondary inflammatory brain diseases are frequently admitted to the PICU. The clinical spectrum includes seizures and status epilepticus, intractable movement disorders, meningitis or encephalitis or stroke symptoms. The underlying pathology is often challenging to determine, however a diagnostic algorithm can facilitate the rapid evaluation. The key is recognition: Any child presenting with a newly acquired neurological deficit or psychiatric symptom should be assessed for an underlying inflammatory brain disease. On the ICU, knowledge of the spectrum of inflammatory brain disease and the differential diagnosis facilitates a rapid diagnostic evaluation and early therapy, which has a high likelihood of preventing long-term brain damage.

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Abusive Head Trauma

38

Rachel P. Berger and Michael J. Bell

Abstract

Abusive head trauma (AHT) (e.g. shaken baby syndrome) is the leading cause of death from child abuse. Proper diagnosis of AHT is critical; if AHT is not identified, children can be inadvertently returned to a violent environment where they can be re-injured or killed. The intensivist plays a critical role in the identification, evaluation, and treatment of AHT. This chapter will focus on the clinical presentation of AHT, the medical evaluation for cranial and non-cranial injuries in cases of suspected AHT as well as the management and treatment of AHT with a focus on the differences between management of children with AHT vs. non-abusive TBI. Current data related to the mechanism of injury and pathophysiology of AHT will also be discussed. Finally, issues related to mandated reporting and legal proceedings related to AHT cases will be discussed as will the role of the intensivist in all of the above.

Keywords

Child abuse • Abusive head trauma • Retinal hemorrhage

Introduction

Abusive head trauma (AHT), defined as traumatic brain injury which is the result of child abuse, is the leading cause of morbidity and mortality from traumatic brain injury in infants and young children [1–3]. AHT is also the leading cause of death from child abuse. The rate of severe or fatal AHT is approximately 1 in 3,300 infants <1 year of age [2], although unpublished data from a multi-center AHT study suggests that severe or fatal cases may comprise only half of the total number of AHT cases (Rachel Berger, unpublished data). Even at a rate of 1 in 3,300, AHT is far more prevalent than other diseases of childhood which we often consider to be "common." For example, the incidence of acute leukemia, the most common childhood cancer, is approximately 1 in 28,000, almost 10 times lower than the rate of AHT in infants [4].

While severe and fatal cases of AHT are the ones more frequently treated by the pediatric intensivist, it is critical to recognize and understand the full spectrum of injury severity in AHT in order to better understand issues of biomechanics and pathophysiology, as well as the spectrum of clinical presentation, intracranial injuries, ophthalmologic findings, and orthopedic injuries. Because of the intense social and legal ramifications of making a diagnosis of AHT, the overall care of a child with possible AHT can be more complex than the care of children with non-abusive TBI. Specifically, standard medical care for children with suspected AHT includes photographic documentation, screening for non-cranial injuries, evaluation and testing for alternative diagnoses, and reporting to Child Protective Services (CPS) – as well as all

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of the care required to take care of the multiply traumatized child outlined in other chapters of this text. The goal of this chapter is, therefore, to provide the pediatric intensivist with an understanding of medical, social and legal issues related to AHT.

Terminology

In 2009, the American Academy of Pediatrics published a policy statement changing the official name from 'shaken baby syndrome' to abusive head trauma (AHT) [5]. While the previous term implied a single injury mechanism – shaking – the new term takes into account improvements in our understanding of the injury in AHT which may include a combination of shaking, blunt impact, spinal cord injury, and hypoxic ischemic injury. The term AHT is focused on the etiology of the injury – abuse – rather than the injury mechanism. While the previous definition only included children who had been shaken, the term AHT also includes children, for example, who sustain TBI during a domestic dispute and children with an isolated impact injury (e.g. child hit over the head with a baseball bat by an angry adult). Shaken baby syndrome is, therefore, a subtype of AHT.

Epidemiology

AHT has traditionally been thought of as a disease of infants. And while infants are at greatest risk, AHT can also occur in toddlers and even older children [6, 7]. For example, in a recent multi-center study of more than 400 children with AHT, 24 % were older than 1 year of age [8]. Interestingly, while children greater than 1 year made up only 24 % of the study population, they accounted for 41 % of the deaths in this multi-center study; the higher mortality rate in older children was also reported among AHT cases in Pennsylvania [9]. Recognizing that AHT can occur in children up to 5 or even 6 year of age is important for the pediatric intensivist; AHT should be part of the differential diagnosis whenever caring for a child whose injuries seem out of proportion to the history provided or when an infant or young children's symptoms cannot be well-explained. While there are demographic, social, child, and parental risk factors for AHT, these risk factors clearly cannot be used to diagnose AHT, [10–13] cases of AHT clearly occur in children with no recognized risk factors. Therefore, while the presence of one or more risk factors should alert the treating physician that an infant or young child may be at increased risk of AHT, the lack of these risks factors cannot be used to eliminate AHT from the list of differential diagnoses.

Clinical Presentation

The clinical presentation of children with AHT can be quite varied, ranging from non-specific symptoms such as irritability or vomiting to extreme cardiorespiratory instability and acute herniation syndromes. In contrast to other disorders that present as critical illnesses, the reliability of the history provided by the caregiver in cases of AHT is always suspect, making the formation of an appropriate diagnosis more difficult. Specifically, in the majority of cases, the caretaker who is providing the medical history does not give the physician any history of trauma [14, 15]. While caretakers may purposely be evasive or lie, it is perhaps more frequent that the caretaker providing the medical history is not the perpetrator and may not know that the child has been abused.

The physical examination, including the neurologic components, can be normal in children with AHT. While bruising can be seen in a subset of children with AHT, children whose primary injury is an acceleration-deceleration injury (e.g. shaking) without an impact would not be expected to have external signs of injury. Even in cases in which there is impact, the impact may be against a soft surface (e.g., a couch) or may not be significant enough to cause a contact injury. Autopsy studies have demonstrated that some infants without bruising on physical examination have signs of impact injury which is only visible when the scalp is retracted [16, 17].

The importance of a complete dermatologic examination in children with suspected AHT cannot be overemphasized. While bruises (particularly of the ears and face), petechiae, and abrasions have little clinical significance and do not require treatment, they can be important for diagnosis. Completing and documenting the result of a comprehensive physical examination is critical so that it is clear which injuries were present upon arrival to the hospital (e.g. did not occur as part of medical care); this is particularly important when children are taken to the operating room for a neurosurgical intervention. Even in hospitals with a Child Protection Team (CPT), the child abuse physician often does not examine the child for several hours after admission. The initial examination by the CPT physician is therefore often after resuscitation and neurosurgical intervention. Injuries such as forehead bruising, for example, often cannot be seen after operative procedures; early and accurate documentation is therefore important. Bruising to the forehead, for example provides evidence of impact which can be critical for diagnosis and possibly for subsequent legal proceedings.

While the lack of a history of trauma and/or a lack of dermatologic findings can be barriers to proper diagnosis of AHT, perhaps the greatest barrier to diagnosis of AHT is the fact that infants and young children with subdural hemorrhages and/or other intracranial injuries can be neurologically

normal or have only non-specific neurologic signs such as irritability. In a classic study by Greenes and Schutzman [18], 19 % of children less than 2 years of age who had a subdural hemorrhage, cerebral edema or cerebral contusions due to abusive or non-abusive injury had a GCS score of 15. Therefore, the challenge for the pediatric intensivist is to recognize AHT when presented with a history which is inherently unreliable and a physical examination that is normal or nonspecific. In order minimize missing cases of AHT (which may prove fatal to the child), it is prudent to consider AHT in the differential diagnosis of any infant or young children (1) with an abnormal head CT where it is unclear whether the mechanism provided by the caretaker explains all of the child's injuries and (2) who has not had a head CT performed and in whom the etiology of the symptoms is not yet clear (e.g. an infant with apnea or a young child with altered mental status).

Mechanism of Injury and Pathophysiology

The mechanism of injury in AHT is among the most controversial issues in all of pediatrics. In his seminal paper, Caffey described the unexplained occurrence of 23 long bone fractures in six children who also demonstrated subdural hematomas. In these cases, a nursemaid admitted to shaking the victims while holding them by the arms and trunk [19, 20]. Since that time, there have been multiple studies which support the hypothesis that shaking is an important mechanism of injury in many cases of AHT [7, 21, 22]. In a recently published international population-based study by Runyan and colleagues, more than 20 % of parents admitted to shaking a child<2 year of age [23], suggesting that shaking may be a more common practice that previously thought. The prevalence of extensive multi-later retinal hemorrhages in many cases of suspected AHT also supports a shaking-type mechanism; retinal hemorrhages rarely occur in even severe non-abusive TBI and when present, do not have the same characteristics as the retinal hemorrhages in AHT [24, 25].

While shaking is likely an important mechanism of injury, in a significant proportion of cases, there is also evidence of an impact to the head based on (i) physical examination, (ii) radiologic evaluation and/or (iii) autopsy. The relative contribution of impact and shaking to the clinical symptoms in AHT has been an area of intense discussion. There are also data which support the importance of hypoxemia in AHT and several studies have suggested that the hypoxic-type injury in AHT may be more fundamental to outcome than direct trauma to the brain/skull [26–29].

The importance of cervical spine injury in the pathophysiology of AHT has also been the subject of debate. Early studies by Shannon and colleagues and others suggest that injury to the cervical spine is common in fatal cases of AHT [30, 31]. More recent studies suggest that spine injury in non-fatal cases of AHT may be far more common than previously thought [32–35]; in a study by Choudhary and colleagues [00], spinal canal subdural hemorrhage was present in more than 60 % of children with AHT compared with only 1 % of children with accidental TBI. Even prior to the Choudary study, a review article by Kemp and colleagues suggest that consideration be given to performing a spine MRI in all cases of AHT [36].

Overall, our understanding of the pathophysiology of AHT has been developed from many years of clinical observations [7, 37–39], histopathologic data from children with fatal injuries [17, 30, 31, 40], confessions of perpetrators [21, 22, 41, 42], and more recently, cases of AHT accidently caught on 'Nanny-cams'. There has also been a significant amount of progress over the past 10 years in the ability to model the injuries in AHT using a combination of animal models, human and animal tissue models, finite element analysis, anthropomorphic dummies, and computer simulation [43–52]. Although an in-depth discussion of these studies is beyond the scope of this chapter, the interested reader is referred to two excellent articles [53, 54].

The pathophysiology of AHT is complex and multifaceted and likely different in each patient. While improving our understanding of the pathophysiology of AHT is important and has improved significantly over the past 10 years, the focus for the clinical intensivist should not be on specific mechanism of injury in each case. Rather, the focus should be on the fact that the child's injuries were caused by an abusive act which was perpetrated by an adult.

Evaluation of Suspected AHT

In many pediatric hospitals in which children with suspected AHT are treated, there is a CPT, a multi-disciplinary team which evaluates cases of suspected child maltreatment and which often includes a board-certified child abuse physician or another physician with expertise in child abuse. The role of the CPT physician is often to provide recommendations related to evaluation for abuse, provide information to CPS about the child's injuries and the likelihood of abuse, and to be in charge of communication between the family, medical personnel, CPS and police as it relates to the abuse-specific issues. In hospitals without a CPT, the pediatric intensivist is often the physician who speaks with both families and CPS about abuse; in these situations, the intensivist must be able to do a comprehensive evaluation for abuse and relay the appropriate level of concern to others. It is important to remember

that CPS is ultimately responsible for the protection of a child who has been abused. If the level of concern about the likelihood of abuse is not properly relayed to CPS, a child may be placed back into a violent environment. We recommend that the evaluation of AHT be thought of as three evaluations: the evaluation of the cranial injuries, the evaluation for non-cranial injuries and the evaluation by CPS which is done based on the information from the first two evaluations.

Intracranial Injuries

Our understanding of intracranial injuries after TBI has improved with the increased availability and sophistication of MRI imaging. As is described within other chapters of this text, newer MRI techniques are now capable of identifying subtle white matter injuries that have previously gone unrecognized. This may be particularly relevant in AHT as diffuse injuries have not been well-recognized in previous studies. In addition to obtaining information regarding white matter injuries, MRI is also helpful in evaluating whether extra-axial collections contain blood products (e.g. chronic SDH) or not.

Within the last decades, it has been recognized that the end-stage of some cases of AHT can be severe loss of cortical and subcortical matter – the so-called "Big Black Brain" or multicystic encephalomalacia (MCE). MCE is a well-recognized phenomenon in the neonatal period and neonatal MCE is thought to be the result of a hypoxic-ischemic event. This has led others to hypothesize that unrecognized hypoxia may be an important contributor in cases of AHT which result in MCE. Animal models [55, 56]as well as clinical experience also suggest that a period of maturational vulnerability at the time of injury may also be important. [57, 58]

Extra-Cranial Injuries

The diagnosis of AHT is rarely based solely on the brain injury itself. With a few exceptions, the brain injuries discussed above are not specific to AHT. The combination of the brain injury and the non-cranial injuries in a patient without a history which adequately explains them is what defines AHT. As a result, identifying the non-cranial injuries can be critical in making the diagnosis of abuse.

Fractures

Up to 50 % of children with AHT will have either an acute or healing non-cranial fracture [59, 60]. In the vast majority of cases, these fractures cannot be diagnosed by physical examination alone. A complete skeletal survey ideally including oblique rib films [61, 62] should be performed whenever AHT is part of the differential diagnosis. In addition, a follow-up skeletal survey [63, 64] should be performed 10–14 days after the initial skeletal survey to assess for fractures which can be difficult to visualize in the acute setting.

Retinal Hemorrhages

A dilated ophthalmologic examination should be performed as soon as possible by an experienced pediatric ophthalmologist. While retinal hemorrhages are not specific for AHT and occur in about 10 % of cases of non-abusive TBI, certain patterns of retinal hemorrhages are highly-specific for AHT [65, 66]. Retinal hemorrhages which are multi-layered and/or extend beyond the periphery are almost unique to AHT. In the absence of significant direct trauma to the eye (e.g. crush injury), retinoschisis is virtually pathognomonic of AHT [24, 67]. In children with severe AHT, a dilated ophthalmologic examination is often not possible in the acute setting because of concern that the mydriatic will interfere with assessment of the pupillary response. The simplest solution to this problem is to request that the ophthalmologist perform an initial, non-dilated exam. Although the view of the retina will be limited to the posterior pole, a non-dilated exam can provide preliminary information about the presence or absence of retinal hemorrhages and a sense of how extensive they are. This can be particularly helpful in cases in which the possibility of AHT is raised, but the concern may not be high enough to make a report to authorities (e.g. there is a history of a fall, but the brain injury seems out of proportion to the history). If there are other young children in the home, timely reporting to CPS is especially important; though the child in the PICU is safe from abuse, other children in the home may still be with the perpetrator. An alternative to an undilated examination is serial dilation of the pupils.

Abdominal Injury

Although it is rarer than AHT, abdominal injuries are the second leading cause of death from abuse [68]. All children being evaluated for AHT should have liver function tests, amylase and lipase. A recent multi-center study evaluating the use of these screening labs suggested a low threshold for obtaining an abdominal CT [69].

Evaluation for Bleeding Disorders

The concern about whether a bleeding disorder could account for the intracranial hemorrhage children with AHT needs to be a consideration in certain cases. Recent clinical and technical reports from the American Academy of Pediatrics provide recommendations for which children with suspected AHT should undergo testing for bleeding disorder and what that testing should be [70, 71]. Briefly, the recommendation is that a CBC with platelets, PT/PTT, Factor VIII, Factor IX, d-dimer and fibrinogen be measured when a bleeding disorder is being considered and that a hematologist become involved if any testing is abnormal. Testing may not be needed when there are other medical findings consistent with abuse (e.g. fractures). The details of these reports are beyond

the scope of this chapter; the reports should be considered required reading for any physicians who evaluates children with suspected AHT.

Evaluation for Disorders Which Can Mimic AHT

The diagnosis of AHT is only occasionally obvious from the outset and AHT is often part of the differential diagnosis for a many infants and young children with TBI. As with every disease, identifying the correct diagnosis is paramount importance to patient care – in cases of AHT, there are additional social and legal implications of the making a diagnosis. There are very few other diagnoses which can result in children being removed from their parents home and/or people going to jail. There are also very few other diagnoses which, if missed, can result in a child being killed. Both sensitivity and specificity are therefore critical; while one does not want a child to be removed from a non-abusive home, one also does not want to return a child to an abusive one.

The most common differential diagnosis is non-abusive TBI. In about 50 % of cases of AHT, the caretaker provides a history of trauma as the explanation for the child's injuries; the issue is whether this history can account for the child's symptoms as well as the constellation of cranial and non-cranial injuries. It is incumbent upon the physician who is evaluating the child to be cognizant of the extensive literature related to injuries in short falls and stair falls, a common history provided by caretakers of children in whom AHT is part of the differential diagnosis [72–75]. In addition to the knowledge of the literature, one should not underestimate the importance of clinical experience. The pediatric intensivist is in the unique position of also evaluating children with non-abusive TBI; assessment of children with non-abusive TBI can provide important information which can be used when assessing children with possible abuse. It can be very instructive, for example, to listen carefully to the histories provided in cases of non-abusive TBI, specifically, the level of detail which the caretaker provides and the consistency with which he/she provides it. It can also be helpful to look at the non-cranial injuries sustained by children with non-abusive TBI – the number and location of bruises (particularly in premobile infants), the prevalence of acute or healing non-cranial fractures or a chronic SDH, and the number and type of retinal hemorrhages. Using this type of evaluation in cases of non-abusive TBI allows the intensivist to better assess the likelihood of abuse in cases which may be due to AHT.

Aside from non-abusive TBI, it is important to consider whether there might be a non-traumatic cause for a child's medical findings. These non-traumatic etiologies are often referred to as 'mimics'. A mimic is defined by Webster's dictionary as "something which closely resembles something else." The most common mimics of AHT discussed in the literature are glutaric aciduria type I [76], hemophagocytic lymphohistiocytosis [76–78] hemorrhagic disease of the newborn [79] and arteriovenous malformations [80]. While these diseases can resemble AHT, they rarely, if ever, share all its characteristics. It is important that the pediatric intensivist consider these mimics and in some cases, it is important to test for these mimics. In most cases, however, the clinical presentation and/or injuries are inconsistent with the mimic (e.g. multiple metaphyseal fractures in hemorrhagic disease of the newborn). When a mimic is strongly being considered and there are no other children in the home, then filing a report with CPS can sometimes wait until if the additional data can be obtained within a day or two. If there are other children in the home, however, reporting should not be delayed since the other children in the home need to be evaluated to ensure their safety; the presence or absence of abusive injuries in contact children can provide important information about the probability of abuse in the index child.

Management and Treatment of AHT

The overall management and treatment of children who have suffered AHT is not significantly different from children with non-abusive TBI. However, given the relatively younger age population (and consequently smaller physical size), performance of some of the interventional procedures for the AHT population may be more challenging. EMS should be activated as soon as it is recognized that the child may be injured. Once the child arrives at a trauma center, assessment of airway, breathing and circulation (the "ABCs") is an essential part of the primary survey. A secondary survey, based on Advanced Trauma Life Support Guidelines, should then be performed to assess for systemic conditions and neurological injuries. The "gold standard" for neurological assessment is the Glasgow Coma Scale (GCS) score. Though there are various adaptations of the GCS score to account for developmental age [81], none have been sufficiently validated as measures of disease severity or as prognostic of outcome and thus the GCS remains the gold standard.

Mild and moderate AHT is generally treated expectantly with supportive measures, essentially to avoid secondary insults (e.g. hypoxia, hypotension, seizures, and hyperthermia). For severe AHT, management from a comprehensive team that includes trauma surgeons, neurosurgeons, intensivists and others is essential. In 2003, evidenced-based guidelines for the medical management of severe TBI in children were published [82]. While this document represents a synthesis of the TBI literature, none of the articles within the document is specific to AHT. In addition, the guidelines include children across the entire age spectrum – therefore, most of the literature includes a subset of children with AHT within a much larger population of children with non-abusive TBI. Despite these limitations, this document represents the best current evidence for caring for children with all types of TBI.

As with children with non-abusive TBI, AHT can lead to intracranial hypertension if the compensatory mechanisms to maintain the volume/pressure relationship within the cranium are overcome. Despite the lack of ossification of the skull of young children (and the presence of membranous fontanels for the first 18 months of life), critical intracranial hypertension leading to cerebral herniation can be observed in children of all ages. Therefore, minimizing intracranial pressure (ICP) and maintaining cerebral perfusion pressure (CPP) is a mainstay of neurocritical care for both non-abusive and AHT. Recent data from a study of young children many of whom had AHT suggest that maintenance of CPP may be more important than ICP control in this population [83].

After a rigorous resuscitation and assessment outlined above, prompt evacuation of extra-axial hematomas that are causing disturbances in cerebrohemodynamics and placement of ICP monitors are the next essential steps. This may be accomplished in the operating room with a basic craniotomy for simple evacuation of a minimal collection of blood or may require a larger craniectomy to decompress the brain. Insertion of an ICP monitor may occur at the time of the surgical procedure or after admission to the PICU. Intraparenchymal monitors or externalized ventricular drains are essential to detect periods of intracranial hypertension and decreased CPP. Precise therapeutic thresholds for these parameters – ICP and CPP (Mean arterial pressure – ICP) – have been sought for decades. In general, most studies suggest that an ICP target less 20 mmHg is associated with the best outcome. Chambers and colleagues found a relationship between age and optimal CPP in children with TBI, with the youngest age group exhibiting slightly lower CPP. Specifically, in the age group of 2–6 years, a CPP threshold of 53 mmHg was observed compared to CPP greater than 60 mmHg for older children [84]. A recent study in children with predominantly AHT (81 % of all subjects) suggests that a threshold of CPP less than 45 mmHg is associated with poor outcome which, if confirmed, may suggest a therapeutic target for a larger study [83].

The high prevalence of seizures in children with AHT has been the subject of a significant amount of literature. In a large series of children with all severities of AHT, 73 % had clinical seizures and an additional 16 % had EEG abnormalities during hospital admission [85]. It has been hypothesized that the high rate of seizures is related to the importance of hypoxemia in the pathophysiology of AHT. In a provocative case study, Hartings and colleagues found that use of electrocorticography could detect multiple depolarizations and seizures in the subcortical region that led to severe tissue hypoxia in an adolescent after severe TBI – implying that if seizures are more frequent after AHT, this mechanism may be even more important in that patient population [86]. Further study is required to understand the secondary insults that may adversely affect outcome after AHT.

Outcomes After AHT

While outcome after AHT is variable between different series, multiple studies demonstrate that mortality and morbidity after AHT is higher than after non-abusive TBI of similar severity [87, 88]. While different studies report on different outcomes (e.g. GOS, disability), the most standard outcome parameter is mortality. In a retrospective review of 11 Canadian trauma centers over a 10-year period, the mortality rate from AHT was 19 % [89]. Scavarda and colleagues found a mortality rate of 28 % and also demonstrated that the Pediatric Risk of Mortality Score II (PRISM II) was associated with mortality in 36 children with AHT. Both of these studies included children with mild, moderate and severe AHT – indicating that overall mortality rates children with AHT are greater than those observed for large studies of children with severe non-abusive TBI. [88, 90]

While mortality is the most commonly used measure of outcome, more detailed neurological outcomes are particularly important after AHT because the GOS score is too gross a measure to use in an age group in which dependency on others for activities of daily living can be age-appropriate rather than a sign of pathology. We recently reported a 50 % rate of unfavorable outcome (defined as GOS = 3–5 [severe disability + vegetative + dead]) of a population of young children who predominantly had AHT [83]. Using more detailed neurological assessments, King and colleagues found that only 22 % of 364 children with AHT demonstrated no neurological sequelae 6 months after injury [89]. Recently, a task force recommended standard outcome assessments for all pediatric TBI studies; this would greatly increase the generalizability of studies that include children with AHT [91]. The reason for the increased mortality and morbidity in AHT compared with non-abusive TBI is not entirely clear. It is likely to due to a combination of factors including characteristics of the injury itself, a delay by caretakers in seeking medical care, a delay by medical providers in identifying trauma, the effect of prior maltreatment, particularly prior AHT, on the response of the brain to subsequent injury and possibly developmental factors. Additional studies are needed to determine the relative impacts of these various putative mechanisms.

Reporting and Legal Issues

In the United States, physicians are mandated reporters of child abuse. As part of the mandated reporting laws, physicians are protected from lawsuits related to reporting suspected abuse as long as the report of abuse is made in good faith. In cases of AHT, particularly severe AHT, first responders and/or emergency department physicians often make the initial report to CPS. The pediatric intensivist, however, is sometimes the first physician to consider the

possibility of trauma and specifically, AHT. This is particularly true in young children with cardiac arrest, for example, who can be admitted to an ICU prior to a head CT or in cases in which infants may be thought to have RSV or meningitis, but who then undergo a head CT when the other diagnostic possibilities seem less likely and/or when the infant does not respond as expected to standard treatment. The pediatric intensivist may also be the one to make a report to CPS when a child is admitted with what is initially thought to be non-abusive TBI, but is later assessed as being the result of abuse when additional testing demonstrates additional injuries which are incompatible with the history provided. When the pediatric intensivist is the first physician to recognize the possibility of AHT, it is his/her responsibility to be sure that CPS is notified. While timely reporting is always important, it is particularly important in cases in which there are other young children in the home. Violence is often a pattern and while the child who is in the ICU is safe from further abuse, other young children may still in the home with the perpetrator. Children who are left in the home may be particularly vulnerable to abuse immediately after one child is brought to for medical care since the perpetrator may be angry and/or stressed about whether the injuries in the index child will be identified as abusive.

In cases in which a child is seriously injured, reporting to CPS will almost always trigger a report to local police. Early scene investigation by police can provide critically important information both about the etiology of the injuries and/or the perpetrator. Most referring institutions have dedicated social services staff or other designated personnel who can assist physicians in making a report to CPS. Notifying parents that a report is being made to CPS can be done at the same time that the physician discusses the child's injuries and treatment plan with the family. Including a hospital social worker or other support staff with expertise in the CPS system can be very helpful when child abuse reporting needs to be discussed. Discussions about the possibility of abuse can be brief. Physicians should tell the parents the injuries which are concerning for abuse, while being respectful and non-accusatory. It is helpful to remember that the parents may not be the perpetrators and may feel intense guilt for leaving their child in the care of someone who abused him/her. Some physicians feel that informing parents of the legal obligation to report abuse makes the discussion less stressful and less accusatory. While notification of parents is important, if no parent is available, physicians should not delay reporting.

Reporting possible abuse to CPS can be similarly brief: list the injuries in language which is as simple and non-medical as possible (e.g. use the word 'bruise' instead of 'ecchymosis'), inform CPS about the severity of these injuries (e.g. whether or not they are life-threatening) and provide information about the strength of the diagnosis (e.g. there is concern for abuse vs. the injuries are diagnostic of abuse). A report to CPS is not a static document and more information including a change in the assessment of the likelihood of abuse can always be added as it becomes available (e.g. after a dilated eye exam or skeletal survey is performed).

Pediatric intensivists are often concerned about the need to testify in legal proceedings related to abuse cases. There are two types of court proceedings: civil and criminal. Civil cases are in family court and revolve around decisions related to safety and placement of children rather than prosecution of perpetrators. Testimony for these cases can often occur by phone and the intensivist is often only needed if there is no CPT physician or if there are specific medical questions which can only be answered by the intensivist. The level of evidence required in civil court is lower than in criminal court in which all statements about the etiology of injury must be "to a reasonable degree of medical certainty." Criminal proceedings relate to crimes such as endangering the welfare of a child or manslaughter that occur in association with AHT. Only a very small percent of cases of even unequivocal AHT go to criminal court; if a physician is needed for testimony, courts are often very flexible and will accommodate schedules, assist with transportation, and reimburse for time and expertise. Because of the difference in the level of evidence required in civil versus criminal court, there are many cases of suspected AHT in which the level of concern about the possibility of abuse is high enough that it is necessary to protect the children – either through a change in caretakers or through placement of services into the home – but not high enough for a criminal prosecution.

Conclusion

In summary, the pediatric intensivist is likely to care for numerous infants and young children in whom the possibility of AHT is being considered in the differential diagnosis. It is incumbent upon pediatric intensivists to be aware of this diagnosis, its epidemiology and its clinical characteristics and to be comfortable obtaining and interpreting the diagnostic testing needed to evaluate a child for AHT. In hospitals without a CPT, it is also imperative that the intensivist be able to relay this information to non-medical personnel (e.g. CPS) so that the proper actions can be taken to protect the child and his/her siblings from further abuse. As with most other diseases, AHT comes in all severities from 'mild' to 'severe' and the strength which one can give a diagnosis ranges from 'possible' to 'definite;' it is important that this information is accurately given to the family, CPS and law enforcement. There are very few clinical scenarios in which failure to make a proper diagnosis carries such a risk of re-injury or death; [92, 93] the pediatric intensivist plays a crucial role in protecting this very vulnerable group of young children.

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Toxic Metabolic Encephalopathy

39

Jorge S. Sasbón and Hugo Arroyo

Abstract

For many centuries it has been known that normal conscious behavior of the human being depends upon intact brain function and that impairment of consciousness is the most important sign of brain dysfunction. As such, altered or decreased levels of consciousness, due to whatever cause, require immediate medical intervention. The central nervous system (CNS) tissue tolerates only a limited amount of physical or metabolic injury before it suffers irreparable damage. A broad spectrum of specific conditions may alter the brain causing progressive impairment of consciousness. In the developing and growing child, the CNS undergoes important structural, physiological, and biochemical changes and is more vulnerable injury from these conditions. The various disorders causing toxic/metabolic encephalopathy all share a common pathophysiological mechanism – the lack of energy substrates with consequent synaptic damage, alterations in cell signaling and neurotransmitter balance, and a deficit of the maintenance of the cell membrane potential through the sodium-potassium pump. Many of these insults are of acute onset and are diagnosed and treated in the Pediatric Intensive Care Unit (PICU), including disorders related to glucose metabolism (e.g. diabetic ketoacidosis complicated by cerebral edema), disorders related to sodium and water metabolism (with special emphasis on the treatment of the hyper and hyponatremia), and related changes to hyperammonemia such as AHF, Reye syndrome and inborn errors of metabolism.

Keywords

Encephalopathy • Cerebral edema • Altered consciousness • Hyperammonemia • Diabetic ketoacidosis • Acute hepatic failure • Inborn errors of metabolism • Inherited metabolic disorders

Introduction

For many centuries it has been known that normal conscious behavior of the human being depends upon intact brain function and that impairment of consciousness is the most important sign of brain dysfunction. As such, altered or decreased levels of consciousness, due to whatever cause, require immediate medical intervention. The central nervous system (CNS) tissue tolerates only a limited amount of physical or metabolic injury before it suffers irreparable damage. A broad spectrum of specific conditions may alter the brain causing progressive impairment of consciousness. In the

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developing and growing child, the CNS undergoes important structural, physiological, and biochemical changes and is more vulnerable injury from these conditions. The basic elements of the CNS include the neurons and their surrounding environment, the neuroglia. Functional integrity depends on the interaction among the neuron, the neuronal cell membrane, the connective tissue, and absorption and utilization of the energy substrate. If these structures are affected, cell biochemistry, nerve conduction and impulses, and nutrient exchange are also altered.

Central Nervous System Physiology

The brain accounts for only 1 % of the total body weight, whereas its energy needs are 20 % of the total energy needs of the body. A neuron obtains energy from glucose and oxygen. This correlation between energy use and production explains the high neuronal sensitivity to anoxia and lack of energy substrates. The metabolic activity of the brain is high, even at rest. Energy requirements are 8 kcal/100 g/min, which are supplied almost exclusively by oxidative metabolism of glucose that has to be transported to the cell across the blood-brain barrier. Each 100 g of brain "captures" 5.5 mg of glucose per minute, and glucose consumption during baseline conditions is almost equivalent to the total glucose production by the liver. Of this glucose, 85 % is destined to oxidative metabolism, in which energy is produced along with the by-products of carbon dioxide and water. The remaining 15 % may be partially oxidized to lactic acid. The neuronal metabolism can also use alternative energy sources, such as membrane phospholipids, albeit at the cost of damage to the cell membranes.

In order to keep up with these metabolic requirements, the brain requires a continuous supply of oxygen, and, unlike for glucose, there are no oxygen reserves. Oxygen consumption of the normal brain is around 3.3 mL for each 100 g of brain per minute. Indeed, as stated earlier, the cerebral metabolic rate for oxygen (CMR02) accounts for 15–20 % of whole-body oxygen consumption. CMR02 decreases in parallel with the degree of CNS depression.

The common denominator for glucose and oxygen requirements is the cerebral blood flow (CBF), which under normal conditions is maintained at around 55 mL/100 g/min or around 15–20 % of total cardiac output. CBF increases and diminishes in response to a great variety of stimuli, but is mainly associated with PCO2 (hypo or hypercapnia). There is a close relationship between pressure and flow with a compensatory mechanism. This autoregulation of the CBF has an upper and a lower limit which is similar in adults and in children. When these limits are surpassed, the brain is at risk of ischemia or hyperemia. When CBF is diminished, the brain extracts more oxygen per volume of blood flow. When oxygen supply is normal, the CMRO2 remains normal in relationship with the reduced blood flow until it reaches 50 % of normal. At that point, brain PO2 diminishes to levels that do not support maintenance of the metabolism and consciousness decreases [1].

The various toxic/metabolic encephalopathies therefore have a common pathophysiological mechanism, namely, the lack of energy substrates with consequent synaptic damage, alterations in cell signaling and neurotransmitter balance, and a deficit of the maintenance of the cell membrane potential through the sodium-potassium pump. Many of these insults are of acute onset and are diagnosed and treated in the Pediatric Intensive Care Unit (PICU) and will be the focus of the remainder of this chapter.

Toxic-Metabolic Encephalopathy and Altered Levels of Consciousness

For the purposes of the present discussion, encephalopathy is defined as a generalized acute, subacute, or chronic disorder of the brain that may be reversible or progressive and that may lead to death of the patient or survival with major sequelae. Toxic-metabolic injury to the CNS is produced by intrinsic or extrinsic disorders of the neuronal metabolism or the glial cells. Primary toxic-metabolic encephalopathies are caused by an alteration of the neurons or glial cells themselves and encompass the degenerative diseases that result in coma and death, which are beyond the scope of this chapter. The second group consists of encephalopathies secondary to extracerebral disease affecting normal brain metabolism. In systemic processes, impairment of CNS function is a fundamental clinical element manifesting with signs and symptoms of an altered level of consciousness, seizures, paralysis, and neuropathies.

Definitions of Altered Levels of Consciousness

Alterations of the level of consciousness encompass a broad clinical spectrum, ranging from drowsiness to coma. Such alterations in the level of consciousness account for up to 3 % of emergency room visits [2]. Approximately 85 % of these have a metabolic or systemic etiology, while the remaining 15 % are due to structural lesions [2]. Approximately 30 children out of the 100,000 admissions per year have a decreased level of consciousness due to a non-traumatic cause. Mortality in this group of patients is alarmingly high at nearly 40 % [3, 4]. These entities may manifest with severe neurologic signs accompanied by metabolic alterations, such as metabolic acidosis and hypo- or hyperglycemia.

Consciousness is the physiological state of brain arousal (wakefulness) and alertness in which the individual has awareness of one's own existence and environment and is capable of spontaneously interacting with both (himself and

his environment). To be awake, adequate function of the reticular formation activating the brain stem and cortex is required. While sleep is a physiological state of unconsciousness without apparent brain activity, an individual can be aroused spontaneously or by means of a stimulus. Two aspects of consciousness are directly affected by different aggressions to the brain: content, which is the sum of mental functions, and stimulation, closely related to the state of alertness. As stated above, alterations in the level of consciousness range along a continuum from drowsiness to coma. Altered levels of consciousness include a spectrum of states that can be divided into several categories by simple observation of the behavior of the patient [5]:

Lethargy: Relatively mild impairment of consciousness resulting in reduced alertness and awareness, memory loss, and drowsiness alternating with irritability, but verbal and gestural communication is preserved.

Obtundation: A state of decreased alertness, which in its mildest form includes excitability and irritability alternating with drowsiness. A more acute state of obtundation is confusion.

Confusion: A state of decreased alertness and disorientation in time and space, with decreased interest in and response to the surroundings. Communication is partially preserved and drowsiness is more severe.

Delirium: A more severe state characterized by disorientation, fear, irritability, altered perception of the sensory stimuli, and often visual hallucinations. Delirium is marked in toxic-metabolic disorders and its finding points to a generalized alteration of brain functions. Periods of alertness and agitation alternate with periods of somnolence.

Stupor: Mimics a state of profound sleep and the patient can only be partially awakened by vigorous and repetitive stimuli. Communication is minimal or absent. As in a delirium, stupor is often observed in toxic insults or metabolic alterations and is a sign of a diffuse brain lesion.

Coma: No response to stimuli. It is a state of maximum compromise of the consciousness. The eyes are closed and patient does not present with any spontaneous movements.

Persistent Vegetative State: A subacute or chronic condition following severe brain injury with recovery of the sleep-wake cycle, but with severe deficit of cognitive and volitive function. The patient opens the eyes in response to verbal stimuli and has stable blood pressure values and respiratory control.

Brain Death: Complete and irreversible loss of all brain functions.

Clinical Assessment of Altered Levels of Consciousness

Clinical examination of a child suffering from encephalopathy will show a common pattern of altered consciousness of variable degree. In some patients, this is the only clinical manifestation of disease, while in others it is part of a more complex picture of other neurological signs and symptoms (e.g. seizures, motor impairment) and/or signs and symptoms of dysfunction of other organs or systems. Clinical assessment of these patients is best performed using a staged approach, as detailed below:

Diagnosis of Severity

Assessment of vital signs and impairment of consciousness first starts by means of the Glasgow Coma Score (GCS). Two scales are used – one for patients under 1 year of age (in which the score ranges from 3 to 14, with a normal score being 14) and one for patients over 1 year of age (in which the score ranges from 3 to 15, with a normal score being 15) (Table 39.1). Initial resuscitation and stabilization is largely dictated by the severity of the altered level of consciousness. For example, patients with GCS > 12 can usually be cared for on a general ward (unless the encephalopathy is traumatic in nature), while patients with GCS < 12 will generally require admission to a PICU or other closely monitored setting. A GCS ≤ 8 usually indicates the need for airway protection by tracheal intubation AND for intracranial pressure (ICP) monitoring.

Topographic Diagnosis

Topographic diagnosis is based on a limited number of neurological signs and allows the clinician to determine the integrity or alteration of different brain levels (cortex, diencephalon, brain stem, pons, and medulla oblongata) and evolution (Table 39.2). Special attention should be paid to the assessment of different functions, including state of consciousness (using the GCS above), respiration, motor responses, pupil size and reactivity, eye movements (oculovestibular and oculocephalic reflexes). Of note, alterations due to metabolic, toxic, and infectious causes are usually characterized by normal pupillary responses (Table 39.3).

Syndromic Diagnosis

Based on the findings of the neurologic examinations, it can be established if the manifestations are the result of a supra- or infratentorial mass or a toxic-metabolic or infectious disorder (Table 39.4).

Etiologic Diagnosis

According to the findings of the above-mentioned assessments, different etiologies are suggested that may be confirmed by complementary studies (Table 39.5). The first studies that should be requested in infants and children with suspected metabolic disease are listed in Table 39.6. In children, hypoglycemia alerts the intensivist to the possibility of toxins, liver disease, organic acidemias, and aminoacidopathies. Similarly, the finding of elevated blood ammonia levels are a warning for urea cycle defects, organic acidurias,

Table 39.1 Glasgow Coma Scale

Eye opening (total possible points 4)			
Spontaneous		4	
To voice		3	
To pain		2	
None		1	
Verbal response (total possible points 5)			
Older children		**Infants and young children**	
Oriented	5	Appropriate words; smiles, fixes, and follows	5
Confused	4	Consolable crying	4
Inappropriate	3	Persistently irritable	3
Incomprehensible	2	Restless, agitated	2
None	1	None	1
Motor response (total possible points 6)			
Obeys	6		
Localizes pain	5	Localizes pain	5
Withdraws	4	Withdraws	4
Flexion	3	Flexion	3
Extension	2	Extension	2
None	1	None	1

The Glasgow Coma Scale
The GCS is the most widely used method of evaluating a child's neurologic function and has three components. Individual scores for eye opening, verbal response, and motor response are added together, with a maximum of 15 points. Patients with a GCS score ≤8 require aggressive management, including stabilization of the airway and breathing with endotracheal intubation and mechanical ventilation, respectively, and, if indicated, placement of an intracranial pressure monitoring device
Adapted from Teasdale and Jennett [6]. With permission from Elsevier

Table 39.2 Location of the level of injury according to neurological signs

Location of the lesion	Breathing	Motor response	Size and pupillary response	Eye movements reflexes
Cortex	Eupnea	Spontaneous movements	Pupillary reflex positive	Positive doll's eye
	Periodic apnea	Abnormal limb extension		Positive oculovestibular reflexes
Diencephalon (talamo-hipotalmo)	Eupnea	Spontaneous movements	Bilateral miosis	Positive doll's eye
	Periodic apnea	Abnormal limb extension	Pupillary reflex positive	Positive oculovestibular reflexes
Midbrain (brainstem)	Central hyperventilation	Spontaneous movements	Intermediate	Positive–negative doll's eye
		Abnormal limb extension	Pupillary reflex negative	Positive–negative oculovestibular reflexes
Protuberance	Apneusis	Abnormal extension of arms and flexion or flaccidity of d legs	Punctiform	High: positive-negative
			Pupillary reflex negative	Low: negative
Bulb	Ataxic	Flaccidity	Unilateral miosis, pupillary reflex negative	Negatives
	Gasping	No motor response		
	Apnea			

Table 39.3 Effect of drugs and metabolic status on the size and pupillary response

Drug or metabolic state	Size of the pupils	Fotomotor reflection
Opiate	Pinpoint	Reagent
Barbiturates	Small or medium <5 mm	Reagent
Metabolic encephalopathy		
Amphetamines	Expanded >5 mm	Reagent
Cocaine	Expanded >5 mm	Reagent
Atropine	Expanded >5 mm	Reagent
Severe hypoxia	Expanded >5 mm	Nonreactive

fatty acid oxidation disorders, and metabolic disorders with onset in the neonatal period or in infancy. When lactic acid levels are elevated, organic acidemia, aminoacidopathy, fatty acid oxidation disorders, and mitochondrial diseases should be considered. Imaging studies and an electroencephalogram (EEG) are also important to establish the final diagnosis.

Table 39.4 Syndromic diagnosis

(I)	**Supratentorial mass that compresses or displaces the diencephalon or brain stem**
(A)	Focal neurological signs
(B)	Progression rostrocaudal of the signs
(C)	Asymmetric motor signs
(D)	Risk of cerebral herniation
(II)	**Infratentorial mass that injures or displace stem reticular formation**
(A)	Stem brain dysfunction or acute onset of coma
(B)	Oculovestibular function abnormality
(C)	Involvement of cranial nerves
(D)	Early respiratory disorders
(E)	Risk of cerebral herniation
(III)	**Toxic metabolic encephalopathies**
(A)	Confusion or stupor preceding motor signs
(B)	Symmetrical motor signs
(C)	Preserved pupillary reaction
(D)	Seizures, tremor, myoclonus
(D)	Changes in the acid base balance

Table 39.5 Etiologic diagnosis

Classification of metabolic toxic encephalopathy
(A) Hypoxic encephalopathy: reduced PaO_2 and/or CaO_2
(B) Ischemic encephalopathy by lowering the FSC
(C) CNS infection
(D) Systemic infection
(E) Exogenous poison
(F) Systemic diseases: hepatic encephalopathy, uremic coma, narcosis CO_2 retention, metabolic, autoimmune, endocrine, thiamine deficiency, high blood pressure
(G) Electrolyte disturbances
(H) Transplant patient encephalopathy

Table 39.6 Further studies

Blood: glucose, urea, serum electrolyte, calcium, magnesium, liver enzymes, blood count, acid-base status and arterial PaO_2, blood ammonia level
Urine: pH, density, glucosuria, reducing substances, cetonuria (dip stick) sediment
Image: CT scan, MRI, magnetic resonance angiography
Neurophysiologic studies: electroencephalogram, evoked potential

General Management of Altered Levels of Consciousness

Concomitant with the diagnostic process, initial management should be focused upon the ABC's (A = Airway protection, B = Breathing, C = Circulation). As discussed above, patients with GCS <8 are unable to protect their airway and generally require tracheal intubation. The next step in resuscitation is to check the blood glucose level and treat hypoglycemia, if present, as the brain is dependent upon glucose metabolism for energy. Indeed, hypoglycemia is such a critical factor that many experts include "D = Dextrose" in the ABC's rubric. Seizures should be treated with either lorazepam 0.1–0.2 mg/ kg (maximum dose 4 mg) or diazepam 0.2–0.5 mg/kg in combination with a loading dose of fosphenytoin. A normal body temperature should be maintained. Hyperthermia is deleterious to the injured brain. While the use of therapeutic hypothermia in many of these disorders is still being studied, most experts generally recommend passive re-warming (if at all) for patients with hypothermia in this setting. In general, normal fluid, electrolyte, and acid-base homeostasis should be achieved. Other important measures include the use of eye protection (in order to protect the cornea), the use of early enteral nutrition, decubitus ulcer prophylaxis, early physical therapy, and prevention of hospital-acquired infection, all of which are discussed in other places in this textbook.

Toxic-Metabolic Encephalopathies in the PICU

Disorders of Glucose Metabolism

Hypoglycemia, diabetic ketoacidosis (DKA), and hyperglycemic hyperosmolar state (HHS) are disorders of the glucose metabolism that may lead to altered levels of consciousness and toxic-metabolic encephalopathy. All three are discussed elsewhere in this textbook, but are mentioned here as well. Clinical manifestations of DKA and HHS include hyperglycemia, ketonemia, and metabolic acidosis. HHS, compared to DKA, is far less common in children, but there are a growing number of reports of pediatric patients with this disorder. Regardless, we will not discuss HHS further here and the interested reader is referred to the appropriate chapter later in this textbook.

Hypoglycemic Coma

Hypoglycemic coma rarely occurs in children and is generally associated with systemic diseases. Hypoglycemic coma may also be the result of an overdose of insulin, dietary or physical transgression, kidney or liver failure, other concomitant hormonal deficits, or interactions of drugs or alcohol. Clinical manifestations of hypoglycemia are divided into two groups: adrenergic symptoms, such as sweating, nervousness, tremor, paleness, palpitations, and feelings of hunger, and neurological symptoms characterized by headache, reduced capacity of concentration, behavior and language disturbances, blurred vision, confusion, loss of consciousness, seizures, and coma. Treatment basically consists of glucose reposition. Glucose solution at 10 % is administered at 200 mg/kg infused over 1 h at 10 mg/kg/min.

Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) is the most frequent cause of morbidity and mortality in children with type I diabetes mellitus. Triggering factors are infection and pharmacological transgression. DKA is generally defined by blood glucose over 300 mg/dL, positive ketone bodies in urine, metabolic acidosis with an increased anion gap, and low plasma bicarbonate concentration. In addition to the typical symptoms of diabetes mellitus, the clinical findings are nausea, vomiting, and abdominal pain. Timely treatment is necessary as metabolic acidosis will lead to obtundation and coma. Treatment involves intravenous fluids to correct dehydration and electrolyte derangements (especially the careful attention to the restoration of intravascular volume and electrolytes slowly) and administration of insulin via a continuous intravenous drip. Notably, even a profound metabolic acidosis will usually correct with insulin and restoration of the intravascular volume, such that administration of sodium bicarbonate is not recommended (and has been shown to be harmful).

Cerebral edema (CE) is the most severe complication and leading cause of death in patients with DKA. CE occurs in approximately 0.5–1 % of pediatric patients with DKA [7, 8]. The mortality rate in patients with CE complicating DKA is high (21–24 %), and a large number (15–26 %) of children have permanent neurological sequelae [9]. It is believed that several treatment-related aspects may cause or exacerbate the development of CE in DKA [7]. Symptoms of CE typically start within 4–12 h after treatment initiation, however, early-onset (i.e., previous to therapy) and late-onset (i.e., between 24 and 28 h) cases have been described. Subclinical or asymptomatic CE is probably present during treatment in the majority of children and may occasionally be seen on computed axial tomography (CT scan) or magnetic resonance imaging (MRI) [10, 11]. Signs and symptoms of CE in DKA include headache, restarting of vomiting, bradycardia, and clinical signs of increased intracranial pressure (Cushing's triad). Changes in the breathing pattern, such as hyperpnea, apnea, and bradypnea, are observed and consciousness is altered showing restlessness, irritability, and stupor. Simultaneously, pathologic neurological signs appear, including oculomotor nerve paresis, abnormal pupillary reflexes, and decorticate posturing. Muir et al. have proposed a system of major and minor criteria for the clinical diagnosis of CE [12], which is shown in Table 39.7.

Table 39.7 Bedside evaluation of neurological state of children with diabetic ketoacidosis

Diagnostic criteria
Abnormal motor or verbal response to pain
Decorticate or decerebrate posture
Cranial nerve palsy (especially III, IV, and VI)
Abnormal neurogenic respiratory pattern (e.g. grunting, tachypnea, Cheyne-Stokes respiration, apneusis)
Major criteria
Altered mentation/fluctuating level of consciousness
Sustained heart rate deceleration (decline more than 20 beats per minute) not attributable to improved intravascular volume or sleep state
Age-inappropriate incontinence
Minor criteria
Vomiting
Headache
Lethargy or being not easily aroused from sleep
Diastolic blood pressure _90 mmHg age _5 years

Signs that occur before treatment should not be considered in the diagnosis of cerebral edema
Based on data from Ref. [12]

Children at a major risk of developing CE in DKA are those who have more severe dehydration, acidosis, and hypocapnia, and obtundation or coma at presentation [8, 13]. The etiology of CE remains unknown. Different treatment-associated theories are related to volume, rate, and osmolality of fluid administration. One of the strongest hypotheses is related to the passage of fluid to the interior of brain cells during treatment, though the majority of clinical studies do not support this hypothesis. No correlation has been found between the decrease in glucose levels and changes in osmolality and the risk of CE, although researchers have described an association between a sudden drop of glucose levels and an inadequate increase of serum sodium concentration as a triggering factor for CE. Treatment with bicarbonate has also been suggested as a cause of CE [14]. Another hypothesis is related to fluid administration at treatment onset. In a recent evidence-based emergency medicine review, the association of intravenous fluid hydration and cerebral edema was assessed. The authors found a lack of consistent results implicating rate or volume of fluid administration as a precipitant cause of CE in patients with DKA [15].

An interesting hypothesis for the pathophysiology of CE in DKA is linked to CBF. The use of MRI with apparent

diffusion coefficients and measurements of cerebral diffusion techniques has allowed for the evaluation of the CBF in patients with DKA. Changes in blood flow were observed that in the first place led to cytotoxic and subsequently to vasogenic edema. Animal models have shown that CBF is reduced before treatment, supporting the hypothesis of cytotoxic edema. Clinical studies using MRI in pediatric patients during rehydration have shown increased cerebral perfusion and elevated apparent diffusion coefficients measuring extracellular fluid, suggesting a vasogenic mechanism [8, 16, 17].

In an evidence-based review of experimental and clinical data, researchers concluded that hypocapnia and acidosis at onset cause cerebral vasoconstriction and reduced CBF leading to cytoxic edema and brain injury. During fluid administration, rehydration provokes cerebral hyperemia resulting in brain injury due to reperfusion and vasogenic edema [8, 18].

Additionally, different experimental studies suggest that activation of ion transporters in endothelial cells of the blood-brain barrier induced by ketosis, inflammatory cytokines, or hypoperfusion may be responsible for the influx of fluid to the brain [19]. These studies support the hypothesis of injury to the blood-brain barrier. Vavilala et al found increased permeability of the blood-brain barrier in 10 of 13 patients with regional and diffuse CE [20]. Levin has published a review of pathophysiological mechanisms of CE in DKA [21] and concluded that causes and mechanisms are still unknown. CE may be due both to a variable individual response to severe metabolic alterations and/or to treatment-related risk factors.

Collectively then, the bulk of the experimental and clinical evidence currently supports that for whatever reason (and perhaps only in a certain sub-group of patients), alterations in CBF in susceptible patients with DKA leads to (1) cytotoxic edema initially and (2) subsequent vasogenic edema [16, 22]. In other words, CE in DKA is a combination of pre-treatment brain ischemia, cytotoxic edema followed by hyperemia, and, once the fluid deficit has been restored and hyperglycemia has been corrected, vasogenic edema. Based on the above-mentioned data, sudden reduction of plasma osmolality and late fluid reposition should be avoided during treatment. Importantly, CT scans are normal in around 40 % of the children who present with clinical signs of CE, although later studies in these patients often show edema, hemorrhage, or stroke [10, 11]. Therefore, a normal CT scan is not necessarily reassuring, especially in the appropriate clinical context and in the presence of classic signs and symptoms of CE. While prevention of CE is paramount [23], treatment of CE in patients with DKA follows general guidelines of intracranial pressure (ICP) management, including administration of mannitol, 0.25–1.0 g/kg in a bolus dose or 3 % hypertonic saline solution at 5–10 mL/kg over 30 min. Endotracheal intubation may be necessary to protect the airways and to secure adequate ventilation, although hyperventilation should be avoided.

Disorders of Sodium Homeostasis

Electrolyte disturbances generally occur in association with other diseases. Continuous progress in life support and treatment of severe pathologies has given rise to new entities in which these alterations are common caused by either the disease or the therapy. These disorders are a frequent cause of altered levels of consciousness and PICU admission in pediatric patients. The etiology of electrolyte imbalance is varied, but in the majority of cases these are usually related to sodium and/or water loss, such as hypo or hypernatremic dehydration and less often due to pituitary disorders, such as the syndrome of inappropriate antidiuretic hormone secretion and diabetes insipidus [24].

The extracellular fluid (ECF) volume is critically dependent upon normal sodium homeostasis. As cell membranes are in their majority permeable to water, tonicity or osmolality balance between extracellular and intracellular fluid (ICF) compartments will always be equal. Water or solutes gain or loss on either side of the permeable membrane will result in a rapid flow of water until reaching osmotic balance, which is 280–295 mosm/L in organic fluids. Changes in the water balance modify serum sodium concentration and tonicity of body fluids. In response to changes in serum sodium concentration, water flows between the intra- and extracellular compartments to maintain the osmotic balance. This flow has major consequences for the brain. The main mechanisms for the regulation of osmolality are the vasopressin antidiuretic hormone (ADH), the thirst reflex, and the ability of the kidney to dilute and concentrate urine.

Hyponatremia

Hyponatremia is defined as a serum sodium concentration less than 135 mEq/L. This electrolyte disorder occurs in 1.5 % of hospitalized children. Severe hyponatremia with clinical consequences is often observed in children who undergo elective surgeries receiving hypotonic intravenous (IV) solutions. Symptoms of hyponatremia usually do not become evident until serum sodium concentration levels have significantly decreased (generally below 125 mEq/L) and are often mistaken for those of the primary disease process. Unlike in hypernatremia, in which hypertonicity is always seen, hyponatremia may be associated with low, normal, or high tonicity. True hyponatremia is associated with low tonicity (hypotonia) or hypoosmolality due to sodium loss or water excess, and is doubtlessly the most frequent.

Although clinical manifestations of hyponatremia are variable, the most severe effects are exerted on the CNS, and these become more evident the greater the rate and the extent

of the serum sodium concentration drop. The resulting plasma hypoosmolality produces an osmotic gradient through the blood-brain barrier with a subsequent influx of water into the brain cells and development of CE with increased intracranial pressure and finally the typical symptoms. In the setting of ICF hypotonicity, the brain has an adaptive response to protect itself from edema formation. Initially, sodium-rich interstitial fluid flows to the cerebrospinal fluid (CSF) and then passes into the systemic circulation through the arachnoid villi. Cell potassium loss occurs subsequently, reaching its peak after 24 h, followed by the efflux of organic osmolytes (mainly aminoacids) from the brain cells if the situation is prolonged.

These mechanisms of protection render the brain more vulnerable during the correction of the underlying electrolyte disturbance. The recovery rate of potassium and intracellular brain organic osmolytes is much slower during correction than the rate of their loss during the development of hyponatremia. This concept should be kept in mind at the moment of treatment initiation [25].

CE is evidenced by the clinical symptoms of nausea, vomiting, headache, irritability, altered state of consciousness, seizures, and coma with a risk of brain herniation and death or permanent neurological damage. These symptoms, however, do not necessarily occur in this order. Together with blood electrolytes measurement and renal function tests, it is useful to measure urine Na concentration, which provides an accurate estimate of extracellular volume. Urine sodium concentration <20 mEq/L may point to ECF contraction, while severe natriuresis (>20 mEq/L) suggests hypervolemia. Based on the clinical and laboratory findings, hypotonic or true hyponatremia (< 280 mOsm/L) may be divided into three categories:

Hypovolemic Hyponatremia

Total body water decreases and total body sodium decreases to a greater extent leading to a decreased ECF volume. Treatment of hypovolemic hypotonic hyponatremia consists of volume restitution with saline solution, and replacement of deficient electrolytes taking into account the previous deficit + baseline needs + concurrent losses.

Euvolemic Hyponatremia

Normal total body sodium levels without edema, although total body water is mildly increased. Urine sodium concentration exceeds 20 mEq/L. The most frequent entity in this group is the syndrome of inappropriate antidiuretic hormone secretion (SIADH), characterized by urinary sodium loss without corresponding water loss, leading to a decrease in plasma osmolality in the presence of hypertonic urine. The causes of this syndrome are multiple and may be tumors, intrathoracic pathologies, and neurologic diseases. SIADH may also be caused by different therapeutic interventions, such as mechanical respiratory assistance. Many of the drugs that can trigger SIADH are used in critically ill patients: opiates, barbiturates, antiepileptic drugs, antineoplastic drugs, etc. Stress, pain, and fear are also triggering factors. The diagnostic criteria are hypotonic hyponatremia (plasma osmolality <280 mOsm/L), normal volemia, inappropriately high urine sodium concentration, and an elevated urine sodium concentration in the setting of normal water and sodium intake. Kidney and endocrine function are normal. The treatment of choice in cases of very severe hyponatremia and/or neurologic symptoms is fluid restriction and administration of hypertonic (3 %) saline. Currently, different VP receptor antagonists (vaptans) have been developed and are being approved, promising an important change in the treatment of water-retaining disorders and heart insufficiency.

Hypervolemic Hyponatremia

Total body sodium and water are markedly increased with peripheral or pulmonary edema, and the capacity to excrete more water than sodium is retained is impaired.

Acute symptomatic hyponatremia develops over less than 48 h and serum sodium concentration is < a 125 mEq/L. The severity of hyponatremia is closely related to the rate at which it develops. When it develops within less than 48 h, there is a greater risk of acute severe CNS involvement at treatment onset with possible neurological sequelae. Overly rapid or excessive correction of hyponatremia can cause osmotic demyelination syndrome, characterized by often irreversible neurologic impairment, such as quadriplegia, pseudo-bulbar paralysis, seizures, coma, and even death. This process results from too rapid increase of extracellular osmolality leading to excessive loss of intracellular water, leaving the defense mechanisms of the brain no time to revert this situation. The risks for this complication are increased in patients who suffer from malnutrition, liver failure, and hypokalemia.

Increasing the [Na+] 5 mEq/L above the serum sodium concentration at which the symptoms appeared, is usually sufficient for remission. The infusion solution is sodium chloride at 3 % = saline solution at 85 cm^3 + sodium chloride 20 % 15 mL, which solution contains 0.51 mEq/mL. Quantity is calculated according to the following formula: mEq Na infusate = 0.6 × KG body weight × (desired [Na +] − serum [Na+])

An infusion rate of 1–2 mEq/L/h is considered safe. Daily sodium increase should not exceed 12 mEq/L. After the CNS manifestations have resolved, fluid restriction is maintained,

associated with sodium supply if necessary. Serum sodium concentration correction beyond 135 mEq/L over 36 h should be avoided. In the case of chronic symptomatic hyponatremia, the correction rate is 0.5–1 mEq/L/h, with fluid restriction and the use of furosemide, if necessary. In the case of hypervolemia with renal failure, the indication is dialysis, either hemodialysis or hemofiltration according to the hemodynamic state and severity of the patient.

The brain natriuretic peptide, with properties that are similar to the atrial natriuretic peptide, is responsible for the cerebral salt wasting syndrome, associated with severe neurologic pathology and leading to severe natriuresis and polyuria. This entity should be taken into account in the setting of clinical, surgical, or traumatic pathologies of the CNS, as it is often misdiagnosed as diabetes insipidus or even SIADH. In this pathology urinary sodium concentration is >20 mEq/L. Both of these conditions (SIADH and Cerebral Salt-wasting Syndrome) are discussed in greater detail later in this volume.

Hypernatremia

Hypernatremia is defined as an increase of sodium concentration over 145 mEq/L. Hypernatremia may occur in children at any age, but in the majority of cases it occurs in children with severe underlying diseases. The increase of sodium always produces hyperosmolality and hypertonia of the ECF, leading to cellular dehydration and deficit of water relative to total body sodium concentration. When hypertonicity of the ECF increases, the defense mechanisms of the body are activated (thirst and ADH secretion). When one of them fails (e.g., when the patient does not have ready access to water, as in a critically ill patient in the PICU), water shifts from the ICF to the ECF resulting in cellular dehydration. This dehydration is most marked in the brain cells and severity is directly related to the magnitude and rate at which serum sodium concentration is increased. Sudden dehydration of the brain cells induces brain shrinkage, which can tear cerebral blood vessels, leading to cerebral hemorrhage and eventually thrombosis, subarachnoid hemorrhage, and severe neurological impairment. As a defense mechanism, the brain increases intracellular osmolality to maintain the brain volume. Initially, adaptation is fast with electrolytes recovery (within hours), and over time organic osmolytes accumulate (slow adaptation over days). As a consequence, intracerebral osmolality increases and thus, overly fast correction of the disturbance results in a rapid gain of intracerebral water and the development of CE.

Hypernatremia results from a sodium gain or hypotonic sodium loss or from a water deficit. In the former case, the signs and symptoms largely reflect CNS involvement and include periods of lethargy and irritability, high-pitched cry, tremor, altered state of consciousness, and coma additional to signs of dehydration. In the majority of cases and mainly in hospitalized patients, the clinical manifestations are intertwined with the underlying disease process. When the etiology of hypernatremia is excess water, in the PICU the most frequent cause is central diabetes insipidus. In patients with brain trauma or occasionally following a neurosurgical procedure, alterations in the hypothalamic-pituitary axis may occur leading to the development of diabetes insipidus characterized by an inability to retain water. This may also occur in healthy patients or have a nephrogenic nature. Additionally to the manifestations of the electrolyte disorder, the associated neurological symptoms range from irritability and drowsiness to coma. The diagnosis is confirmed by increased plasma osmolality, polyuria, and markedly diluted urine, with a specific gravity of 1.005 or less.

Treatment of hypernatremia should be focused on the underlying causes and the correction of extracellular hypertonia. As in any other setting, when hypovolemia is found, the first step is to restore the intravascular volume with saline solution. Correction should be performed carefully, considering that Na correction should not be exceed more than 6 mEq/L during the initial resuscitation, and the infusion rate should not exceed 1 mEq/L/h. To this end, free water deficit should be calculated with the following formula:

$$\text{Desired total body water}\left(\text{TBW}\right) = \text{Current serum Na} \times \text{Current TBW / Desired Na}$$

$$\text{Desired TBW} - \text{Current TBW} = \text{ml to infuse}$$

Once the initial, life-threatening symptoms have resolved, a balanced salt solution can be used with the goal of not correcting more than 12 mEq/L/day and reducing serum sodium to 145 mEq/L over approximately 48 h. Treatment should also take into account several considerations, including gradual replacement of the previously estimated deficit, replacement of the normal daily maintenance needs, and replacement of any concurrent and ongoing losses. Notably, patients with hypernatremic dehydration secondary to gastroenteritis with water loss exceeding sodium concentration generally do not present with the classic signs of iso- or hypotonic dehydration, as dehydration is essentially intracellular and CNS symptoms predominate.

Hyperammonemia

Ammonia is a byproduct of normal metabolism and is converted to the less toxic substance – urea – in the liver prior to excretion in urine by the kidneys. Hyperammonemia may be caused by congenital deficiency of enzymes of the urea cycle, acute liver failure (ALF), Reye's syndrome, valproic acid or salicylate poisoning, and inborn errors of metabolism (organic acidemias, congenital lactic acidosis, and fatty acid oxidation disorders). Clinical signs and symptoms of

hyperammonemia include altered levels of consciousness that may range from lethargy to coma, dehydration, nausea/vomiting, hypotonia, and a bulging fontanelle (in infants) caused by increased ICP. In the PICU, the most commonly found of these diseases are ALF, Reye's syndrome (largely now only of historical significance), and inborn errors of metabolism, which will be discussed here.

Table 39.8 Classification of hepatic encephalopathy, adapted for infants and children

Grade 1: Confusion, mood changes
Grade 2: Inappropriate behavior, drowsiness
Grade 3: Stupor, but respond to simple stimuli. Drowsy but responds to stimuli and wakes
Grade 4A: Comatose but responds awake to painful stimuli
Grade 4B: Deep coma, do not wakes up with stimuli

Acute Liver Failure (ALF)

ALF is classically described as a severe lesion of the liver in a patient with no recognized underlying chronic liver disease who develops encephalopathy within 8 weeks of symptom onset [26]. However, this definition is not appropriate for pediatric patients who may not develop encephalopathy in the course of the disease or in whom encephalopathy may not become evident until the final stages of the process. A more accurate definition of ALF in pediatric patients has been proposed by the Pediatric Acute Liver Failure Study Group (PALFSG). Using this definition, ALF is present when there is biochemical evidence of liver injury, no history of known chronic liver disease, and coagulopathy not corrected by vitamin K administration (defined further as INR greater than 1.5 if the patient has encephalopathy or greater than 2.0 if the patient does not have encephalopathy) [27]. The true incidence of ALF in children is not known and depends on geographic region. The etiology of ALF varies with age. The most common causes in neonates are metabolic abnormalities, neonatal hemochromatosis, acute viral hepatitis, and unknown (idiopathic) causes. In children older than 1 year viral hepatitis, drugs and unknown causes, as well as non A, non B, and non-C hepatitis are the most common etiologies [28, 29]. The cause of hepatic encephalopathy (HE) is not always ALF. In the International Working Party at the 11th World Congress of Gastroenterology (Vienna 1998), HE was classified according to underlying cause into A: Associated with acute liver failure, B: Associated with portal-systemic shunting without associated intrinsic liver disease, and C: Associated with cirrhosis and portal hypertension. In the pediatric population, type A is the most common [30].

The initial clinical symptoms of ALF are often nonspecific, consisting of general malaise, fatigue, and fever, but may also be more specific characterized by rapid-onset jaundice and severe alterations of liver function. Rapid decrease of liver size is observed together with an increase in serum bilirubin levels and a decrease of serum aminotransferase levels, reflecting generalized hepatocellular necrosis and parenchymal collapse. Clinically, ALF is characterized by coagulopathy, jaundice, and the development of encephalopathy. At this moment, the patient is at risk for developing multiple organ dysfunction syndrome (MODS), characterized by generalized vasodilatation which results in increased cardiac output and reduced systemic vascular resistance and mean arterial pressure. These circulatory changes may lead to acute kidney injury (AKI), which is common and is associated with worse prognosis. The incidence of AKI in this population is as high as 50–80 %. HE has been classified into four grades, from 1 to 4B. Children with grades 3, 4A, and 4B are likely candidates for liver transplantation (Table 39.8).

Severe HE is associated with a poor prognosis. The development of CE, and as a consequence, increased ICP is the main cause of death in patients with ALF. HE generally appears 48–72 h before the onset of CE. Of all patients who develop HE, 80 % present with cytotoxic CE and 30–50 % have increased ICP. There are differences between HE and CE, although the pathogenesis may be the same. There are three main causes of HE in patients with ALF, all of which are interrelated – hyperammonemia, cerebral vasodilation leading to increased ICP, and an increased systemic inflammatory response. Ammonia metabolism within the astrocytes is directly related to CE due to the increase in intracellular osmolality. The net increase of water content defines the presence of CE, although hyperammonemia in itself does not predict increased ICP. Hyperammonemia indirectly stimulates the generation of nitric oxide, causing secondary vasodilation and increased ICP. Increased levels of mercaptans, short-chain fatty acids, aromatic aminoacids, endogenous benzodiazepines, phenols, manganese, gamma-aminobutyric acid (GABA), and glutamate also play a role in the pathogenesis of HE, explaining why in some cases no relationship is found between serum ammonia levels and the grade of encephalopathy [31, 32].

The main aims of treatment for HE are prevention itself, reduction of the ammonia load, correction of the electrolyte and metabolic alterations, treatment for possible infection, treatment of CE, surveillance for MODS, and emergency liver transplantation. In HE stage III–IV, the patient should be adequately sedated, tracheally intubated, and mechanically ventilated. The most important aspects to take into account are the predisposition to develop hypoglycemia and loss of nitrogen, especially in patients treated with extracorporeal support systems. Glucose should be administered continuously at 4–10 mg/kg/min. In addition, prolonged periods of protein restriction are to be avoided. Parenteral nutrition significantly decreases protein catabolism. Laxatives should be used to reduce the luminal content ammonia. Lactulose, a non-absorbable disaccharide, is

metabolized by the intestinal bacteria providing acidification of the colonic secretions reducing and facilitating cathartic action. Antibiotics also reduce the production of intestinal ammonia. The most frequently used are neomycin and metronidazole, although in the case of the latter neurotoxicity should be taken into account. Neomycin may be administered in combination with lactulose. Hyperthermia should be avoided and the patient should be maintained normothermic and normoventilated.

The treatment of intracranial hypertension is covered elsewhere in this textbook. However, suffice it to say that many of the same principles apply to the patient with HE and increased ICP. First and foremost, imaging is not a useful modality to assess the evolution of HE or the presence of increased ICP. In many patients with increased ICP secondary to HE, initial head CT may in fact be normal. Direct measurement of ICP is the only way to determine if there is increased ICP. Unfortunately, ICP monitoring in this clinical setting is controversial [33, 34]. The main concern with ICP monitoring is the risk of intracranial bleeding as a complication of catheter insertion. Thus, the risk of complications must be weighed against the benefits of the procedure. A careful neurologic evaluation should be performed and coagulopathy should be controlled to allow safe insertion of the catheter. Recent studies suggest administration of activated factor VII, fresh frozen plasma, and platelets 30 min previous to the procedure [35–37]. The best candidates for ICP monitoring are those patients with progressive encephalopathy who have an outlook for spontaneous recovery or those who are on the waiting list for liver transplantation.

Hyperventilation as a means to lower ICP is no longer recommended. While hyperventilation has been shown to reduce ICP by lowering PaCO2 and thereby reducing CBF, it may also reduce CBF to critical levels and increase cerebral lactate production as a result of precapillar vasoconstriction and local hypoxia. Hyperventilation should only be used for emergency treatment of refractory increased ICP (i.e. impending herniation).

The mainstay of ICP management is the use of osmotherapy. Mannitol or 3–7 % hypertonic saline may be used in this clinical setting to reduce ICP. Mannitol reduces brain water and improves cerebral blood flow, although its repeated use may allow entry into cerebral tissue and exacerbate cerebral edema. Administration of hypertonic saline to induce hypernatremia (>150 mEq/L) is especially useful to lower increased ICP and keep it at adequate levels [38, 39].

While therapeutic hypothermia at a core temperature of 32–33 °C has been shown to effectively reduce ICP levels to normal levels, the currently available studies have not shown a reduction in mortality. Therapeutic hypothermia in this setting therefore remains controversial. Arterial ammonia levels and cerebral oxygen consumption may be diminished, and reduced cerebral hyperemia and improved cerebral perfusion pressure are observed. The main risks associated with therapeutic hypothermia are infection and bleeding. Mild hypothermia may be used in patients with CE refractory to conventional therapy. The duration and degree of hypothermia have not been adequately evaluated and a multicenter study on the use of hypothermia in ALF should be performed [40].

Aside from general supportive care and ICP-focused management, there are several other options to managing critically ill children with HE. Intravenous N-acetylcysteine has shown to improve survival in mild or moderate cases in adults with acute HE [41, 42], though a recently published pediatric trial showed no benefit [43]. In ALF due to Hepatitis A virus (HAV) or toxic causes, the liver has the capacity for spontaneous regeneration. Indeed, 20–30 % of patients are expected to recover with medical treatment alone. The prognosis of ALF has improved considerably with the advent of emergency orthotopic liver transplant (OLT), which is now the most important treatment option. Nevertheless, OLT does have some limitations, including shortage of donors, long waiting lists, and ALF due to HAV in endemic regions. The concept of bridging patients to OLT or recovery with led to the development of extracorporeal liver support techniques. These modalities substitute the complex metabolic functions of the liver and help to reduce the risk of MODS, which may lead to death of the patient [44]. Extracorporeal liver support techniques are based on the elimination of circulating toxins that have been generated or were not metabolized by the damaged liver. Among the currently used devices is the molecular adsorbent recirculating system (MARS). MARS is the most widely studied extracorporeal liver support technique with a detoxifying function which allows to prolong the survival time of patients with liver failure in good conditions until an organ has become available or until the native liver recovers function, even allowing for recovery of analytical coagulation parameters. It consists of the circulation of the patient's blood through a depuration system of charcoal in combination with albumin and a second system of hemodialysis. It is based on a countercurrent dialysis system using albumin as the transporting medium for toxins to achieve more selective detoxification [44]. The device is used in chronic liver disease in the context of acute decompensation or in patients with acute liver failure. It is currently also applied after initial transplant dysfunction. Other extracorporeal liver support techniques are available (e.g., Prometheus), but are more difficult to use in pediatrics due to the necessary high volumes required.

High-flow continuous venovenous hemodiafiltration (CVVHDF) has also been used as a supportive modality in critically ill patients with HE. Ammonia can be removed by dialytic methods, and CVVHDF is the usual renal replacement therapy. CVVHDF reduces vasopressor requirements in septic shock possibly due to modulation of proinflammatory

Table 39.9 Diagnostic criteria of Reye syndrome

Acute noninflammatory encephalopathy-(documented clinically by an altered level of consciousness and, if possible, a CSF leukocyte count less than or equal to 8 per mm^3 or a histological study demonstrating cerebral edema without perivascular or meningeal inflammation)
Liver disease with liver biopsy showing fatty infiltration or increased more than three times the upper limit of normal values for plasma GOT, GPT and/or ammonium
No clinical explanation for these findings
Clinical diagnosis is not conclusive and there are no specific tests, so the diagnosis is made by exclusion

mediators. A preliminary investigation in patients with ALF showed similar benefits [45, 46]. Extracorporeal renal support also provides an opportunity for improved management of CE allowing removal of fluid and reducing ammonia concentration. There is a paucity of controlled studies to firmly support the use of these different therapeutic options. Until such studies will be performed, however, each patient should be evaluated individually and treatment should be selected based on the experience of each center [47].

Reye's Syndrome

Reye's syndrome (RS) is a mitochondrial lesion of unknown cause manifesting as acute encephalopathy associated with liver failure and infiltration of fat into different organs, especially the liver [48]. Numerous modifications have been made to the initial definition established by the Centers for Disease Control and Prevention in the United States in 1990 [49] (Table 39.9). Although the etiology of RS remains unknown, it has been associated with different viral infections. Influenza type A, influenza type B, and varicella-zoster virus have been most frequently implicated, but others, such as parainfluenza, adenovirus, coxsackie A and B, echovirus, Epstein-Barr, rubella, measles, cytomegalovirus, herpes simplex virus, parainfluenza, and poliomyelitis virus have also been associated with RS as well. RS may manifest after vaccination with live, attenuated virus, with active viral infection, or with salicylate intake. Microscopic and spectrometry studies have shown aspirin to cause or exacerbate mitochondrial damage [50, 51].

RS is a typically pediatric disease, mainly occurring in children between 5 and 15 years of age without gender preference, however, rare cases in adults have also been observed. The disease is potentially lethal and early diagnosis and adequate management in the PICU is essential to diminish morbidity and mortality. Over the past few decades, congenital metabolic defects with Reye's-like clinical manifestations have been described, such as amino- and organoacidopathies, urea cycle defects, and disorders of the fatty acid – and beta oxidation metabolism, specially medium-chain acetyl-CoA dehydrogenase defects [52]. Both the discovery of these diseases and the decreased use of salicylates in children and adolescents since 1980 have led to a lower incidence of this disease to currently less than 0.03–1 case per 100,000 persons younger than 18 years in the United States [53]. According to the current consensus, in a child with suspected RS, inborn errors of metabolism should be ruled out. An inborn error of metabolism is very likely and should be strongly suspected in the following scenarios:

1. Symptom recurrence or precipitating factors, including prolonged fasting, change of diet, or some type of associated metabolic stress
2. Compatible clinical findings in a relative
3. Absence of a viral prodrome
4. Occurrence in children younger than 3 years, especially younger than 1 year
5. Occurrence in children younger than 3 years, especially younger than 1 year
6. Preexisting growth failure
7. Preexisting neurological alterations.

The pathogenesis of RS is not clear, but a mitochondrial defect seems to exist inhibiting oxidative phosphorylation and beta-oxidation of fatty acids due to a viral infection in a sensitivized host. Histological changes include fat vacuolization of the hepatocyte cytoplasm, edema, loss of brain neurons, and fatty infiltration of the renal tubules. Hepatocellular dysfunction generates hyperammonemia, leading to CE and increased intracranial ICP.

In the typical case, patients start with a viral prodrome (upper respiratory tract infection, varicella, or gastroenteritis) during the initial phase that is followed several days or weeks (mean 3 days) later by the sudden-onset profuse vomiting and altered state of consciousness. Neurological symptoms generally appear 24–48 h after the first symptoms appear. Lethargy is in most cases the first neurologic symptom, followed by irritability, delirium, seizures, or coma. The degree of neurological impairment varies and is determined by the grade of CE and the presence of increased ICP. A staging system of encephalopathy was initially described by Lovejoy [54], although subsequent modifications were made (Table 39.10). RS is associated with hepatomegaly in 50 % of the cases. Characteristically, jaundice is not found or is minimal. Serum ammonia levels are usually 1.5- to 2-fold the upper limit of normal, 24–48 h after onset of the neurological signs and symptoms, but tend to normalize in stages IV–V. Transaminases, ALT and AST, increase up to three times and also return to normal in the more advanced stages of encephalopathy. Bilirubin is low, generally <3 mg/dl. If bilirubin is found to be higher or direct bilirubin is greater than 15 %, other diagnoses should be considered. Prothrombin time and partial activated thromboplastin time are more than 1.5 fold increased in 50 % of the cases. Levels of coagulation factors II, VII, IX, and X as well as fibrinogen are low. Lipase and amylase, BUN, and creatinine are elevated. Hypoglycemia is a diagnostic finding, especially in infants younger than

Table 39.10 Stages of encephalopathy in Reye Syndrome

	I	II	III	IV	V
Level of consciousness	Lethargy obeys orders	Agitation /stupor, inappropriate words	Coma	Coma	Coma
Posture	Normal	Normal	Decortication Extension	Decerebration Flexion	flaccidity
Locate response to pain	Locate	Locate/flex	Decortication Extension	Decerebration Flexion	absent
Pupillary reactivity	Normal	Slow	Slow	Slow	absent
Oculocephalic reflexes	Normal	conjugate deviation	conjugate deviation	Indifferent or absent	absent

Based on data from Ref. [54]

1 year. The anion gap is normal. The CT scan is generally normal, although diffuse CE may be found [55].

No specific treatment exists and thus supportive management should be individually tailored to each child and for each clinical stage. Early suspicion and aggressive treatment of electrolyte imbalances, hypoglycemia, and hyperammonemia are crucial to minimize mortality and maximize neurologic recovery. The aim is to prevent and control CE. ICP monitoring is controversial. A worse outcome is expected when the disease occurs in a child younger than 2 years, serum ammonia levels are elevated, encephalopathy is grade IV–V or there is rapid progression from I to III, and when there is an association of increased liver transaminases and elevated muscle enzymes. No consensus exists on the cut-off point for serum ammonia to determine risk of mortality, nevertheless high levels of serum ammonia are the best predictive factor for mortality.

Inborn Errors of Metabolism and Mitochondrial Disorders

Generally, inherited metabolic disorders (IMD) or inborn errors of metabolism and mitochondrial disorders (MD) are clinically manifested by acute encephalopathy. They occur in apparently healthy children without previous symptoms. The initial clinical signs may be mistaken for behavioral disturbances. At onset, the children do not show focalized neurological signs and progression to stupor and coma is irregular, with alternating periods of alertness and obtundation.

Acute encephalopathy of infancy, a Reye's-like syndrome, is a common presentation of IMDs , especially of fatty acid oxidation disorders. The most common IMD is medium-chain acyl-CoA dehydrogenase (MCAD) deficiency. Affected children are healthy during the first 2 years of life. After that, they may develop general malaise, anorexia, vomiting, hypotonia, lethargy, and obtundation. Impaired consciousness rapidly progresses to stupor and coma associated with hepatomegaly, liver failure, hypoglycemia, and moderate hyperammonemia. The IMD is triggered by an infectious disease and/or fasting. Although clinically the disorder is indistinguishable from RS, onset in the first years of life, family history, and recurrence during an infectious episode or fasting are findings suggestive of MCAD deficiency and other fatty acid oxidation defects. The diagnosis is confirmed by organic acid levels in urine during an episode of decompensation and by the study of serum aminoacids. Carnitine and acyl carnitine measurements are useful for the differential diagnosis.

Other fatty acid oxidation disorders as a cause of acute encephalopathy are less common. Carnitine deficiency and long-chain acyl-CoA deficiency may present with Reye's-like clinical manifestations, but are generally associated with muscle disorders. Even less frequently found are hyperammonemias (citrulinemia, argininemia, ornithine transcarba moylase deficiency, urea cycle defects) and organic acidopathies (e.g., maple syrup disease). The clinical features are vomiting at disease onset, altered levels of consciousness, metabolic acidosis, increased lactic acid levels, hypoglycemia, and hyperammonemia. Urea cycle defects and organic acidemias may have an acute presentation with seizures and encephalopathy, in some cases triggered by processes that increase protein breakdown, such as infection or multiple trauma. The diagnosis is confirmed by the measurement of serum lactic acid, ammonia, aminoacids, and carnitine and acyl carnitine levels and urine organic acid levels. Defects in gluconeogenesis, such as galactosemia, may manifest with hypoglycemia and secondary encephalopathy.

Mitochondrial and peroxisomal disorders are a complex group of diseases with clinical manifestations of acute onset associated with acidosis and shock or only encephalopathy in the neonatal period and during infancy. These disorders are the result of a nuclear or mitochondrial DNA mutation and are characterized by transport defects (e.g. carnitine, acetyl carnitine) and substrate oxidation (e.g. Krebs cycle, fatty acid, and pyruvate deficiencies and respiratory chain defects). The most common mitochondrial disorders are mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes (MELAS) and myoclonic epilepsy and ragged-red fibers (MERRF). In some mitochondrial disorders, patients have lactate levels that are normal in serum but elevated in CSF, suggesting a brain mitochondrial disorder. MRI findings are suggestive of mitochondrial disease. Cerebral hemorrhage is common in MELAS. Hemorrhages in the thalamus and midbrain are common in Wernicke's encephalopathy, which is due to a thiamine-responsive

Table 39.11 Allograft-specific neurologic complications

Allograft	Syndrome	Manifestations
Liver	Central pontine myelinolysis	Stupor, quadriparesis
Heart	Cardioembolic stroke	Focal weakness, numbness, aphasia
Kidney	Diabetic neuropathy	Weakness, numbness, neuropathic pain
Lung	Phrenic nerve palsy	Dyspnea
Bone marrow	Graft-versus-host disease	Weakness, myalgia (polymyositis)

Reprinted from Živković and Abdel-Hamid [55]. With permission from Elsevier

Table 39.12 Neurotoxic effects of immunosuppressive medications

	Common	Uncommon
Corticosteroids	Tremor (*mild*), dysthymia	Epidural lipomatosis, psychosis
Tacrolimus, cyclosporine	Tremor, headache, confusion, PRES	Ataxia, polyneuropathy, CRPS
Sirolimus	Tremor, headache	PRES, CRPS
Mycophenolate	Headache	
Muromonab	Aseptic meningitis	

CRPS complex regional pain syndrome, *PRES* posterior reversible encephalopathy syndrome
Reprinted from Živković and Abdel-Hamid [55]. With permission from Elsevier

reduction in the activity of enzymes such as pyruvate dehydrogenase that are necessary for carbohydrate oxidation. Wernicke's encephalopathy and the mitochondrial encephalopathies of infancy may present with hypothermia without other evidence of shock, presumably due to hypothalamic injury. Leigh's syndrome, also known as subacute necrotizing encephalopathy presents in infancy with symmetrical injuries to the basal ganglia and thalamus, deep white matter, brain stem, cerebellum, and spinal cord, with relative sparing of the cerebral cortex.

Post-transplant Encephalopathy

Altered states of consciousness are common after organ transplantation, occurring in up to 20 % of patients, and may range from delirium to stupor and coma [56–58]. The etiology is multifactorial, related to the surgical procedure, primary dysfunction of the graft, opportunistic infections, and neurotoxicity of the immunosuppressive drugs. The underlying disease, age, previous malnutrition, and delay to transplant increase the risk of post-transplant encephalopathy [59, 60]. Characteristically, the etiology varies according to the time lapsed after transplantation. Immediately after transplantation, brain damage may be due to hypoxia during the surgery, associated with cardiorespiratory arrest, hemodynamic alterations, or primary graft dysfunction. Later, toxic and metabolic disorders and opportunistic infections prevail.

Viral CNS infections may be due to the reactivation of a latent infection or a newly acquired infection. The most common causes of viral encephalitis are herpes viruses 1 and 2 (HSV 1 and 2), varicella-zoster virus (VZV), Epstein–Barr virus (EBV), and cytomegalovirus (CMV). Toxoplasmosis is the most-common parasitic infection and is related to the reactivation of a previously latent infection.

Altered levels of consciousness are also associated with metabolic disorders, such as hyperammonemia, elevated urea levels, and glucose imbalance (hypo- or hyperglycemia). Central pontine myelinolysis is rare in pediatric patients, but may be observed in liver allograft recipients and manifests with pseudobulbar palsy and stupor and generally occurs in the first weeks after transplantation (Table 39.11). Many of these share the same features as the ones discussed previously in the paragraphs above.

In the clinical setting, neurotoxic effects of immunosuppressive drugs, specifically calcineurin inhibitors (tacrolimus, cyclosporine) are frequently seen. Symptoms of neurotoxicity are mainly seizures, although altered levels of consciousness and even cortical blindness may be observed in some patients [61]. These symptoms have diminished with the oral administration of the drugs avoiding the intravenous route in the immediate post-operative period [62–65]. Corticosteroids are associated with tremor, myopathy, steroid psychosis, metabolic disorders, and epidural lipomatosis. Neurological complications have also been observed with other immunosuppressive drugs, such as antilymphocytic antibodies and antithymocytic antibodies (aseptic meningitis), mycophenolate (headaches), and sirolimus [66] (Table 39.12). Impaired renal function may precipitate neurotoxicity and so may the administration of drugs that are metabolized in the kidney, such as acyclovir, cephalosporins, and benzodiazepines. Neurological complications seem to be less frequent and more severe in pediatric patients. Nevertheless, due to the plasticity of the brain recovery is good, without long-term neurological impairment [67, 68].

Immune-Mediated Encephalopathies

Acute disseminated encephalomyelitis (ADEM) is an immune-mediated disease caused by viral infections, predominantly of the upper respiratory tract, and after immunization. The clinical features include altered state of consciousness of acute onset, seizures, myelopathy, and other

neurological manifestations. ADEM may be associated with optic neuritis. The clinical diagnosis is confirmed by the MRI showing typical focal disseminated lesions in the white matter, basal ganglia, and brain stem consisting of edema, inflammation, and demyelinization, enhancing following gadolinium administration. Hemorrhage may be seen in the white matter. An MRI of the spine may be helpful to support the diagnosis of ADEM as the process is usually accompanied by myelopathy. Early diagnosis is important for a better response to administration of high-dose steroids and/or immunoglobulin therapy.

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CNS Infections

40

Simon Nadel and Mehrengise Cooper

Abstract

Infections affecting the Central Nervous System (CNS) in children have a varied and unpredictable outcome, often with a high morbidity and mortality, despite advances in available antimicrobial therapy and other adjunctive modes of treatment. Death or permanent disability is a common occurrence.

Keywords

Meningitis • Encephalitis • Malaria • Intracranial collections • Shunt infection

Introduction

Central nervous system (CNS) infections have a varied and unpredictable outcome, often with a high morbidity and mortality. There are many different causative organisms which initiate a variety of pathological processes leading to the resulting clinical patterns. The subsequent conditions include meningitis, encephalitis, intracerebral abscesses, transverse myelitis, and non-infectious complications of systemic infection such as HIV. The offending organism varies with age, immune function, and immunization status of the patient. While much of the focus in the management of these conditions is on the eradication of a pathogen, many of these patients require organ-specific supportive care, including mechanical ventilation, and neuroprotective strategies where there is intracranial hypertension.

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Meningitis

Although the spectrum between meningitis and encephalitis is wide, it is important to understand the pathophysiological processes which take place that lead to meningitis and encephalitis. Meningitis is an inflammation of the pia and arachnoid meninges that surround the brain and spinal cord.

Acute Bacterial Meningitis

Acute bacterial meningitis (ABM) remains a serious global health threat with high mortality and morbidity, despite advances in antibiotic therapy and modern vaccination strategies. Children are particularly vulnerable to ABM because of their relatively immature immune systems. It has been estimated that over 75 % of all cases of ABM occur in children under 5 years of age, and it is one of the most common life-threatening infections in children. The WHO estimates that about 170,000 deaths occur annually from the disease worldwide. The case fatality rate can be as high as 50 % if inadequately treated [1, 2]. The estimated median risk of at least one major or minor sequela from ABM after hospital discharge is 19.9 % (range 12.3–35.3 %) [3]. Adverse outcome varies with age group, geographic location, and the infecting organism. In middle- and low-income countries, ABM remains the fourth leading cause of disability.

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The definitive diagnosis of ABM requires the isolation of the pathogen from cerebrospinal fluid (CSF). If for clinical reasons, obtaining CSF is not possible, a clinical diagnosis of meningitis can be made by the finding of clinical signs of meningeal irritation (nuchal rigidity or neck stiffness; positive Kernig's sign – painful extension of the knee when the thigh is flexed at the hip and knee at 90° angles; or Brudzinski's sign – involuntary lifting of the legs when the patient's head is lifted off the examining table), together with positive blood culture, latex agglutination test for bacterial polysaccharide in blood or urine, or positive polymerase chain reaction for bacterial DNA in blood. Definitions of CNS infection have been recently proposed and for meningitis are divided into definite, probable, or possible bacterial meningitis (Table 40.1) [4].

Table 40.1 Definitions and clinical features of acute bacterial meningitis in infant and children > 8 week of age

Bacterial meningitis in infants and children >8 weeks old
Definite bacterial meningitis
Compatible clinical syndrome+
All ages: fever, 94 %
1–5 months: irritability, 85 %
6–11 months: impaired consciousness, 79 %
>12 months: vomiting, 82 %, neck rigidity, 78 %
+ positive culture of CSF or positive CSF Gram stain, or bacterial antigen
Probable bacterial meningitis
Compatible clinical syndrome +
Positive blood culture + one of the following CSF changes
>5 leucocytes, glucose < 0.5 CSF/serum ratio, protein >1 g/l
Possible bacterial meningitis
Compatible clinical syndrome +
One of the following CSF changes
>100 leucocytes, CSF/serum glucose ratio <0.5, protein >1 g/l +
Negative cultures or antigen for bacteria, viral, fungal, or mycobacteria
Neonatal meningitis <8 weeks old
Compatible clinical syndrome +
Isolation of likely pathogenic organism from CSF or positive bacterial antigen
Or abnormal CSF consistent with bacterial infection

Following ABM, a poor outcome is common with death or serious long-term sequelae occurring in up to 50 % of patients, depending upon age, causative organism, and clinical status at presentation [5]. The incidence of ABM worldwide is difficult to ascertain because of wide variation in surveillance in different regions of the world, together with underreporting from many developing nations. The incidence is approximately 1–3 cases per 100,000 population per year in the developed world [6]. During pandemic meningococcal meningitis in Sub-Saharan Africa, attack rates exceed 100–800 cases per 100,000 population per year, with the highest attack rates reaching as high as 1 in 100 [7].

Etiology

Most of the human pathogenic bacteria can cause meningeal infection, but three bacterial species, namely *Haemophilus influenzae* type b (Hib), *Streptococcus pneumoniae*, and *Neisseria meningitidis*, are responsible for over 90 % of reported ABM cases in the world beyond the neonatal period [3]. However, the epidemiology of ABM has changed dramatically in the last two decades with the introduction of new, highly effective vaccines.

Prior to introduction of the conjugate polysaccharide vaccine against Hib, Hib was the most common cause of ABM worldwide. More recently, *S. pneumoniae* and *N. meningitidis* have become the most common causes of ABM due to a dramatic decline in the incidence of Hib meningitis [8]. International efforts to tackle the problem have taken a new direction since recent epidemiologic data revealed that Hib and pneumococcus are directly responsible for as many childhood deaths as HIV/AIDS, malaria, and tuberculosis combined [3]. Causative organisms of ABM vary according to the population studied, age of the study group, and geographic area studied. Table 40.2 lists the causes of ABM according to age and underlying conditions. The microbial epidemiology of meningitis is also changing in older children and adults, in whom nosocomial meningitis accounts for an increasing proportion of infections. Many of these are associated with recent neurosurgical intervention or trauma. In such cases, *Pseudomonas aeruginosa*, enterococci,

Table 40.2 Causes of acute bacterial meningitis according to age and underlying condition

Age	Organisms
<1 month	*Streptococcus agalactiae* (Group B Streptococci), Enteric bacilli (*Escherichia coli*, *Klebsiella pneumoniae*, Proteus spp.), *Listeria monocytogenes*
1–3 months	*S. agalactiae* (Group B Streptococci), Enteric bacilli (*E. coli*, *K. pneumoniae*, Proteus spp.), *L. monocytogenes*, *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae* type b (Hib)
3 months to 5 years	*S. pneumoniae*, *N. meningitidis*, Hib
>5 years	*S. pneumoniae*, *N. meningitidis*
Immunocompromised	*S. pneumoniae*, *N. meningitidis*, Hib, *L. monocytogenes*, Gram negative bacilli, Salmonella species, *Enteric bacteria*, *Pseudomonas aeruginosa*, *Cryptococcus neoformans*, other fungi, *Nocardia* spp.
Post-neurosurgery, post neurotrauma, CSF shunt	*S. pneumoniae*, *N. meningitidis*, Hib, *Staphylococcus aureus*, Coagulase-negative staphylococci, Gram-negative bacilli, *Streptococcus pyogenes*, enterococci

Staphylococcus aureus, and the coagulase-negative staphylococci are the most common causative organisms.

In neonates, pathogens causing meningitis are usually acquired from the maternal genital tract during delivery. These pathogens include *Streptococcus agalactiae* (group B streptococci), *Escherichia coli* and other organisms that colonize the perineal area. Neonates are also at risk of infection from *Listeria monocytogenes*, acquired transplacentally. Neonates are particularly vulnerable to bacterial infections because of their immature humoral and cellular immunity and phagocytic function, in addition to the fact that their inefficient alternative complement pathway compromises their defense against encapsulated bacteria [9]. In addition, preterm infants do not get adequate transplacentally-derived maternal immunoglobulins [10]. The incidence of neonatal meningitis is approximately 0.3 per 1,000 live births in industrialized nations [11]. It is difficult to estimate the incidence in developing countries due to under-developed surveillance systems. Some reports have suggested an incidence as high as 6.1 per 1,000 live births in Africa and South Asia [12]. Mortality has decreased significantly in developed countries from nearly 50 % in the 1970s to <10 % in the last two decades [13]. However, long-term complications are still a major cause of concern, especially neuromotor disabilities such as cerebral palsy [14]. Group B streptococcus (GBS) is the most common cause of neonatal meningitis in the developed world, accounting for nearly 50 % of all cases, followed by *Escherichia coli* (20 %) and *Listeria monocytogenes* (5–10 %) [15]. Intrapartum antibiotic chemoprophylaxis in high-risk groups has reduced the incidence of early onset GBS disease, although the incidence of late-onset GBS disease has remained unchanged [16]. There is some evidence to suggest that Gram-negative bacilli, including Klebsiella and *E. coli*, are more common in underdeveloped nations in comparison with developed nations [13].

Pathophysiology

Bacterial invasion of the CSF causes a host inflammatory response, and ultimately it is this response which results in neuronal damage and death and the subsequent morbidity and mortality. Infecting pathogens reach the CSF by hematogenous spread following colonization of the skin, the mucosal surface of the nasopharynx [17], or the respiratory or gastrointestinal tract. The organisms then translocate across the endothelial cells of the blood-brain barrier (BBB) in order to reach the CSF. Once in the CSF, bacterial products (e.g. peptidoglycan, techoic acid, endotoxin) stimulate the production of pro-inflammatory cytokines [8–10], including Tumour necrosis factor-alpha (TNF-α), interleukins 1-beta and 6, (IL-1β, IL-6)), and other mediators (e.g. Nitric Oxide (NO), reactive oxygen species). The activation of inflammatory activity occurs via sensing of bacterial products by host-cell receptors including the Toll-like receptors (TLR) 2 and 4, as well as the TLR-co-receptor MyD88 [18]. This leads to influx of leukocytes into the subarachnoid space, which is further enhanced following the induction of endothelial-derived adhesion molecules on the cerebral endothelium [19]. These blood-derived leukocytes, pro-inflammatory cytokines, and other inflammatory mediators cause an increase in BBB permeability, resulting in the leakage of plasma proteins into the CSF, further contributing to the development of cerebral edema and subsequent neuronal damage. The damaged cerebral endothelial cells leads to vasospasm and thrombosis, resulting in abnormal cerebral vascular autoregulation and a reduction in cerebral perfusion, and therefore further neuronal damage.

The inflammatory effects of cytokines are opposed (counterregulated) by the anti-inflammatory cytokines, which include IL-10 and transforming growth factor-beta (TGF-β). It is the inflammatory response to an invading organism rather than direct effects of the pathogen itself, which appears to cause most of the damage leading to morbidity and mortality in ABM.

In older children, ABM is usually acquired via haematogenous spread, and the most common infecting organisms are *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* (type b) (Hib)[6]. Routine vaccination programs primarily in the developed world have practically eradicated bacterial meningitis due to Hib. Meningitis due to *Listeria monocytogenes* may also occur in the immunocompromised. In addition, direct invasion by skin, respiratory pathogens and nosocomial infection may occur following trauma and neurosurgical interventions [20]. The organisms that predominate under these circumstances include *Pseudomonas aeroginosa*, enterococci, *Staphylococcus aureus* and the coagulase negative staphylococci. Table 40.2 lists the pathogens associated with acute bacterial meningitis according to age.

Clinical Manifestations

The classical signs of meningitis include fever, headache, photophobia, vomiting, neck stiffness (i.e., nuchal rigidity) and an altered level of consciousness or mental status, including seizure activity. In young children and infants, the signs may be non-specific and fever may be absent [21]. Where a child has fever with an altered level of consciousness, meningitis must be high in the differential diagnosis.

Diagnosis

Obtaining cerebrospinal fluid (CSF) for culture is the gold standard investigation for the diagnosis of meningitis. When performing a Lumbar Puncture (LP), it is essential to measure and record CSF opening pressure (normally, <15 cm H_2O), appearance, cell count and type, glucose, protein, gram stain, microbiological culture (including for viruses and fungi), viral and bacterial PCR, and stain for acid-fast

bacilli if indicated. Prompt diagnosis is essential, as a delay in commencing antibacterial therapy may be associated with an increased likelihood of morbidity, although the clinical evidence to support this assumption is lacking [22].

Purulent meningitis is associated with intracranial hypertension, and brain-stem or tentorial herniation may occur even in the absence of lumbar puncture (approximately 5 % of cases). Taking an accurate history, with appropriate recognition of the early systemic and neurological signs of meningitis allows an informed decision about whether a lumbar puncture can be performed safely [23]. Performing a lumbar puncture in the presence of intracranial hypertension may cause cerebral herniation. If signs of raised ICP are present, it is not safe to undertake a lumbar puncture even in the presence of normal brain imaging [24]. In addition, lumbar puncture is contraindicated when there is significant respiratory and/or hemodynamic compromise, in the presence of a bleeding diathesis, in the presence of focal neurological signs and a fluctuating or significantly reduced (GCS $\leq$ 13) level of consciousness (which usually indicates raised intracranial pressure). If there will be a delay in performing lumbar puncture, due to concerns about clinical status, it is important to start appropriate antimicrobial therapy as soon as possible. Table 40.3 shows the typical CSF findings in the differentiation between different types of meningitis.

There are several indications for obtaining radiologic imaging of the brain in a child with suspected or confirmed meningitis. The differential diagnosis for a child presenting with fever and signs of intracranial infection is broad. In addition, the complications of CNS infection include intracranial hypertension and the presence of a space occupying lesion, which also may be evaluated with radiologic imaging. However, some studies have suggested that radiologic imaging plays a relatively limited role in the clinical management of children admitted with fever and altered mental status in the absence of focal neurological signs [25, 26]. In addition, cranial CT scans have a poor correlation with the detection of intracranial hypertension, and therefore determining the safety of lumbar puncture [27].

However, abnormal CT findings in children with ABM include subdural effusion, focal infarction, mild ventricular widening, contrast enhancing basal meninges, cerebral edema, and pus and widening in the basal cisterns [28]. Focal infarction and pus in the basal cisterns were associated with long-term neurological sequelae. Transient dilatation of the subarachnoid space is a relatively common finding, though not necessarily associated with long-term sequelae [29]. Performing imaging for prognostication appears to be of benefit [30]. All children had neurological impairment at the time of CT, and during follow up, those with mild or moderate changes recovered without neurological sequelae, whilst those with severe changes suffered severe sequelae.

Partially Treated Bacterial Meningitis

Up to 50 % of children with meningitis receive oral antibiotics before a definitive diagnosis is made due, often to a non-specific presentation [31]. This partial treatment often leads to delay in presentation to hospital and may cause diagnostic confusion [32]. CSF cultures may be rapidly sterilized, although cellular and biochemical changes will persist. The only bacterium whose growth is likely to be significantly affected following oral antibiotic administration is meningococcus, and this is thought to be due to the high sensitivity of the organism to low concentrations of antibiotics [33]. It is essential that CSF is sent for PCR and bacterial antigen detection as these will not usually be affected by the low CSF antibiotic concentrations found following oral administration.

Treatment

The management of ABM requires specific antimicrobial agents, as well as organ specific supportive treatment targeted at reducing raised intracranial pressure with neuroprotective strategies. Bacterial multiplication within the CSF occurs quickly owing to a poor host immune response at this relatively immune-isolated site [34]. The CSF contains relatively low levels of specific antibody and complement, resulting in poor opsonisation and phagocytosis [35].

Some children may require tracheal intubation and mechanical ventilatory support. These measures may occur for the following reasons: treatment of intracranial hypertension, seizure management, coma, shock, acidosis, and the respiratory depression that sometimes follows antecedent anti-convulsant medication. The best factors that predict outcome in ventilated patients are the admission Pediatric Risk of Mortality (PRISM) score, hypotension and tachycardia within the first 24 h were associated with worse outcome [36].

Neuroprotective Strategies and the Management of Raised Intracranial Pressure

All patients with bacterial meningitis will have evidence of raised intracranial pressure [37]. Raised intracranial pressure together with cerebral vasculitis and cerebral dysfunction are responsible for acute neurological complications including depression of conscious level, focal neurological signs and potentially cerebral herniation in the acute phase, together with longer-term neurological sequelae. Therefore, neuroprotective strategies are essential in patient management.

Patients with raised ICP due to bacterial meningitis and other intracranial infections should be assessed for airway, breathing, and circulation [38]. In those with a rapidly deteriorating Glasgow Coma Scale (>3 points in an hour), those with a GCS $\leq$8, those with a fluctuating level of consciousness, and those with any associated respiratory or cardiovascular organ failure should have their trachea intubated to protect their airway and be mechanically ventilated to

Table 40.3 Cerebrospinal fluid findings in different types of meningitis

Condition	Leukocytes/mm^3	Glucose mmol/l	Protein g/l	Specific tests
Bacterial meningitis	100–500 (sometimes thousands) Polymorphs	1.1–1.6 <0.5 < 40–60 % of simultaneous blood glucose	0.4–1.5	Gram stain, rapid antigen screen positive
Tuberculous meningitis	25–100 Lymphocytes/monocytes predominate	<2.2 May be normal in early stages	Progressive increase to very high	Acid-fast organism on smear. Specific mycobacterial culture and PCR
Viral meningitis	25–500 Usually lymphocytes. Maybe polymorphs in first 24 h	Usually normal	Mild increase < 1	Viral culture, PCR
Fungal meningitis	0–500 Lymphocytes	Mildly reduced/normal in early stages	Moderate increase	Fungal culture India Ink, cryptococcal antigen
Partially treated bacterial meningitis	100–5,000 Polymorphonuclear/lymphocytes (50/50)	Low/mildly reduced	Mild to moderate increase	Cultures negative, rapid antigen and gram stain positive
Parameningeal infection	Upto 100 s variable mononuclear and polymorphonuclear cells	Normal/mildly reduced	Mild to moderate increase	Cultures negative, cerebral imaging

maintain oxygenation and facilitate carbon dioxide removal. Ventilation must be tailored to achieve $PaCO_2$ in the normal range [39], which avoids the dynamic complications associated with hyper- or hypocarbia. Normal oxygenation should also be maintained. There is no evidence that the use of Positive End Expiratory Pressure (PEEP) exacerbates raised ICP, and its use is associated with a reduction in the risk of atelectasis [40].

It is important to achieve a blood pressure which will achieve adequate Cerebral Perfusion Pressure (CPP). CPP is the difference between Mean arterial blood pressure (MAP) and the intracranial pressure.

$$\text{CPP} = \text{MAP} - \text{ICP} \quad (1)$$

It has been shown that CPP of ≤ 40 mmHg is associated with a worse outcome as determined by mortality and long-term disability in children with non-traumatic coma [41]. Recent studies have confirmed that maintenance of MAP with vasoconstrictors such as norepinephrine have better protection of cerebral cellular oxygenation than other methods to support blood pressure, in the presence of adequate intravascular volume [42, 43].

Patients should be positioned appropriately to prevent obstruction to cerebral venous drainage, with elevation of the head of the bed by 20–30° and head position maintained in the midline. Placement of internal jugular venous catheters should be avoided if possible as they may obstruct venous drainage from the brain. Hyperthermia must be avoided [44], and where necessary active cooling measures instituted. In addition tight control of serum electrolytes and blood glucose is required. There is some evidence that moderate hypothermia may be protective [45, 46], however there is no data for its routine use in this setting.

Fluid management for bacterial meningitis is controversial. The guidelines recommending fluid restriction have been based on the frequent development of hyponatremia seen in children with bacterial meningitis, often found in conjunction with an increase in circulating concentrations of anti-diuretic hormone (ADH), as part of the Syndrome of inappropriate ADH secretion (SIADH) [47]. SIADH is associated with total body water overload and thus contributes to cerebral swelling. By restricting intravenous fluid administration in the presence of SIADH, the risk of developing cerebral edema is likely to be diminished. Some groups have found that children with bacterial meningitis who received maintenance fluid, as well as replacement of any deficits had normal levels of ADH, while those who received restricted fluids had elevated ADH levels, suggesting that the increased ADH noted in meningitis was an appropriate response to dehydration. The explanation is that children who present to the hospital with bacterial meningitis have often had several days of fever and may have been vomiting, in addition to diarrhea and inadequate fluid intake. In children with bacterial meningitis who were randomized to fluid restriction, where there was a reduction of >10 ml/kg in extracellular water, there was an increase in mortality and long-term neurological morbidity [48]. Where there is hyponatremia and normal ADH levels, it is thought that cerebral salt wasting contributes to the hyponatremia, the mechanism of which is unclear. Overall, while there is not enough data to firmly recommend fluid restriction, the main consideration should be avoidance of overzealous fluid administration.

Where there is an acute neurological deterioration with signs of impending brain stem herniation, management includes the administration of hyperosmolar therapy with mannitol or 3 % saline [49]. There is no good evidence for

one therapy over another. In addition, in ventilated patients, short-term hyperventilation may prevent herniation [39].

Antibiotic Therapy

Empiric antibiotic therapy should be initiated based on the most likely causative organism for the individual patient, taking into account the patient's age, vaccination status, immune competence and local patterns of antimicrobial resistance. In developed countries, most authorities recommend a third-generation cephalosporin such as ceftriaxone or cefotaxime that have good CSF penetration, and are active against most pathogens causing bacterial meningitis [34, 50]. *Listeria monocytogenes*, more common in infants under 3 months and adults over 50 years, is not sensitive to the cephalosporins; therefore addition of a penicillin to this regimen is recommended [51]. However, antimicrobial resistance among the common causes of acute bacterial meningitis is of increasing clinical importance worldwide. The increasing emergence of resistant bacteria, particularly *Streptococcus pneumoniae*, Meticillin Resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE) and the extended spectrum beta-lactamase producing gram-negative organisms has presented enormous difficulties in the selection of adequate empiric antimicrobial therapy, before results of bacteriologic testing are available.

Factors to be taken into consideration when selecting the appropriate antibiotic for the therapy of bacterial meningitis include activity against the likely causative pathogen and its ability to penetrate and attain effective bactericidal concentrations in the CSF. The integrity of the BBB is compromised during meningitis, resulting in increased permeability to most antibiotics [52]. Beta-lactam antibiotics achieve levels of 5–20 % of concomitant serum concentrations. Highly lipid soluble antibiotics (e.g. rifampin, chloramphenicol and fluoroquinolones) achieve 30–50 % of their serum concentrations in CSF, even in the absence of BBB dysfunction. In contrast, the concentration of vancomycin is less than 5 % of its serum concentration. Experimental models of bacterial meningitis in animals suggest that prompt bacteriologic cure is associated with antibiotic concentration in CSF that are 10–30 times the minimal bactericidal concentration (MBC) for a specific microorganism [53].

The pharmacodynamic properties of different antimicrobials also affect their efficacy. Aminoglycosides and fluoroquinolones exhibit concentration-dependent activity. Their effectiveness is determined by the ratio between the peak concentration, or area under the concentration curve of the antibiotic, and the MBC of the infecting pathogen. In contrast, the beta-lactams and vancomycin show concentration-independent activity. The time over the MBC during which the drug concentration exceeds the minimum inhibitory concentration (MIC), appears to be important in determining drug effectiveness. These drugs should therefore be administered at frequent dosing intervals.

Table 40.4 Empiric choice of antimicrobial by age

Age	Empiric choice of antibacterial[a]
<1 month	Penicillin or Ampicillin and Gentamicin Second line Ceftriaxone or Cefotaxime
1–3 months	Ceftriaxone or Cefotaxime and Ampicillin
>3 months	Ceftriaxone or Cefotaxime
Immunocompromised	Ceftriaxone and Ampicillin and Gentamicin Second line Meropenem and Gentamicin
Post-neurosurgery, post neurotrauma, CSF shunt	Ceftazidime, and Gentamicin and Vancomycin Second line Meropenem and Gentamicin and Vancomycin

[a]See text for caveats regarding resistant *Streptococcus pneumoniae*

In patients with a possible nosocomial infection, other broad-spectrum agents such as vancomycin and ceftazidime may be considered. Meropenem has been shown to be an excellent single agent in patients where resistant bacteria are likely, or in those who have failed to respond to the primary choice [54]. However, there have been reports of treatment failures in patients with resistant pneumococcal meningitis and other resistant organisms [55, 56].

The fluoroquinolones have been increasingly recognised as an important therapeutic option in both gram negative and gram positive meningitis, where their excellent CSF penetration and the potential for synergistic activity in combination with the cephalosporins and the carbapenems, may indicate that they may play an important future role in the management of resistant pneumococcal and nosocomial meningitis [57]. Linezolid is the first agent of a new class of antibiotics called the oxazolidinones. Linezolid possesses excellent microbial activity against a wide variety of Gram-positive pathogens including those resistant to methicillin and vancomycin. There have been several reports of its successful use in the management of resistant gram-positive meningitis [58, 59]. Table 40.4 shows the most common antibacterial agents used in the treatment of bacterial meningitis.

Antimicrobial resistance of organisms causing bacterial meningitis is becoming increasingly problematic in all parts of the world, with different resistance patterns emerging for different organisms in different places.

Streptococcus pneumonia

Penicillin-resistant *S. pneumoniae* were first reported in 1967 [60] and have subsequently spread worldwide. Strains highly resistant to the penicillins, defined by the U.S. National Committee for Clinical Laboratory Standards [61] as a minimal inhibitory concentration (MIC) of >2 μg/ml, are more likely to be resistant to other B-lactam and non-B-lactam antibacterials. The proportion of pneumococci causing invasive disease that are resistant to penicillin are reported

to be as high as 59 % in Hungary [62], 55 % in Spain (pediatric patients) [63], 25 % in Atlanta, USA [64], and 3.6 % in the United Kingdom [65]. A Spanish study in 1999 found 38 % of all CSF isolates of pneumococci were resistant to penicillin [66]. More recently pneumococcal strains resistant to the cephalosporins have been described [67]. In pneumococcal meningitis strains are considered resistant to cefotaxime and ceftriaxone if the MIC is greater than 0.5 μg/ml and highly resistant if the MIC is > 2.0μg/ml There are several reports of treatment failure with third-generation cephalosporins [68, 69], but there is some evidence to suggest that intermediate resistance (MIC = 1.0 μg/ml) is not associated with an altered clinical outcome when the third-generation cephalosporins are used for treatment [70]. The risk of colonization with penicillin-resistant pneumococci increases with previous antibiotic use, in children aged <5 years, and with daycare attendance.

Therapeutic modifications in light of increasing bacterial resistance to current antimicrobials have included the addition of vancomycin or rifampicin to a third generation cephalosporin [71]. However penetration of vancomycin into CSF is variable, particularly when concomitant corticosteroids are given, and there are recent reports of vancomycin-tolerant strains of pneumococci causing meningitis, and of treatment failure in adults receiving vancomycin, 30 mg/kg/24 h [72]. Experimental evidence in animal models lends support to the possibility of delayed CSF sterilization when vancomycin is given with dexamethasone, as steroids reduce BBB permeability [73].

Vancomycin resistance to pneumococci has not yet been reported as a significant clinical problem, and combination therapy with vancomycin and a cephalosporin is now recommended for children in the US when pneumococcal meningitis is suspected [74].

In pneumococcal meningitis, vancomycin (at a dosage of 60 mg/kg/day) in combination with dexamethasone achieves good penetration across the CSF [75], and there is some evidence of synergism when vancomycin is combined with ceftriaxone or cefotaxime [76]. However, there are some reports of vancomycin-tolerant pneumococcal strains associated with meningitis [77], and of treatment failures in adults that were associated with poor CSF penetration of vancomycin at a dosage of 30 mg/kg/day [72]. There is experimental evidence of delayed sterilization of CSF in animal models when vancomycin is administered with dexamethasone [73], and there are concerns about the potential effect of this finding on clinical outcome in adult patients [78]. Considering the growing impact of resistant pneumococci, the National Institute of Health and Clinical Excellence (NICE) in the UK has recommended vancomycin to be added to a third-generation cephalosporin in suspected bacterial meningitis if the patient has travelled outside of the UK or has had prolonged or multiple exposure to antibiotics in the past 3 months [79]. However, this has been questioned by some experts in view of the negligible incidence of cephalosporin-resistant pneumococci in the UK [80].

Rifampicin has been used successfully in combination with other antibiotics in the treatment of cephalosporin-resistant pneumococcal meningitis [81]. It is recommended in pediatric practice when the combination of vancomycin and cephalosporin is failing [74].

Its use has also been recommended in adults receiving adjunctive steroid therapy and in children failing therapy on a combination of a cephalosporin and vancomycin.

Neisseria meningitidis

Widespread penicillin resistance in *N. meningitidis* has been reported [82], mainly due to reduced affinity of penicillin for the penicillin binding proteins (PBP) 2 and 3 [83]. In addition there are extremely rare, but worrying, reports of B-lactamase producing meningococci [84]. A recent Spanish report suggests that penicillin-resistant meningococcal strains may be associated with a worse clinical outcome [85], but there is no evidence of treatment failure with the third-generation cephalosporins or the newer flouroquinolones. However the emergence of rifampicin-resistant meningococci has important public health implications for chemoprophylaxis of close contacts of the index case [86].

In the meningitis belt of Africa, the WHO recommends use of a single 100 mg/kg dose of oily chloramphenicol for the treatment of meningococcal meningitis in patients above 2 years of age, during epidemics [87]. There is little reported resistance against chloramphenicol, and the drug is also effective against pneumococci and haemophilus [88].

The third-generation cephalosporins, and vancomycin, are prohibitively expensive in these resource-poor countries, and regular use of rifampin is avoided because of the fear of an increase in resistant tuberculosis. Therefore, despite the increased side effects of chloramphenicol, it remains the drug of choice for the treatment of meningococcal meningitis in these regions. There is an emphasis on developing cheaper third-generation cephalosporins for use in the developing world, and ceftriaxone is being recommended as a single-dose treatment for meningococcal meningitis during epidemics [87]. In developed countries, third-generation cephalosporins are used as first-line therapy for the treatment of meningococcal meningitis; no resistance has been reported against these drugs.

Urgent chemoprophylaxis is indicated to eradicate nasopharyngeal colonization of *N. meningitidis* in close contacts of the index case, which usually reduces nasopharyngeal carriage by 90 % [89]. Rifampin and ciprofloxacin are commonly used for prophylaxis, but some resistance to rifampin has been reported in Germany, the US, and Italy [90–92]. Ciprofloxacin as a single dose appears to be effective in clearing meningococci from the nasopharynx. Resistance of *N. meningitidis* to fluoroquinolones is rarely reported [93].

Haemophilus influenzae Type B

In countries that have not adopted the Hib conjugate vaccine, meningitis due to penicillin and chloramphenicol-resistant strains is a continuing clinical problem. The third-generation cephalosporins, cefotaxime and ceftriaxone are effective in the treatment of chloramphenicol- resistant strains of Hib [94]. In the post vaccine era, other non-Hib encapsulated Haemophilus (especially type f haemophilus), accounted for 10 % of all Haemophilus isolates from a recent epidemiogical study from Spain [95]. Most of these infections occurred in children < 14 years of age, and 62 % were ampicillin-resistant, as well as being resistant to tetracycline and chloramphenicol. Chemoprophylaxis with rifampin can be used with high efficacy to prevent secondary cases in close contacts of an index case with Hib disease [89].

Evaluation of Newer Antibiotics Because of increasing reports of resistant bacteria causing ABM, some exploration of other antibiotics active against the three commonly incriminated bacteria is warranted. Meropenem has good CSF penetration and a broad spectrum of activity against Gram-positive and Gram-negative bacteria, including many of those that produce β-lactamase [96]. Animal and human studies have shown the efficacy of meropenem in penicillin- and cephalosporin-susceptible and resistant pneumococcal meningitis [97]. Cefepime, a fourth-generation cephalosporin, has showed superior CSF pharmacodynamics against pneumococci compared with ceftriaxone in one recent study [98]. Some of the quinolone derivatives, such as gatifloxacin, garenoxacin, and moxifloxacin, have shown good penetration in inflamed meninges [99, 100]. They are lipophilic in nature and can achieve peak concentrations rapidly with an extended halflife. Ciprofloxacin has been used in the treatment of Gram-negative ABM [74]. However, fluoroquinolones should only be used in multidrug-resistant meningitis or where standard therapy has failed, because the efficacy of fluoroquinolones as monotherapy has not been established in penicillin-resistant pneumococci and there are only limited data in children and neonates. Linezolid is another antibiotic that has been suggested as an alternative to vancomycin and rifampin in combination with ceftriaxone for use against penicillin-resistant pneumococcal strains [101]. Daptomycin, a lipopeptide with excellent action against a variety of Gram-positive bacteria, acts by disrupting several aspects of bacterial cell membrane function and shows high bactericidal activity in animal models of ABM [102].

Anti-Inflammatory Agents

Despite effective antimicrobial therapy, neurologic morbidity and mortality remains a major problem in ABM. Meningitis-induced tissue injury appears to be dependent on the release of both host-derived and bacterial-derived toxins, suggesting that an ideal therapy for bacterial meningitis should interfere with both kinds of toxins.

Cell-wall derived bacterial products, including endotoxin and peptidoglycan lead to the activation of host inflammatory pathways, which further contribute to brain inflammation and oedema. The release of pro-inflammatory cytokines including the interleukins (IL-1β, IL-6) and TNFα lead to stimulation of the inflammatory cascade with the release of platelet activating factor (PAF), IL8, and interferon gamma (IFNγ). The result of this is the up-regulation of cellular adhesion molecules in the vascular endothelium and blood leucocytes and the release of toxic products from activated neutrophils, which mediates meningeal inflammation, disruption of the blood brain barrier (BBB), microvascular thrombosis and both vasogenic and cytotoxic cerebral edema [103, 104]. Collectively, these data have led to the hypothesis that brain injury may be reduced by the use of anti-inflammatory therapy.

Adjunctive Corticosteroids

Animal studies have suggested that following antibiotic treatment, bacterial lysis induces inflammation in the subarachnoid space. When dexamethasone was used, the inflammatory changes were reduced, together with the sequelae observed in untreated animals [105]. Dexamethasone down-regulates meningeal inflammation and reduces cerebral edema and therefore intracranial hypertension, thereby leading to a reduction in neurological damage and the development of long-term sequelae.

The role of adjunctive corticosteroids in ABM has been widely studied in the last three decades. Initial trials showed a clear benefit from dexamethasone, with a decrease in neurologic sequelae, particularly nerve deafness [106]. Subsequent studies from other countries also reported a reduction in neurologic sequelae following the use of dexamethasone [37, 107]. However, there were some problems with applying the results of these trials widely. Most patients in these early studies were infected with Hib, and studies specifically addressing pneumococcal meningitis in children, although demonstrating an improved neurologic outcome, did not reach statistical significance [108]. In 2007, a Cochrane analysis published a review of 20 randomized clinical trials on the safety and efficacy of corticosteroid use in ABM [109]. According to this analysis, adjuvant corticosteroids were associated with lower case fatality rates (relative risk [RR] 0.83; 95 % CI 0.71, 0.99), lower rates of severe hearing loss (RR 0.65; 95 % CI 0.71, 0.99), and fewer long-term neurologic sequelae (RR 0.67; 95 % CI 0.45, 1.00). In children, the beneficial effects of corticosteroid use were less convincing, although there was a trend towards reduced hearing loss and short-term neurologic sequelae in non-Hib meningitis, with the effect statistically significant in high-income countries compared with low-income countries. Subgroup analysis

suggested that the case-fatality rate was reduced by adjuvant steroids in patients with pneumococcal meningitis (RR 0.59; 95 % CI 0.45, 0.77) and that hearing loss was reduced in patients with Hib meningitis [174]. A more recent meta-analysis by the same group showed no significant reduction in death and neurologic disability with corticosteroid use in any of the prespecified age groups [110].

There are theoretical disadvantages to the use of corticosteroids, such as the reduction of vancomycin penetration into the CSF in animal models of pneumococcal meningitis (a finding not confirmed in children) [75], the possibility of neuronal injury [111], and the potential down-regulation of potentially beneficial anti-inflammatory cytokines, such as IL-10 [112]. However, a recent trial in adults did not substantiate the effect of dexamethasone on reducing vancomycin levels in the CSF [112].

To be able to offer any benefit, dexamethasone needs to be administered early in the course of the meningitic illness. Despite a lack of robust evidence for the beneficial effects of routine dexamethasone use in children with ABM from various meta-analyses, subgroup analyses have suggested that it may have a beneficial role in high-income countries. In the absence of any potentially significant harmful effects, dexamethasone is recommended for use in children with ABM above 3 months of age in the UK [79] and above 6 months of age in the US [113]. The recommended dosage is 0.6 mg/kg/day in four divided doses for 4 days prior to or simultaneously with the first dose of antibiotic, or within 4 h of antibiotic administration [79]. In adults, the evidence is less convincing. However, in severe ABM, there are theoretical grounds for using steroids at the same recommended dosage as above; there is little evidence of a worse outcome [114]. There is no good evidence to date to recommend the routine use of steroids for ABM in neonatal meningitis or in post-neurosurgical patients.

Inhibition of Leukocyte Recruitment

Experimental data have recently suggested that an enhanced lifespan of activated neutrophils in the CSF substantially contributes to leukocyte accumulation and, thus, meningitis-induced tissue injury. More recently, induction of apoptosis in neutrophils using roscovitine to induce caspase-dependent apoptosis in neutrophils in a pneumococcal meningitis model, showed that inflammatory activity and disease severity can be modulated by targeting the apoptotic pathway in neutrophils without affecting bacterial clearance [115].

Non-bacteriolytic Antibiotics

ß-Lactam antibiotics which are part of the standard therapeutic regimen in ABM result in an abrupt release of bacterial components which causes a strong, albeit transient, increase in meningeal inflammation and cytotoxicity. Bactericidal, but non-bacteriolytic antibiotics may represent a major opportunity to improve outcome in ABM. Two non-bacteriolytic antibiotics, rifampicin and daptomycin, have been evaluated in animal models of pneumococcal meningitis. Rifampicin inhibits DNA-dependent RNA polymerase in bacterial cells by binding its ß-subunit, thus preventing transcription to RNA and subsequent translation to proteins [116]. Daptomycin, on the contrary, is inserted into the bacterial cell wall, resulting in consecutive pore formation, loss of electrical membrane potential, and inhibition of peptidoglycan synthesis [117]. In an infant rat model of pneumococcal meningitis, daptomycin monotherapy was found to clear bacteria more efficiently from the CSF than ceftriaxone. It was also shown to reduce the inflammatory host reaction and to prevent the development of cortical injury [118]. Similar effects were also obtained with rifampicin monotherapy in rabbit and mouse meningitis models [119, 120].

Since neither rifampicin (due to the rapid development of bacterial resistance), nor daptomycin (due to a lack of efficacy against pneumococcal pneumonia), can be used as a single agent for treatment of ABM, recent studies have assessed whether combining these drugs with ceftriaxone is superior to ceftriaxone monotherapy. In a rabbit model, short-term pre-treatment with rifampicin reduced β-lactam-induced release of bacterial products, attenuated inflammation, and decreased neuronal cell loss [121]. In an infant rat model, co-therapy of rifampicin with ceftriaxone also reduced CSF inflammation, but did not attenuate brain damage and hearing loss. In contrast, the combination of daptomycin with ceftriaxone led to less neuronal injury and improved hearing capacity [122]. This discrepancy, and also open questions such as the comparison of antibiotic co-therapies with standard therapy (antibiotics and dexamethasone) underline the need for further experimental investigations before clinical trials can be attempted [18].

Hypothermia

Induced hypothermia in experimental models of meningitis has been shown to attenuate the inflammatory response and to be neuroprotective. In such models hypothermia reduces changes in CSF glucose, protein, lactate, excitatory neurotransmitters, TNF-α and leukocytes [123, 124]. A reduction in intracranial pressure and cerebral edema, as well as an improvement in cerebral perfusion have been demonstrated in a rabbit model of severe Group B streptococcal meningitis [125]. Similar neuroprotective benefits have been proposed for the adjunctive treatment of severe head injury with hypothermia. There are proposals for the use of moderate hypothermia (35 °C) as an adjunctive treatment of bacterial meningitis in humans. There is a case series reporting use of induced hypothermia in adult ABM [126]. However, it is clear that properly conducted randomized controlled studies are required before this therapeutic modality is widely introduced.

Other Agents

There are no reported clinical studies of the use of other anti-inflammatory therapies in the treatment of ABM. However, there are several potential target therapies, which are in the experimentation phase at present. These include neutralization of bacterial factors that induce host inflammatory cytokines, modulation of host inflammatory cytokines, and neutralization of the consequences of injury [88]. There is some evidence for the use of glycerol as a hyperosmolar agent to reduce neurologic sequelae [127]. However, more recent evaluation from the same study group did not show a role for either dexamethasone or glycerol in reducing hearing loss when used to treat ABM [128].

Duration of Therapy

Most recommendations for duration of therapy are based on historical data with antimicrobials that are either no longer used or have become obsolete. There is little data on adequacy of length of therapy with the more commonly used modern antimicrobials (Table 40.5). A recent meta-analysis of the duration of antibiotic therapy in children, and its impact on outcome, has not shown any conclusive evidence to support long or short courses of antibiotics, and the authors emphasized the lack of evidence in the field. [129]. For pneumococcal meningitis, 14 days of therapy is recommended; group B streptococcal or *L. monocytogenes* meningitis should be treated for 14–21 days, and Gram-negative infections should be treated with at least 21 days of antibiotics. Clinical trials have confirmed that antibiotic therapy with ceftriaxone, cefotaxime, chloramphenicol, or penicillin for 7 days was very effective for meningococcal meningitis, and that many patients were cured within 5 days [130, 131]. *H. influenzae* meningitis can also be treated effectively with a 7-day course of antibiotics. However, these recommendations should be reviewed in light of the clinical and microbiologic response to therapy, and may need to be adapted for the individual patient, especially if there are complications or if the individual is immunocompromised.

Table 40.5 Recommended Duration of therapy by organism

Infecting organism	Duration of therapy
S. pneumococcus	14 days
S. agalactiae (Group B streptococci)	14–21 days
Listeria monocytogenes	14–21 days
Neisseria meningitidis	7 days
Haemophilus influenzae type b	7 days
Gram negative organisms	21 days

Based on data from Ref. [51]

Prevention of Bacterial Meningitis

Hib

Disease due to serotype b (Hib) was the most common cause for ABM prior to introduction of the conjugated proteinpolysaccharide Hib vaccine in the early 1990s [8]. Although a highly effective and safe Hib vaccine has been available for nearly two decades and is used as a part of the routine infant immunization schedule in the US, UK, and most countries in Western Europe, vaccine availability in the developing world is still constrained by cost factors [132, 133]. The estimated global incidence of Hib meningitis for the year 2000 was 31 cases per 100,000 children younger than 5 years, with a case fatality rate of 43 % in unimmunised populations [134]. There has been no significant increase in invasive non-type b haemophilus disease in these countries since the introduction of Hib vaccine [135]. The global vaccine coverage for Hib in 2009 reported by the Centers for Disease Control and Prevention was only around 30 % in infants <12 months of age [136].

N. meningitidis

N. meningitidis is the leading cause of ABM worldwide and is known to cause endemic and epidemic disease, with the greatest burden of disease in children and adolescents. *N. meningitidis* is an obligate human commensal living in the upper respiratory tract. The estimated nasopharyngeal carriage ranges from 0.6 % to 34 % and is higher in adolescents and individuals living in overcrowded and confined spaces [137]. An estimated 500,000 cases of meningococcal disease occur annually worldwide with a case fatality rate of at least 10 % [138]. Most cases occur during winter months and early spring. The incidence of endemic disease is 0.5–5 per 100,000 population. There are at least 13 known serogroups of *N. meningitidis*; however, more than 90 % of disease is caused by serogroups A, B, C, W-135, X, and Y [137]. The distribution of serogroups varies with age group and geographic location. Serogroup A causes the highest number of cases and primarily causes large epidemics in the meningitis belt in Sub-Saharan Africa, with an incidence as high as 1 case per 100 population, and a case fatality reaching 75 % in children and adolescents [137–139]. Serogroup B causes endemic disease in much of the developed world, including the US, Western Europe, Australasia, and South America. Serogroup C is also common in the developed world, and is occasionally known to cause epidemics and outbreaks [140, 141]. The incidence of serogroup C disease has decreased in those parts of the world, such as Europe and North America, following the introduction of effective conjugate vaccines against serogroup C; subsequently, serogroup B disease has emerged as the predominant cause of meningococcal disease due to lack of an effective vaccine against this serogroup. Serogroup Y has become an increasingly important cause of meningococcal disease in the US and serogroup X is becoming more common in parts of Africa [142].

There are two main types of vaccines used for protection against meningococcal infection: pure polysaccharide vaccines and protein/polysaccharide conjugate vaccines. The polysaccharide quadrivalent vaccine against serogroups A, C, Y, and W-135 is poorly immunogenic in children <2 years of age, and gives temporary immunity for 3–5 years in older people; it does not have any effect on nasal carriage of the bacteria [137, 143, 144]. Repeated usage may cause immune hypo-responsiveness and should be instituted with caution [145]. More recently, conjugate vaccines have become available against serogroup A, C, Y, and W-135. Conjugate serogroup C vaccine has been introduced successfully into several countries in Europe as a part of the routine immunization schedule in infants [143]. This vaccine is not only strongly immunogenic, giving a lasting immune response and immunologic memory, but it also confers herd immunity by decreasing nasal carriage. Since its introduction in the UK in 1999, the incidence of disease due to meningococcal serogroup C has decreased by 94 % in immunized populations and 67 % in unimmunized populations, with no increase in the nasopharyngeal carriage of other serogroups [146].

In the US, a protein conjugate quadrivalent vaccine against serogroups A, C, Y, and W-135 has been licensed since 2005 for routine single-dose immunization in children aged 11–18 years, and in people at high risk of ABM (i.e. immunocompromised individuals, college students living in dormitories, microbiologists or laboratory workers routinely exposed to meningococcal samples, army recruits, close contacts and travelers to meningococcal endemic areas) [147]. This vaccine has also been approved for use in 2- to 10-year-olds, but is not a part of the routine immunization schedule in this age group. This is due to concerns regarding adequate lasting response from a dose at 2 years of age, and also because the largest proportion of meningococcal disease in this age group is caused by serogroup B [148].

As serogroup A meningococcal disease is a major public health concern in the meningitis belt of Sub-Saharan Africa, the WHO initiated a Meningitis Vaccine Project (MVP), which has developed a low-cost conjugate vaccine against serogroup A (MenAfriVac TM) [149]. This vaccine has been successfully tested in phase I, II, and III clinical trials and has been launched in mass vaccination campaigns as a single dose to a target population of 250 million people aged 1–29 years across 25 countries in the African meningitis belt. More than one million people have already received the vaccine in the region. Serogroup B still remains an important cause of meningococcal septicemia and meningitis, and has accounted for more than 50 % of cases in the US [7] and as many as 90 % of cases in Europe [150] since the introduction of the MenCvaccine. Serogroup B has a poorly immunogenic capsule, which has hindered progress on developing a vaccine against it. However, vaccines are now being developed targeting non-capsular structures, such as outer membrane porins, vesicles, and lipopolysaccharides [151, 152].

An outer membrane vesicle (OMV) vaccine against serogroup B has been recently tested in New Zealand and is reported to have 73 % overall efficacy and 80 % efficacy in children aged between 6 months and 5 years [153]. The OMV vaccines are useful for control of epidemics because they are directed against specific surface proteins, which are antigenically variable; therefore, the vaccines can be tailored to a predominant strain during an epidemic. However, these vaccines do not confer cross-protective immunity against other strains of serogroup B meningococci. Other vaccines against serogroup B containing recombinant human factor H binding protein, along with other components of the bacterial outer membrane or cell wall, are undergoing clinical trials [154] and one such vaccine has recently been licensed in Europe. Further studies are required to prove vaccine efficacy and safety before their widespread use.

S. pneumonia

S. pneumoniae is an important cause of invasive disease in children <2 years of age, the elderly, and in immunocompromised hosts [155]. Like H. influenzae, *S. pneumoniae* spreads from the nasopharynx; the highest rate of *S. pneumoniae* nasopharyngeal carriage is noted in children <6 years of age. The estimated global incidence of pneumococcal meningitis published by the WHO in 2009 was 17 per 100,000 population in children for the year 2000, with a case fatality rate of 59 % (23 % in western Pacific regions to 73 % in Africa) [156]. It is the most severe form of ABM in children, with the highest mortality and morbidity. A 7-valent pneumococcal conjugate vaccine (PCV7) was introduced for use in children in 2000. The high cost of the vaccine prohibits its use in the routine infant immunization schedule in resource-poor countries. Vaccine efficacy is estimated to be approximately 80 % against the seven serotypes included in the vaccine, 58 % against all pneumococcal serotypes, and 11 % for all-cause mortality [157]. The incidence of invasive pneumococcal disease has decreased since the introduction of this vaccine in those countries where it is part of the national immunization schedule, and there is some evidence of herd immunity, as suggested by the decreasing incidence of invasive pneumococcal disease in adults [158]. The incidence of invasive pneumococcal disease due to vaccine serotypes fell by over 89 % since its introduction, and by 63–74 % for all serotypes. The most dramatic reduction was reported in White Mountain Apache children <5 years of age, where the rate of disease due to vaccine serotypes decreased from 275 cases per 10,0 000 in 1991–7 to 0 in 2004–6 [159, 160].

There are 91 distinct serotypes of pneumococcus identified. However, only 20 of these account for >80 % of invasive pneumococcal disease. The most common serotypes associated with invasive infection are 14, 4, 1, 6A, 6B, 3, 8, 7F, 23F, 18C, 19F, and 9V [161]. The pathogenic serotypes vary

depending on age (the majority of childhood disease is caused by serotypes 6, 14, 18C, 19F, or 23F), geographic location (serotypes 1 and 5 are common in developing countries, but rare in the US and Europe) and organ affected [162]. There has been a temporal change in the distribution of pathogenic serotypes. The serotypes covered in PCV7 (4, 6B, 9V, 14, 18C, 19F, and 23F) more commonly cause invasive disease than the non-PCV7 serotypes; however, there has been a reported increase in invasive disease due to non-vaccine serotypes in countries where PCV7 has been introduced into the routine infant immunization schedule. Some of the non-PCV7 serotypes, such as 19A, have become more virulent with increased nasopharyngeal carriage; increasing incidence of invasive disease due to serotype 19A has been reported since 2000 [163]. This increase has threatened the efficacy of PCV7 and led to the development of vaccines with more inclusive coverage. A study from the US showed a decrease of 76 % and 94 % in invasive disease due to serotypes 6A and 6B, respectively, between 1999 and 2007; however, invasive disease due to serotype 6C, which is not part of PCV7, increased by 164 % during the same period (from 0.22 per 100,000 to 0.58 per 100,000) [164]. To counter the increase in non-PCV7 vaccine serotypes, newer vaccines have been developed. These vaccines all include the same seven serotypes as PCV7 as well as other serotypes. A 9-valent conjugate vaccine, which also includes serotypes 1 and 5 in addition to the serotypes present in PCV7, has been found effective in reducing mortality in Gambian children [165]. There are also 10- and 13-valent pneumococcal conjugate vaccines; the 13-valent (PCV13) vaccine was licensed for use in infants in the US and the UK from 2010 and is expected to further reduce the incidence of invasive pneumococcal disease [166].

PCV13 contains an additional six serotypes over and above the PCV7 serotypes, and is likely to cover serotypes that cause 64 % of all invasive pneumococcal disease [167]. This vaccine was introduced into the routine infant immunization schedule in the UK in April 2010, replacing PCV7.

The other available pneumococcal vaccine is 23-valent polysaccharide vaccine, which is not suitable for infant vaccination as it is not protein conjugated and thus poorly immunogenic in young children [168]. This 23-valent polysaccharide vaccine encompasses most of the penicillin-resistant and macrolide-resistant pneumococcal serotypes and is used to protect patients at high risk of invasive pneumococcal disease (e.g. immunocompromised patients, elderly patients with chronic obstructive pulmonary disease, patients with severe asthma, and patients with splenic dysfunction). Vaccine efficacy is estimated to be 60–80 % in adults, although it is somewhat less effective in immunocompromised patients in whom frequent re-vaccination is necessary, which leads to a possible decrease in efficacy. Despite these failings, this vaccine has been effective in decreasing the incidence of invasive pneumococcal disease in adults since its introduction in the 1980s [169].

The epidemiology of disease due to antibiotic-resistant pneumococci is changing because of selection pressure from antibiotic use, immunization, and the spread of a few international resistant clones [155]. Some serotypes are specifically associated with increased antimicrobial resistance. For example, since the introduction of PCV7 vaccine in the US, there has been an increase in antimicrobial resistance among non-vaccine serotypes due to a threefold increase in the prevalence of erm(B) and mef(A) isolates of serogroup 19; the relative distribution of 19A serotype has increased since vaccine introduction [170]. Similarly, there are reports of increasing invasive pneumococcal disease due to non-PCV7 serotypes: the 19A and 6A subtypes in Korea and the 19A subtype in Taiwan [155]. Six serotypes (6A, 6B, 9V, 14, 19F, and 23F) account for more than 80 % of penicillin- or macrolide-resistant pneumococci worldwide [171]. There are some multidrug-resistant clones in select regions, which are worrying and signify the importance of judicious use of antibiotics and development of vaccines with extended serotypic coverage for these drug-resistant organisms.

Viral Meningitis

Viral meningitis is as an infection of the leptomeninges with viral particles. Many viruses may cause viral meningitis in children. Prior to the introduction of the combined MMR vaccine (measles, mumps, rubella), mumps was the most common cause of meningitis in children in England and Wales. Although recent outbreaks of infection with mumps have been reported, there have been no reported cases of mumps meningitis. The common causes of viral meningitis include the enteroviruses, herpes viruses, lymphocytic choriomeningitis, cytomegalovirus (CMV), adenovirus, rubella, varicella, the arboviruses, influenza and Epstein-Barr virus [172]. There is some overlap between meningitis and encephalitis. However, the majority of organisms generally lead to either meningitis or encephalitis. Death following viral meningitis is rare.

The enteroviruses are thought to be responsible for the majority of cases of viral meningitis. At least 70 different enteroviruses have been found, and those most likely to cause meningitis are polio, the coxsackie (types A, B) and ECHO viruses (enteric cytopathogenic human orphan) [173]. These viruses are transmitted via the fecal, oral and respiratory routes, and viral particles are shed in stools and may be detected for several weeks following infection. The enteroviruses generally lead to gastrointestinal upset, however, when present in the bloodstream, they have a predominance for different organ systems including the CNS. The enteroviral serotypes which have been found in the majority of CSF isolates are A9, E7, E9, E11, E19, and E30 [174]. Large outbreaks of Enterovirus 71 have been seen in Asia-Pacific countries in the

past 10 years. This virus mostly affects children, manifesting as hand, foot, and mouth disease, aseptic meningitis, poliomyelitis-like acute flaccid paralysis, brainstem encephalitis, and other severe systemic disorders, including pulmonary oedema and cardiorespiratory collapse [175].

Children with viral meningitis usually have fever, headache, neck stiffness, photophobia, vomiting, irritability, and lethargy. The signs and symptoms are even more non-specific in neonates. There may be associated signs such as a maculopapular rash, which is more common in ECHO virus infections, a parotitis in mumps or Coxsackie infections, and a myalgia with Coxsackie infections.

A lumbar puncture usually confirms the diagnosis (see LP findings above). At the onset of disease, there is often a polymorphonuclear predominance (with up to 1,000 wbc/mm^3), which becomes lymphocytic within the next 12 h; this is seen typically with enteroviral infections. Specimens should be obtained for viral culture from CSF, blood, and stool, if appropriate. Viral culture has a relatively low sensitivity for diagnosis of enteroviral meningitis and the poor growth of some enteroviral phenotypes [175]. Serology requires acute and convalescent samples and is therefore a relatively slow process. Techniques that use PCR-based assays of CSF are more sensitive and diagnostically accurate.

Often bacterial and viral meningitis are indistinguishable, and as bacterial disease is associated with high long-term morbidity and mortality, it is prudent to start treatment with an appropriate broad spectrum antibiotic. The management of viral meningitis includes the support of systems that are affected, such as neurointensive care, management of seizures, and airway protection. Some antivirals are available and may be considered for specific viruses or in immunocompromised hosts.

Tuberculous Meningitis

Tuberculous meningitis (TBM) is a severe complication of infection with Mycobacterium tuberculosis. TBM has been reported worldwide and is an important public health problem in many developing countries and in poorer socioeconomic groups in developed countries. Where HIV is endemic, an ever-increasing number of patients are developing infection with TB (up to 18 % HIV + patients reported in endemic areas) [176]. It is associated with both high morbidity and mortality. The tubercle bacteria reach the CNS through hematogenous spread from a primary pulmonary focus; this hematogenous seeding can lead to other syndromes including tuberculoma, TB brain abscess, and spinal cord tuberculous leptomeningitis [177]. TBM arises following the rupture of a caseous focus into the ventricles or meninges.

Tuberculous meningitis usually has an insidious onset. The presentation is non-specific with a variable fever, headache, and neck stiffness, often with an altered mental status, seizures and focal changes [178]. Because of this there is often a delay in presentation and diagnosis. Diagnosis is confirmed by LP, and the findings are typically a leukocytosis (mostly lymphocytes), elevated protein, and a CSF:plasma glucose < 50 %. The interferon-γ-release assays (QuantiFERON –TB gold and T-SPOT-TB) are a recent advance in the diagnosis of infection with TB. These tests measure the in-vitro production of interferon-γ by sensitized lymphocytes in response to *Mycobacterium tuberculosis-specific* antigens. The genes which encode these antigens are present in *M. Tuberculosis*, therefore these tests are more specific in the diagnosis of infection [179]. Currently these tests are only licensed for the diagnosis of latent tuberculosis, and cannot be recommended for the diagnosis of acute CNS Disease [180]. A Mantoux test is positive in the majority of patients, and a chest radiograph may be abnormal in upto 50 % of cases. Therapy should not be delayed while awaiting microbiological confirmation of the diagnosis. Bacilli may be present in the CSF following the start of treatment; cultures will confirm the diagnosis, but these results can take several weeks to become positive. Cranial CT scan may be of value in making the diagnosis; characteristic appearances include basal enhancement, cortical thrombophlebitis, or tuberculomas, together with ventricular dilatation in up to 84 % of cases [181, 182].

The outcome of TBM is dependent upon the stage at which appropriate treatment is commenced [183], and of course, where this is delayed, neurological sequelae will result. The most important factor appears to be delay in presentation prior to admission to hospital. While most studies show that appropriate therapy is started within 4 days of admission, there is no clear evidence that delay beyond this is associated with a worse outcome. It may be that children where there is this degree of delay are already in a poor prognostic group, so any further delay does not significantly worsen outcome. The presence of hydrocephalus on scanning is particularly associated with advanced stage of disease and a worse outcome [184]. The presence of HIV infection does not appear to be a significant factor as long as therapy for the TBM is not significantly delayed.

The optimal treatment has been under considerable discussion and the optimal regimen is still not fully established. Since the advent of bactericidal drugs that penetrate the BBB well, this has avoided the need for intrathecal therapy. Isoniazid (INH), rifampin and pyrazinamide penetrate the BBB well, whether or not there is meningeal inflammation [185], while ethambutol, and streptomycin only achieve therapeutic levels where meningeal inflammation is present. Current regimens involve a combination of INH, rifampin and pyrazinamide, together with ethambutol or streptomycin, as INH resistance is becoming increasingly common. Monitoring of liver function is essential during the early weeks of treatment. Although it has been suggested that

treatment for 6 months is probably sufficient where the likelihood of drug resistance is low, treatment is recommended for 12 months [186]. Treatment with INH, Rifamipicin, Pyrazinamide and Ethambutol can be given for 2 months, with Isoniazid and Rifampicin treatment required for 12 months. Several studies have reviewed the use of adjunctive corticosteroid treatment, and the British Infection Society guidelines recommend their use in TB meningitis regardless of the severity of disease at presentation. Children should be given either prednisolone (4 mg/kg/day) or dexamethasone (0.6 mg/kg/day) for 4 weeks, followed by a reducing course over a 4 week period [180]. Where there is obstructive hydrocephalus, neurosurgical intervention is required and early ventriculo-peritoneal shunting should be considered. In addition, with the emergence of drug resistant *M. tuberculosis*, the presence of risk factors should lead to susceptibility testing and additional treatment may be required.

Fungal Meningitis

Fungal meningitis is more common in the immunocompromised population. Cryptococcal meningitis has been more commonly identified and the population at highest risk include those with HIV infection [187]. Cryptococcal infection is less common in children than adults, and more commonly is seen in adolescents. Symptoms include headache, fever, neck stiffness, photophobia, with focal findings (e.g. VI nerve palsy), and subtle neurological signs. There may be other lesions in extra-neural areas, including liver, lymph nodes, and the lungs.

Diagnosis is by the identification of *Crypotococcus neoformans* in culture specimens of CSF or cryptococcal antigen test in serum or CSF. When the diagnosis has been confirmed, treatment is with Amphotericin B +/− Flucytosine or Fluconazole. The choice of therapy is dependent upon the severity of disease and degree of immunocompromise. A communicating hydrocephalus may complicate this, and serial LPs to relieve pressure or placement of a lumbar CSF drain may be required. These procedures have their own risks including the risk of introduction of infection and should be carried out weighing risks versus benefits in this population. The duration of therapy is life-long in patients with HIV infection. Intrathecal treatment with Amphotericin B is indicated for some patients.

Encephalitis

Encephalitis is inflammation of the brain parenchyma and presents as diffuse or focal neuropsychological dysfunction. It can occur following any infective process, the more common organisms include *Mycoplasma pneumoniae*, herpes simplex virus (HSV), the enteroviruses, adenoviruses, influenza viruses and Japanese B virus. The CNS may be affected leading to a variety of "syndromes", which vary from the more benign to catastrophic CNS illness and post-infectious encephalopathies.

Pathophysiology

Viruses spread to the CNS via hematogenous or neuronal routes. Hematogenous spread is more common and leads to an alteration in the BBB, as seen in arthropod-borne viral infections. Following an insect bite, there is a local viral replication in the skin, followed by transient viremia, seeding of the reticuloendothelial system and sometimes muscle. Continued replication and secondary viremia leads to infection of other organs. In acute viral encephalitis, capillary and endothelial inflammation of cortical vessels is seen and this takes place within the grey matter or at the grey-white junction. Perivascular lymphocytic infiltration occurs following passive transfer of a virus across the endothelium at pinocytic junctions of the choroid plexus or due to active viral replication in the capillary endothelial cells [188].

Viruses also move into the CNS via intraneuronal routes, for example the herpes virus [189]. Other data suggest the olfactory tract a route of access [190]. On reaching the brain, either the virus lies dormant, or replication can take place intraneuronally or can lead to cell-to-cell or extracellular spread. Encephalitis due to *M. pneumoniae* may occur following direct bacterial invasion of the brain parenchyma, or due to auto-immune or thrombo-embolic phenomena [191]. The organism has been isolated following brain culture in a patient who died from disseminated infection. In other patients with encephalitis, *M. pneumoniae* has been cultured or identified by PCR.

Clinical Presentation and Diagnosis

The classic features of acute encephalitis are fever, headache, together with an altered level of consciousness, which typically follow a prodrome including myalgia, with perhaps a respiratory infection. Several other findings include disorientation, behavioural disturbances, focal neurological signs, and seizures, including status epilepticus [188]. The clinical signs and symptoms represent disease progression and specific areas of brain involvement, which may be due to the action of the specific microbe (e.g. herpes virus has a predilection for the temporal lobe).

When searching for an infecting pathogen, it is important to establish certain epidemiological features including time of year, travel, and contacts. For example in temperate climates, enteroviral infections are predominant during late

summer and early winter. As long as there are no contraindications, an LP is essential. Typical findings include pleocytosis (mononuclear cells predominate) with an increase in CSF protein. Some patients (3–5 %) may have normal CSF, and under these circumstances, the diagnosis is made using assays to detect viral antigens or nucleic acids, as viral culture is of limited use. Cerebral imaging is a valuable tool and MRI changes may be present early on the disease. Characteristic changes may be present on an electroencephalogram (EEG). For example, the periodic high-voltage spike wave activity seen coming from the temporal lobes and slow-wave complexes at 2–3 s internals are often seen in patients with HSV infection [192].

Immunocompromised children may be at risk from other causative organisms, and these may include infection with the following: Cytomegalovirus, Ebstein Barr Virus, Human Herpes Virus 6/7, Polyomavirus J-C, HIV, and Lymphocytic choriomeningitis virus [193].

Therapy

It is not always possible to isolate the causative organism. In such circumstances, it is prudent to commence treatment with broad-spectrum antimicrobials and to cover the more common causative agents. Where identification has been possible, therapy must be tailored to the appropriate clinical context. There are some specific therapies available for specific organisms as described below. Appropriate supportive intensive care may be required including the use of neuroprotective strategies. Newer antivirals are continually being identified and may be more useful in the future. Where organisms which cause encephalitis are endemic, such as Japanese B virus, then vaccination programs will lead to a reduction in prevalence and incidence of disease.

Mycoplasma pneumoniae Encephalitis

Mycoplasma pneumonia is thought to be responsible for up to 10 % of acute childhood encephalitis in Europe and North America. One group reported *M. pneumoniae* associated with 70 % of patients with a confirmed etiology. The association of CNS complications with *M. pneumoniae* infection were confirmed in the last 25 years, following isolation of the organism in the brain and CSF [194]. In the majority of patients who develop an encephalitic illness there is a history of a respiratory tract infection, but this is not seen in all cases [195]. Other neurological manifestations include myelitis and cranial nerve palsies [196].

The pathogenesis of *M. pneumoniae* leading to an encephalitic picture is not fully clear. There are reported cases where the pathogen has been reported as both present or not present in the CSF. Therefore, it is presumed that there are different pathogenetic mechanisms [197]. In children, it appears that there may be an early-onset and a late-onset encephalitis; the early is likely due to direct invasion and the later, a post-infectious illness [198]. In addition to direct spread of the organism, *M. pneumoniae* has also been demonstrated in the bloodstream using real-time PCR. Other postulated mechanisms include the formation of immune complexes, the formation of cross-reacting antibodies, and the production of a neurotoxin. The production of cytokines may also play a part in the pathogenesis of this encephalitis, with increased levels of interleukin-6, interleukin-8 and interleukin-18 present [199].

Confirming the diagnosis of *M. pnuemoniae* infection may be undertaken by several modes. These include culture of the organism itself, PCR, and serology. *M. pneumoniae* replicates slowly and may take up to 4 weeks for isolation. The investigations are labor intensive and overall the yield is better in respiratory secretions. CSF culture is rarely positive. Several PCR assays have been described, and these have a more rapid turnaround time and are more sensitive tests. The mainstay of diagnosis of infection with mycoplasma is by the use of serology. This is a complement fixation test, and for respiratory disease, the tests have good sensitivity and specificity, however, for non-respiratory infection, the specificity is reduced. Immunoglobulin M (IgM) complement-fixing antibodies may be detected 1 week after the onset of the illness, while IgG antibodies are present 5 days later. The peak IgM response is from day 10–30, usually falling to undetectable by 3–6 months [200]. There are no CSF, EEG or neuroimaging findings, which typically follow mycoplasma infection.

In patients with *M. pneumoniae* encephalitis, a temporal clinical improvement has been reported in children treated with antibiotics. On the other hand, some children recovered with no antimicrobials. Macrolides are considered the antibiotic of choice for infection with *M. pneumonia*. The disadvantages of macrolides lies in their poor penetration of the BBB in order to achieve therapeutic levels within the CNS, although azithromycin has been found to achieve a high concentration in brain tissue [201]. Macrolides may also have a beneficial anti-infammatory activity. Other agents which have been used for CNS disease include erythromycin, clarithyromycin, tetracycline, doxycyline, chloramphenicol, ciprofloxacin and streptogamins. The choice of antibiotic is based on several factors. Where there is likely direct CNS invasion, based on clinical presentation, and detection of *M. pneumoniae* in CSF, then antibiotics that achieve therapeutic levels in the CNS should be used. Where there is no direct CNS invasion and the clinical syndrome is due to an autoimmune or thromboembolic process, then the need to achieve high CNS levels is less urgent. However, if there is any doubt appropriate antibiotics should be commenced while awaiting diagnostic reports.

Herpes Simplex Encephalitis

HSV is the most common cause of acute viral encephalitis [188]. It is characterised by an often focal necrotising process, although in neonates there is more widespread destruction. The estimated frequency is one case per 250,000–500,000 population per year, with 30 % of cases affecting individuals under 20 years old [202]. Without effective treatment the mortality is greater than 70 % [177]. In immunocompetent adults, over 90 % of cases of herpes simplex encephalitis are due to HSV-1 infection, and the rest are due to HSV-2 infection. A large majority of these are due to reactivation of latent HSV-1.

Neonates infected with HSV can have a devastating disease. The incidence varies between 1.65/100,000 live births in the UK to 20–50/100,000 live births in the USA [203, 204]. Infection may result from either HSV-1 or HSV-2, and disease associated with HSV-2 has been shown to have a worse outcome. HSV-2 is the type found in 70 % of neonatal HSV infection worldwide. Neonatal HSV infection is largely acquired during vaginal delivery due to virus which has been shed in the maternal genital tract. Up to 5 % of cases may be due to congenitally acquired infection, either following ascending infection, or transplacental trasnsmission. Infection may be acquired postnatally in up to 10 %, usually following contact with an environmental source of HSV. HSV infection in neonates leads to different disease patterns: (a) disease localized to the skin, eye and mouth, (b) CNS disease (with or without skin, eye, and mouth involvement), (c) Disseminated disease with multi-organ failure [205].

The clinical features of HSV encephalitis are fever, altered conscious level, behavioral disturbance, and focal neurological signs, often being seizures or motor deficits. Less common are signs more consistent with a meningeal syndrome. Some case reports describe an anterior opercular syndrome as occurring as an early presentation of HSV encephalitis in children [206]. Opercular syndrome consists of the development of oro-facial palsy, dysarthria and dysphagia due to a loss of voluntary muscle control.

In HSV encephalitis, the following abnormalities are typically seen on examination of the CSF: elevated mononuclear cells, elevated protein, a lymphocytic pleocytosis of 10–500 cells/mm^3 is present in 85 %, there may be an increase in red blood cells (10–500/mm^3) and there may be a reduction in glucose. PCR of the CSF is the gold standard investigation. In one study, CSF PCR was positive in 98 % of patients, with biopsy-proven disease, this equates to a sensitivity of 98 % and specificity of 94 % [207]. After 10 days of treatment, HSV DNA may not be detectable in CSF and PCR results will be negative. CSF antibody measurements may be then useful for retrospective analyses, or where CSF was obtained late and therefore PCR was negative. Where the index of suspicion is high, where there is for example an acute meningo-encephalitic process, and the initial PCR negative, the result should be interpreted with caution, and repeat LP should be performed, while continuing appropriate therapy. Indirect serological assays can be used to confirm a diagnosis with the presence of HSV IgM, where making the diagnosis is more challenging. In addition, virus cultures are only of value in patients older than 6 months.

The majority of patients have abnormal neuroimaging. Cerebral CT scans may be normal early on in the illness, and then go on to show changes consistent with cerebral lesions. MRI is more sensitive and changes are demonstrated early in the course of the illness [208]. The typical findings seen are edema and necrotic-hemorhagic of the medial temporal lobes, the lingual and the orbital area of the frontal lobes. The EEG is a very sensitive test and typically shows changes consistent with non-specific slow-wave activity early in the illness, moving to paroxysmal sharp waves or triphasic complexes in the temporal lobes. In some cases periodic-lateralising epileptiform discharges arise from the temporal lobe at 2–3 Hz.

Where HSV encephalitis is suspected, then appropriate treatment must be commenced as soon as possible, as antiviral treatment is effective and reduces the morbidity and mortality. Aciclovir is the treatment of choice. The current standard of care for adults and children over the age of 3 months is intravenous aciclovir at a dose of 10–20 mg/kg every 8 h for 21 days. Neonates should be treated with 20 mg/kg every 8 h or 500 mg/m^2 every 8 h for 21 days, and with this regimen, mortality from neonatal HSV encephalitis has fallen to 5 %; 40 % of survivors develop normally. It is recommended that CSF PCR be repeated following completion of therapy in order to monitor treatment response. This may be challenging to do in a clinically improved child. Persistence of HSV DNA in the CSF may indicate persistent active viral replication. The concern is that this might indicate an early relapse if antiviral treatment is stopped, or, might represent HSV DNA that persisted in brain cells and later released in CSF due to the ongoing neuronal damage [209].

Outcome is dependent upon age of patient, level of consciousness at presentation, duration of encephalitis, and viral load in patients treated with aciclovir. If Glasgow Coma Score (GCS) <7, outcome is universally poor. Where treatment was instituted less than 4 days following the onset of symptoms, the survival at 18 months increased from 72 % to 92 % [210].

Relapse may occur despite appropriate therapy, with some studies quoting relapses in upto 26 % of patients [211]. Where neonates with HSV encephalitis were treated with acyclovir 10 mg/kg every 6 h for 10 days were found to have a virological relapse. Relapses tend to occur between 1 week and 3 months following an initial improvement following a course of treatment between 10 and 14 days. Where treatment

regimens last for 21 days at higher doses, relapse has not been documented. There have been anecdotal reports examining the use of oral valaciclovir as adjunctive therapy for a prolonged period following an intravenous course of aciclovir, to prevent CNS relapses. However, no trial data is available.

The recommended treatment for HSV encephalitis remains intravenous acyclovir. However, in resource-poor countries, intravenous formulations are usually unavailable or unaffordable. A recent report examined the penetration of acyclovir into the CSF in patients with HSV encephalitis, treated with the oral prodrug valacyclovir at 1,000 mg three times daily. The oral therapy achieved adequate acyclovir concentrations in the CSF and may be an acceptable early treatment for suspected HSE in resource-limited settings [212].

Enteroviral Encephalitis

The enteroviruses include polioviruses, coxsackie viruses, and echoviruses, and infection with these lead to a wide variety of clinical illnesses. Infection with some of these pathogens results in a neurological syndrome, for example the poliomyelitis. As discussed previously, enteroviral infection may result in aseptic meningitis, and less commonly in infancy, encephalitis. The use of real-time PCR has made diagnosis of enterovirus more specific, faster and sensitive than viral culture. Culture is no longer necessary for clinical diagnosis and should only be performed on PCR-positive samples to obtain isolates for typing purposes [213].

In 1998, cases of enteroviral encephalitis due to enterovirus 71 were reported in Taiwan [214]; the majority of patients were less than 5 years old, with a reported mortality of 19.3 % in this group. The enterovirus 71 was isolated in 75 % of patients and 92 % patients who did not survive. The clinical syndrome at presentation was rhombencephalitis with myoclonus, tremors, ataxia, and cranial nerve involvement. Some children had brain stem dysfunction, which was associated with a poor prognosis. MRI scans in these patients revealed high-intensity lesions localised to the midbrain, medulla and pons. There was a high incidence of long-term neurological sequelae among survivors. Par-echo virus as a cause of meningitis, encephalitis, sepsis syndrome and myocarditis has been recently recognised. The virus has been isolated in the CSF of infants, more commonly in younger infants and neonates. Disease is noted to be more prevalent in the late summer and early autumn and has been associated with leukpenia. The virus is detected using real-time PCR [215].

There is no effective antiviral therapy for the treatment of enteroviral encephalitis, therefore management is supportive. There are reports of the use of IVIG in immunocompromised children with chronic enteroviral meningoencephalitis [216].

Rabies

Rabies follows infection with a rhabdovirus and is virtually uniformly fatal, with 300,000–700,000 deaths each year. Rabies is typically transmitted through infected animal bites; however, it is possible to prevent Rabies developing by appropriate immunisation (active and passive) even when infection has occurred [217]. The primary vector for infection is an infected dog, but transmission can also occur from bats and wild terrestrial mammals [218]. Rabies is caused by an RNA rhabdovirus, belonging to the rhabdoviridiae family, genus *Lyssavirus*. There appear to be several viruses with at least six types of serotypes identified, leading to the clinical picture of Rabies. Using genetic sequencing, it is possible to clarify which animal was the vector for transmission to human [219].

The incubation period is typically between 20 and 60 days, but may vary from 5 days to several months. The prodrome with fever, malaise, anxiety and itching at the site of inoculation is followed by an encephalitis or paralytic illness. This is then followed by coma, cardiorespiratory failure and death. This is followed by an acute neurologic syndrome which develops 2–7 days following the prodrome. The features within this include dysarthria, dysphagia, excessive salivation (the popularised feature of "frothing at the mouth"), diplopia, vertigo, nystagmus, restlessness, agitation, visual and auditory hallucinations, manic behaviour alternating with lethargy, hydrophobia due to pharyngeal muscle contraction, and polyneuritis. This encephalitis is seen in 80–85 % of cases, whereas the paralytic illness is less common. This is then followed by coma, cardiorespiratory failure and death. The diagnosis is made by detection of the rabies virus RNA in saliva using reverse transcriptase PCR, or by biopsy of brain showing viral antigen [220]. It is possible to isolate virus-specific fluorescent material in skin biopsy specimens; antirabies antibodies in serum or the CSF of unimmunized patients. Management of infected patients is supportive, and once patients have symptoms, there is no benefit from the use of antirabies vaccine of rabies immune globullin.

Arthropod-Borne Encephalitis Viruses

Bites from arthropods are major causes of encephalitis worldwide. The viruses transmitted by arboviruses are from the following families:

Togaviridae – Alphavirus (Eastern equine, Western equine, Venezuelan equine)

Falviviridae – West Nile complex (St. Louis, Japanese, Murray Valley, West Nile, Ilheus, Rocio)

Tick-borne complex – Far Eastern, Central European, Kyasanur Forrest, Lopuing-III, Powassan, Negishi

Bunyviridae – Bunyavirus (California, La Crosse, Jamestwon Canyon, Snowshoe Hare, Tahyna, Inkoo), Phlebovirus (Rift Valley)

Reoviridae – Orbivirus (Colorado tick fever)

These viruses commonly cause an encephalitic illness, but we will concentrate on a limited number of important viruses associated with encephalitis.

Japanese Encephalitis

Japanese encephalitis, which is transmitted by the Culex species of mosquitoes, is responsible for the majority of arthropod-borne viral encephalitis. Japanese encephalitis is concentrated largely in China and Southeast Asia although it has been spreading to India, Pakistan, Russia, the Philippines and Australia [221]. Children are predominantly affected. The typical disease presentation is a non-specific illness followed by fever, headache, vomiting and altered mental status, with seizures and neck rigidity reported in 85 % of children. There is a coarse tremor, dystonia, rigidity, and a characteristic "mask-like" facies. MRI shows a pattern of mixed intensity or hypodense lesions in the thalamus, basal ganglia and midbrain. LP confirms the diagnosis with the presence of specific IgM in the serum and CSF [222]. Therapy is supportive only. There is a mortality rate of up to 30 %; and up to 60 % of survivors are left with severe neurological sequelae.

Tick-Borne Encephalitis

Tick-borne encephalitis is caused by another member of the Flavivirus family. It is transmitted from the bite of infected ticks, although occasionally infection may occur following the consumption of unpasteurised milk. It is predominantly found in Northern and central Europe, but has spread as far as northern Asia and Japan. The incidence in Western Europe has increased over the last 30 years. Between 1990 and 2007 there was an average of 8,755 reported cases of TBE per year, an increase of 400 % [223]. The virus replicates at the inoculation site, then spreading to local lymph nodes, followed by viral replication. This is followed by the development of plasma viraemia and via haematogenous spread to other organs, and across the blood brain barrier. The clinical course is bi-phasic with a non-specific febrile illness following the 7–14 day incubation period leading to a clinical picture of meningo-encephalitis. Features include seizures, tremors, ataxia, cranial nerves dysfunction. The disease may become chronic with epilepsy, parkinsonism or neuritis. Most children recover without sequelae. Diagnosis is thorough blood PCR, and virus isolation and treatment is supportive.

West Nile Virus

West Nile Virus is now endemic in the United States, but it is usually found in Africa, Asia, Australia and Europe. The mode of transmission is via the mosquito, although human-to-human transmission has been reported through blood transfusion from viremic patients, transplantation of infected organs, intra-uterine infection and potentially through breast milk [224]. Encephalitis, meningitis, tremore and paralysis have been reported in children. Onset of illness is usually abrupt with fever, headache, myalgia and weakness. In neuroinvasive disease there may be headache, neck stiffness, mental state changes, parkinsonism, seizures or acute flaccid paralysis, similar to that seen in poliovirus infection. Diagnosis is by the detection of WNV IgM antibodies in cerebrospinal fluid. Management, as in most athropod-borne viral encephalitis, is supportive.

Cerebral Malaria

Malaria is the most common parasitic disease worldwide affecting about 5 % of the world's population at a single time, leading to 0.5–2.5 million deaths each year [225]. *Plasmodium falciparum* is responsible for the majority of deaths and long-term sequelae. Those at highest risk include the local population in endemic areas and travellers to these regions. The incubation period of cerebral malaria is 2 weeks, and without treatment it is rapidly fatal, with up to 50 % mortality. Severe malaria may manifest as anemia, hypoglycemia, metabolic acidosis, repeated seizures, coma or multiple organ failure.

Cerebral malaria is the most severe neurological manifestation of severe malaria. With an incidence of 1,120/100,000/year in the endemic areas of Africa, children are primarily affected. Peak incidence is in pre-school children and at least 575,000 children in Africa develop cerebral malaria annually [226].

Clinical Features and Diagnosis

Cerebral malaria has been defined by the World Health Organisation as a coma in the presence of a *P. falciparum* asexual parasitaemia, after the correction of hypoglycemia and exclusion of other encephalopathies [225]. The clinical spectrum of cerebral malaria varies from impaired consciousness to coma. It is thought that the clinical manifestations are due to parasitized red blood cells being sequestered in the cerebral microcirculation, together with other factors including metabolic derangements and inflammatory mediators. Typically there is a 1–3 day history of fever, followed by the sudden onset of seizures; the seizures often proceed to coma. The more commonly seen seizures are focal motor and generalized tonic-clonic, and subclinical seizures may be seen on EEG. There may be other features of disease present including headache, malaise, vomiting and diarrhea, followed by

the development of jaundice, anemia, thrombocytopenia and splenomegaly, together with a marked metabolic acidosis and electrolyte abnormalities. Patients may have features of intracranial hypertension, retinal changes and brainstem signs. Clinical shock may be seen as part of the disease spectrum in severe cases. The morbidity and mortality associated with cerebral malaria is high, with neurological sequelae that vary from devastating global injury to transient abnormalities. The sequelae are more commonly associated with prolonged seizures, coma, hypoglycemia, and in some studies severe anemia.

Pathophysiology

The precise mechanisms of brain injury associated with cerebral malaria are not clearly defined, and the following factors will be discussed in more detail.

Parasitic Sequestration in Cerebral Microvasculature

It is thought that parasitic sequestration of red blood cells in the cerebral microvasculature has a key role leading to neural dysfunction following changes that occur in the tissue around sequestered parasites. Sequestration results from adherence of pRBCs to the endothelial lining (cytoadherence) using parasite-derived proteins exposed on the erythrocyte surface. A group of parasite antigens including Plasmodium falciparum erythrocyte membrane protein-1 (PfEMP-1) mediate binding to host receptors of which, intercellular adhesion molecule-1 (ICAM-1) is the most important. The sequestered parasite mass is further increased when adherent erythrocytes agglutinate with other pRBCs, form rosettes with non-parasitized erythrocytes, or use platelet-mediated clumping to bind to each other. Sequestration impairs perfusion and may aggravate coma through hypoxia. Furthermore, the ability of pRBCs to deform and pass through the microvasculature is decreased [227]. Therefore, hypoxia and inadequate tissue perfusion may be major pathophysiological events. Although a critical reduction in metabolite supply (oxygen and glucose) may occur, in the majority of children, significant neural tissue necrosis is unlikely since with specific antimalaria treatment, coma is rapidly reversible. However, in the presence of increased metabolic demand such as during seizures and fever, the risk of neural injury is higher and may be worse if the patient is hypoglycemic or if blood flow is further compromised by intracranial hypertension.

Cytokines, Chemokines and Excitotoxicity

Tumor necrosis factor (TNF), the most extensively studied cytokine in cerebral malaria, upregulates ICAM-1 expression on the cerebral vascular endothelium increasing the cytoadhesion of pRBCs. Several other cytokines and chemokines are important and in particular, interleukin (IL)-1b, IL-6 and IL-10. The role of nitric oxide (NO) is controversial. NO is involved in host defense, maintaining vascular status and in neurotransmission and is thought to be an effector for TNF. It is suggested that inflammatory cytokines upregulate inducible NO synthase in brain endothelial cells leading to increased NO production. Nitric oxide can cross the blood brain barrier (BBB), diffuse into brain tissue and interfere with neurotransmission and may therefore partly be responsible for the reversible coma [228].

Other inflammatory products such as the metabolites of the kynurenine pathway - quinolinic and kynurenic acid - may also be important in pathogenesis. Quinolinic acid is a NMDA receptor agonist and an excitotoxin. It causes seizures in animal models of brain disease while kynurenic acid is an antagonist and is generally thought of as neuroprotective. Excitation by quinolinic acid may contribute to convulsions in cerebral malaria. In children, there are graded increases in CSF concentration across outcome groups of increasing severity [229]. Because of the role of NMDA receptors in modulating neurotransmission and as agonists, high levels of quinolinic acid may have long-term deleterious effects on cognitive function.

Endothelial Injury, Apoptosis, BBB Dysfunction and Intracranial Hypertension

There is widespread endothelial activation in vessels containing pRBCs and in addition, interactions between pRBCs and platelets cause further injury to endothelial cells through a direct cytotoxic effect. Intracranial hypertension is common in African children; up to 40 % of children with deep coma have brain swelling on computerized tomography scans. BBB dysfunction may contribute to the hypertension although increased cerebral volume could be caused by sequestration and increased cerebral blood flow from seizures, hyperthermia or anemia. Intracranial hypertension reduces cerebral perfusion pressure, nutrient and oxygen delivery and can lead to global ischemic injury, herniation, brainstem compression and death. Ischemic injury is seen on acute computerized tomography and pattern of injury is consistent with a critical reduction in perfusion pressure [226].

Cerebral Blood Flow and Perfusion

Patients with cerebral malaria have increased cerebral blood flow. This increase is probably an adaptive response to high a metabolic demand to match oxygen and nutrient delivery to requirements [230]. Because the patches of brain affected are small, with early treatment and rapid relief of obstruction, there is minimal tissue necrosis and early restoration of perfusion may explain the near complete recovery of gross neurological function in most patients. However, hypoxia still leaves many children with subtle (e.g. cognitive) deficits. In

those who die or develop severe brain injury, the sequestered mass may be higher, blood flow obstruction not readily reversed and hypoxic and ischemic injury more widespread.

Seizures

Plasmodium falciparum is epileptogenic and the risks of seizures increases with parasitaemia. Any form of seizure disorder is at risk of brain injury and the prolonged seizures that take place in children with cerebral malaria will place patients at risk of long-term neurological sequelae.

Depth, Duration and Cause of Coma

Where there are multiple factors associated with the development of coma, this will of course be associated with further compromise in neurological status and increase the risk of death,

Management

Immediate treatment involves management of airway, breathing and circulation together with management of intracranial hypertension as described previously. Hypoglycemia must be corrected immediately and acid-base and other electrolyte abnormalities should be corrected. Where shock is part of the clinical presentation, appropriate fluid management is vital. Where acidosis and shock co-exist with coma this presents a challenge. A recent study of fluid management in children with clinical underperfusion in Africa, the majority of which had severe malaria noted that bolus fluids in these children increased the risk of mortality compared to maintenance fluid management. It is clear that in this population, careful fluid management is vital [231].

Guidelines for antimalarial therapy are determined by local resistance patterns. Intravenous artemensin derivatives such as artesunate have replaced Quinine as first-line therapy for patients with severe malaria [232]. Other adjunctive therapies include exchange transfusions, and are used when patients are on maximal therapy with a high peripheral parasitemia; but no properly conducted trials have been undertaken to evaluate any of these therapeutic modalities.

Brain Abscess/Subdural Empyema

Intracranial collections of pus, while they are eminently treatable, are serious and potentially life-threatening conditions where the consequences of delay in diagnosis can be catastrophic. Optimal management requires close cooperation between pediatrician, radiologist, neurosurgeon and microbiologist. Brain abscesses are unusual, but they are the most common cause of focal CNS infection.

Predisposing Factors, Incidence and Epidemiology

Intracranial pus collection results from the invasion of infectious organisms as a consequence of spread of contiguous infection from non-neural tissue, the result of hematogenous spread from a remote site, or direct mechanical introduction following penetrating trauma or surgical procedure. In children with normal immunity, brain abscess most commonly occurs in those with chronic suppurative upper respiratory tract (URT) infection – in particular of sinuses, middle ear and mastoid air cells, infection of the soft tissues of the face, orbit or scalp; penetrating skull injury; comminuted fracture of the skull; cranial surgery, including the insertion of ventriculoperitoneal (VP) shunt; congenital lesions of the head and neck, including dermal sinuses usually located over the posterior fossa – or in those with cyanotic congenital heart (CHD) disease. It is relatively uncommon for bacterial meningitis to be complicated by abscess formation in children, but this is the most common cause of brain abscess in neonates and infants [233]. Children with defects in cellular immunity, such as occur in HIV infection and AIDS; following therapy for malignancy, or bone marrow transplantation are at increased risk of cerebral abscess caused by the protozoal pathogen Toxoplasma Gondii, or fungi such as Aspergillus species. About 15 % of brain abscess seem to occur without any clear predisposing factor. Subdural empyema, as in brain abscess, is also associated with chronic URT infection, but in contrast to brain abscess, has a strong association with bacterial meningitis, particularly that due to *Haemophilus influenzae* and *Streptococcus pneumoniae*.

Both brain abscess and subdural empyema are rare. The incidence of brain abscess at all ages has been estimated at about 1/100,000, and subdural empyema appears to be even more rare [20]. The incidence of brain abscess varies considerably between populations, particularly in relation to the different predisposing conditions. It is relatively more common where chronic URT infection is widely found, and in childhood occurs particularly in adolescents with chronic sinus or mastoid disease. For example, otitis media is the primary infection in almost 70 % of brain abscesses observed in China, but only about 30 % of those in Europe.

Intracranial extensions of sinusitis are infrequent in the antibiotic era, and occur in about 4 % of patients hospitalized with sinusitis. Despite being uncommon, subdural empyema and brain abscess is the second most common complication of acute sinusitis. Even though the exact incidence of suppurative intracranial complications in sinusitis is unknown, paranasal sinusitis and dental infections are the origin of a third to two thirds of these complications [234]. Intracranial complications of sinusitis are potentially life threatening and include meningitis, epidural empyema and abscess, venous sinus thrombosis (cavernous and sagittal), and intraparen-

chymal brain abscess. Usually, abscesses are single, but they are multiple in 13 % of cases. These complications, even though rare, should always be watched for in patients with sinusitis. Where antibiotics are routinely prescribed for upper respiratory infection, the incidence of brain abscess has declined, and the majority now occur in children with CHD, although even in this condition it is rare below the age of 2 years.

The prevalence of brain abscesses in children with cyanotic congenital heart disease is 6–51 %. Of patients diagnosed with a brain abscess, 30–34 % have underlying heart defects. Pronounced right-to-left shunting secondary to cardiac defects increases the risk of brain abscesses due to paradoxical emboli. Most cyanotic lesions and large shunts are known to predispose children to brain abscesses.

Available data indicate that the underlying cause of brain abscesses is endocarditis in about 10 % of patients, bacteremia in 8 %, immune deficiency in 12 %, skin follicultis in 1–3 %, and pulmonary infection in 0.7–9.8 % [235]. The contiguous spread of infection into the cerebral parenchyma is another significant cause of brain abscesses in children. Otitis media, sinusitis, mastoiditis, dental infections, and meningitis are predisposing factors. Temporal lobe or cerebellar abscesses can occur by direct extension of infection via the tegmen tympani, or translabyrinthine spread in otitis media or mastoiditis. Frontal or temporal lobe abscesses can occur with direct spread of infection caused by paranasal sinusitis. It has been hypothesized that the anatomy of the paranasal sinuses provides a favorable environment for the intracranial extension of infection. Venous mucosal drainage occurs through the small diploic veins extending through the bony sinus wall, which communicate with the venous plexuses of the dura mater of the inner table, the periorbita for the orbital plate, and the cranial periosteum for the outer table. Up to 16 % of brain abscesses in children are a result of cranial injuries.

Pathophysiology

At the histological level, pyogenic brain abscess formation is typified by a number of sequential pathological changes that have been elucidated using experimental animal models. In humans, staging has been based on findings obtained using CT and MRI scans. There are four histological stages. The early stage is that of evolving cerebritis (usually days 1–3), typified by neutrophil accumulation, tissue necrosis and edema. Microglial and astrocyte activation is also evident at this stage. The late cerebritis stage (days 4–9), is associated with a predominant macrophage and lymphocyte infiltration, leading to central liquefaction with early formation of a capsule of vascular connective tissue (days 10–13) and later maturation of this capsule (day 14 onwards), effectively sequestering the lesion and protecting the surrounding brain parenchyma from additional damage. In addition to limiting the extent of infection, the immune response that is essential for abscess formation also destroys surrounding normal brain tissue [236]. In the context of chronic suppurative URT infection, the initiating event is probably thrombophlebitis spreading from an extracranial focus via penetrating emissary veins to a venous sinus, leading to congestion and inflammation of the underlying brain. Abscesses that occur in this scenario are usually single and predictably located: frontal, or occasionally temporal when related to paranasal sinusitis; temporal or occasionally cerebellar when associated with ear infection. Children with CHD are at risk of developing microscopic areas of brain infarction due to severe hypoxaemia, coupled with the increased viscosity of polycythemic blood, in particular when reduced blood flow in brain microcirculation becomes critical during episodes of dehydration or cardiac dysfunction. Episodes of low-grade bacteremia are common as right-to-left shunting of blood bypasses the pulmonary capillary bed filter, and seeding of these devitalised areas establishes foci of cerebritis. In these conditions, abscesses are often multiple and may be located anywhere, though they are most commonly found in the distribution of the middle cerebral artery. In addition, brain abscess has been reported as a complication of skin infection of the scalp, pulmonary infection, dental abscess and bacterial endocarditis.

Table 40.6 depicts the most common signs and symptoms in children with brain abscess. Intraventricular rupture of the abscess or herniation may be indicated by exacerbation of a headache or a decline in the child's Glascow Coma Scale score, particularly in the context of meningeal signs. Neonates frequently present with signs of infection and increased intracranial pressure, seizures, and increased head circumference with bulging fontanelles. Additionally, children with brainstem abscesses typically present with fever and headache early in the infectious course, and paresis and cranial nerve palsies subsequently develop, especially involving cranial nerves III, VI, and VII. Classic brainstem syndromes are not frequently observed because the lesions

Table 40.6 Signs and symptoms in children with brain abscess

Symptoms and signs	Percent of children
Headache	65
Fever	55
Vomiting	53
Papilledema	48
Focal neurologic deficit	47
Change in mental status	43
Meningeal irritation	36
Seizure	34

Reprinted from Brook [234]. With permission from Elsevier

are more likely to elongate into the brainstem than expand laterally. The location of the abscess determines focal neurological signs, which can include paresis, visual field deficits, cranial nerve palsies, nystagmus, and other cerebellar signs. Papilledema has been reported in up to 70 % of cases. The incidence of hemiparesis is thought to be higher in children than in adults, possibly due to the result of a higher frequency of metastatic abscesses. In addition, larger abscesses may be associated with a significant mass effect and vasogenic edema. This may cause symptoms related to increased intracranial pressure and impending herniation.

Brain abscess should always be considered as part of the differential diagnosis of a febrile child with CHD or chronic URT infection, and delay in making the diagnosis usually represent a failure to consider the diagnosis where the presentation is with a non-specific illness, aggravated by a lack of ready access to computerised tomography (CT) imaging of the brain. Cases may occasionally present in a more fulminant fashion, with signs of rapidly progressive raised intracranial pressure, leading quickly to coma and impending herniation [235].

As the presentation is essentially that of an intracranial mass lesion, tumor is important in the differential diagnosis. Viral encephalitis (particularly those with a predilection for a focal encephalitis, such as Herpes simplex) can present with a similar constellation of symptoms and signs. Bacterial meningitis generally presents more acutely, but there are important examples with an insidious onset, such as tuberculous and cryptococcal meningitis. Similarly, acute vascular events, such as infarction and hemorrhage may present with similar features, as may acute hydrocephalus.

Imaging in Brain Abscesses

Computed tomography imaging has proved a valuable asset in the diagnosis of brain abscesses. This imaging modality allows localization of the abscess and demonstration of any associated edema or mass effect. Depending on the stage of the abscess, the lesion typically has a hypodense center with ring enhancement on contrast-enhanced studies.

The sensitivity of CT has been shown to be between 95 % and 99 %, and the specificity is decreased because of the difficulty in differentiating these lesions from other pathological processes such as tumors, cysticercosis, tuberculomas, or some vascular lesions. In cases in which the diagnosis is questionable, radiolabeled leukocyte scanning can be utilized. There have been reports of good diagnostic accuracy with this modality.

Magnetic resonance imaging (MRI) can be used to demonstrate even more anatomical detail and with superior resolution than CT scanning. Abscesses appear slightly hypointense on T1-weighted and hyperintense on T2-weighted images. On contrast-enhanced T1-weighted images, the lesion has a hypointense center and ring enhancement. Similar to CT, MRI's specificity may be compromised in differentiating abscesses from other lesions with similar imaging characteristics. The advantages of MR imaging over CT include better differentiation of edema from liquefactive necrosis, greater sensitivity for early satellite lesions, and more sensitivity in the detection of early cerebritis. Diffusion-weighted imaging has been shown to be a useful additional diagnostic modality in identifying brain abscesses. Restricted diffusion in brain abscesses has been assumed to be a consequence of inflammatory cells, necrotic debris, and the viscosity of the purulent material contained within the abscess [235].

Surgical and Medical Management of Brain Abscesses

There have been no randomized, controlled trials of the various treatments for brain abscesses. The management of brain abscesses may be influenced by the neurological status of the patient, the location of the abscess, the number and size of the abscesses, and the stage of abscess formation.

Medical Management

Brain abscesses in children should be managed by a multidisciplinary team that includes neurosurgeons and infectious disease practitioners. Systemic treatment with appropriate antibiotic agents plays a critical role. Patients usually require a minimum of 6–8-week course of intravenous antibiotics, which may be prolonged depending on the clinical context, such as in immunocompromised patients. Empiric antibiotic treatment with broad-spectrum agents is usually started until intraoperative cultures can be obtained, allowing tailoring of the antimicrobial agents to the identified pathogens. If possible, antibiotics should be held until after surgery to improve the yield of positive culture. However, antibiotics should not be delayed pending surgery.

In patients with surgically inaccessible lesions, early cerebritis, multiple small abscesses, or medical comorbidities, surgical drainage may not be possible and therefore specimens for culture will not be available. Broad-spectrum antibiotics are required in these cases in an attempt to target the possible microorganisms. Serial imaging studies are conducted to assess the effectiveness of antibiotic therapy.

Non-surgical management of intracranial abscesses is controversial. Selected cases may be suitable of the lesion(s) is (are) small, multiple and/or the surgical risk is high.

Cranial CT is not only useful in diagnosis, but may also monitor response to therapy. If therapy with aspiration and antimicrobial therapy is successful, repeat CT scanning should show decreases in degree of ring enhancement, edema, mass effect and size of lesion. The majority of abscesses that will resolve with antibiotics alone will do so within 4 weeks.

Antibiotic choice is directed initially by the likely microorganisms involved, later modified by results of microbiological evaluation. The usual empiric recommended regimen consists of a third generation cephalosporin (such as Cefotaxime or Ceftriaxone), Metronidazole and an antistaphylococcal penicillin (such as Flucloxacillin). However, this may be modified dependent on the child's underlying immune status, presumed etiology of the abscess and local resistance patterns. Once aspiration and culture have been performed, antimicrobials should be adjusted accordingly.

The place of intracavitary antibiotic therapy is not clearly defined, and carries the risk of direct cerebral toxicity of high concentrations of antibiotics on surrounding brain tissue. In the acute phase of the illness where surrounding cerebral edema may contribute to dangerously raised intracranial pressure, measures such as intravenous mannitol, or placement of an intraventricular drain, and the use of high-dose steroid therapy may be life- saving.

Corticosteroid use in the management of brain abscesses is controversial. The use of steroids is generally considered indicated when there is considerable mass effect secondary to significant cerebral edema leading to neurological deficits and/or impending herniation. There are no data regarding the use of steroid therapy in the routine management of cerebral abscesses.

It is unlikely that antibiotics alone can ever be sufficient once cavitation occurs, though there have been convincing successes where diagnosis has been early, in the cerebritis stage.

Surgical Management

Operative management provides therapeutic and diagnostic benefits in patients with brain abscesses [237]. There is relief of mass effect for larger, encapsulated abscesses, and cultures can be obtained. Typically, abscesses > 2.5 cm require surgical intervention. Stereotactic aspiration can be conducted at any stage of evolution of the abscess, and a biopsy may still yield positive cultures in the early cerebritis stage. Stereotactic aspiration has been demonstrated to have a diagnostic yield of up to 95 %. Brain abscess secondary to traumatic head injuries should be strongly considered for surgical excision because of the possibility of retained foreign bodies and/or bone fragments. Moreover, intraventricular rupture of an abscess, evident due to hydrocephalus and enhancement of ventricular walls, requires surgical debridement, ventricular drainage, and intraventricular and systemic antibiotic treatment. Alterations in the level of consciousness may herald impending herniation and should prompt surgical drainage of the abscess to alleviate mass effect.

Outcome and Complications

Where the diagnosis has been made promptly by appropriate imaging, the mortality is around 10–15 %, with about 50 % of survivors having significant long-term neurological deficits. Rupture of an abscess into the ventricular system is a particularly dangerous complication, with high mortality. Seizures occur in up to 75 % of patients with brain abscesses. In most children with brain abscesses, the onset of seizures is delayed, with only 50 % occurring within the first year after treatment. Early aspiration is advocated in infants because of the propensity for early seizures with meningitis and hydrocephalus, all of which suggest a poor prognosis.

Although there have been significant advances in the treatment and diagnosis of brain abscesses, there remains significant rates of mortality and morbidity. The overall outcome in children with brain abscesses is determined by a myriad of factors, such as the virulence of the pathogen, the location and number of the abscesses, the underlying source of infection, and the clinical status of the patient at the time of presentation. The patient's neurological status at presentation has been shown to be a significant predictor of outcome with an increased mortality rate in those who present with altered mental status and rapid neurological deterioration [235, 238]. Current death rates have been reported in the 4–12 % range. Most of the complications and deaths in children with brain abscesses may be attributable to multiple abscesses, the presence of low Glascow Coma Scale scores, and/or meningitis. Because earlier detection may affect rates of morbidity and mortality, children with neurological deficits, altered mental status, headaches, and/or seizures should be evaluated for a brain abscess, particularly if the patient has a predisposing factor such as sinusitis, congenital heart disease, otitis media, or an immunocompromised state. Overall, a worse prognosis has been found in patients with multiple deep-seated and/or large abscesses, intraventricular rupture, congenital heart disease, hydrocephalus, poor neurological status, and associated meningitis. Neonates and infants have a much worse prognosis, as do those in whom there was an initial error in diagnosis and/or an unknown source of infection.

Subdural Empyema

Much of the clinical presentation and epidemiology of subdural empyema parallels that of brain abscess in general. Most cases occur in the second decade of life, in patients who are otherwise healthy. Compared with other causes of intracranial suppuration, a greater proportion of subdural empyemas, up to 70 %, result from sinusitis. Other causes of subdural empyema include meningitis, otitis media, postsurgical infection, previous head trauma, or bacteraemic seeding of a previous subdural haematoma [239]. Most subdural empyemas in infants occur when a subdural effusion related to meningitis becomes infected. When sinusitis is the cause, the frontal sinus is most often implicated, though

pansinusitis and involvement of the posterior ethmoid cells are also common. Concomitant intracerebral abscess occurs in up to 25 %.

The presenting symptoms of subdural empyema are related to increased intracranial pressure, meningeal irritation, and cerebritis. If the empyema overlies the frontal lobe, the clinical presentation may involve subtle changes in personality or mood without focal neurological symptoms. The most common features are headache, fever, and neck stiffness. Concerning features reflective of raised intracranial pressure may evolve rapidly and include depressed level of consciousness, focal neurological deficits or cranial nerve palsies, hemiparesis, papilloedema, vomiting, and septic shock. Seizures occur in the majority and are more common in subdural empyema than with other intracranial complications.

Radiographic imaging should be done in all patients in whom subdural empyema is suspected. Although magnetic resonance imaging (MRI) is more sensitive in showing parenchymal abnormalities such as abscess, cranial CT is often the first neuroimaging carried out because of more widespread availability and the need for a rapid diagnosis. It is also the test of choice for visualisation of the paranasal sinuses and associated bony abnormalities. Early in the course of evolution, CT might not show a fluid collection, so consideration should be given to repeated CT imaging or MRI as the clinical scenario dictates. Mass effect is generally caused by oedema and ischaemia rather than mass effect from the collection. The sinuses might appear opacified, with air-fluid levels and bony erosion evident in some cases. MRI appearance is similar; T1-weighted images show mass effect and hypointense areas of purulence, which are hyperintense on T2-weighted images. Diffusion-weighted images (DWI) on MRI may be helpful in differentiating subdural and epidural empyemas [240].

Complete blood count almost always reveals leukocytosis, with increased polymorphonuclear cells and band forms. Erythrocyte sedimentation rate is usually less than 100 mm/h. Lumbar puncture in patients with subdural empyema is contraindicated, particularly if mass effect is present on CT or if the patient has papilloedema. In patients who have a lumbar puncture done, the CSF shows a parameningeal formula, with elevated protein, normal glucose, and pleocytosis with polymorphonuclear predominance. The CSF Gram stain usually does not show organisms and CSF cultures are usually negative. The CSF may be normal. No single organism predominates, although members of the Streptococcus milleri group are over-represented. Anaerobes are more likely to be present if the empyema is associated with sinusitis compared with other causes of subdural empyema. The presence of anaerobes and a conspicuous absence of pathogens associated with acute sinusitis (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*) suggest that most subdural empyemas arise from chronic sinusitis. Operative cultures are negative in about half the cases, presumably because of previous administration of antibiotics or failure to use proper anaerobic culture technique.

Antimicrobial therapy should be directed against the more commonly found organisms. Recommended empiric therapy is a third-generation cephalosporin plus metronidazole, which offers broad coverage and good CSF and abscess penetration. Once microbiological identification and susceptibility results are available, antimicrobial therapy can be adjusted accordingly. It should be recognised, however, that cultures might be negative and continuation of empiric antimicrobial therapy, including anaerobic coverage, is reasonable. The appropriate duration of therapy has not been studied in randomised, controlled trials, but reports suggest at least 2 weeks of intravenous therapy should be given; parenteral or oral therapy is frequently continued for up to a total of 6 weeks of antimicrobials. If adjacent osteomyelitis is present, prolonged parenteral therapy should be considered (e.g., for a minimum of 6–8 weeks) [235].

Adjunctive care includes prophylactic anticonvulsants, and management of cerebral edema and intracranial hypertension with measures such as corticosteroids, ventriculostomy, and osmotic therapy. Isolated medical management is only rarely successful. Surgical management of subdural empyema is integral and should be performed without delay. The goals of surgical intervention are decompression of the brain and complete evacuation of pus. There is controversy in the neurosurgical literature regarding the preferred surgical intervention – burr hole versus craniotomy. In addition to drainage of intracranial pus, definitive management of the infected sinuses should be carried out, preferably at the same time as empyema drainage.

Before the availability of antibiotics, subdural empyemas were almost always fatal, even with surgical drainage. Antimicrobials and the advent of CT imaging have reduced mortality to around 10 %. Survivors may exhibit substantial morbidity, including seizures in up to 40 % of cases, hemiparesis in 35 %, and residual neurologic deficits in nearly half of cases [241].

Shunt Infection

The treatment of many CNS diseases involves gaining access to the CSF. Indications for such access can be classified as diversion, drainage or monitoring. All of these involve prosthetic implants, which may be temporary or permanent. The usual reason is for continuous CSF diversion, or “shunting” for the treatment of hydrocephalus. The risk of infection continues to be a major cause of morbidity and mortality for patients with CSF shunts.

Epidemiology

As patients who require CSF shunting usually require their shunt for life, and those with benign diseases will probably require several shunt revisions for non-infectious reasons, a distinction must be made between "case infection rate" and "operative infection rate". The former refers to the infection rate per patient, and the latter refers to the infection rate per procedure. Even if the operative infection rate remained constant, the case infection rate increases as the patient gets older and requires more revisions. Approximately 40 per 100,000 individuals in the US have shunts in place, most of these being children [242].

The most significant complication resulting from intracranial ventricular shunts is infection. In recent years the case infection rate has ranged from 10 % to 40 % and the operative infection rate from 5 % to 14 % [243]. Shunt infection occurs in a bimodal distribution from the time of shunt placement; 70–80 % of infections occur within 6 months of the placement, with a second peak after 12 months [244]. The most important of the host factors that determine the incidence of shunt infection is age: children < 6 months old at the time of first surgery, and particularly neonates, are at increased risk [245].

Several studies have reported a greater operative infection rate for shunt revision. In the United States about 33,000 CSF shunts are placed each year, with about half of these being shunt revisions [242]. While the proportion of revisions has remained fairly constant, the proportion involving shunt removal has decreased in recent years which may reflect a decline in the operative infection rate. Factors which are implicated in this include: changes in materials used in shunt manufacture; changes in packaging and sterilization procedures; fewer pre-shunting invasive procedures (lumbar puncture, pneumoencephalography, ventricular tap); improvements in operating room facilities; improvements in surgical technique, preoperative patient preparation and reduced duration of surgery. There is an increased risk of infection in patients undergoing shunt revision following treatment for shunt infection, with an operative incidence of 10–20 %. In these the same organism is cultured in up to 50 % of cases [244].

A recent systematic review has suggested that there is a benefit of reduction of shunt infection by 50 % with the use of periprocedural systemic prophylactic antibiotics in patients undergoing implantation of internal ventricular shunts, regardless of the patient's age and the type of internal shunt used. Nonetheless, it was not possible to clearly evaluate the incidence of adverse effects of the antibiotics, there are sparse mortality data, and the type and dose of antibiotics need to be optimized. Currently the available evidence only suggests a benefit for the use of prophylactic antibiotics for no longer than the first 24 h postoperatively. The benefit of antimicrobial prophylaxis after the first 24 h postoperatively remains uncertain. No conclusions were reached regarding the administration of prophylactic antibiotics for EVDs [243].

Table 40.7 Shunt infections

Organism	Infection rate (%)
Gram positive	
Coagulase-negative Staphylococci	45–70
Staphylococcus aureus	10–30
Streptococci	8–10
Diphtheroids	1–15
Gram-negative	
Escherichia coli	8–10
Klebsiella species	3–8
Pseudomonas/Proteus	2–8
Anaerobes	6
Mixed cultures	10–15

Adapted from Kielian [236]. With permission from BioMed Central Ltd

Table 40.7 shows the most common organisms isolated from infected shunts. Most infections are due to skin or bowel flora. There is no difference in the distribution of organisms associated with acute or delayed infection. There is also no obvious contribution from the position of the distal end of the shunt. The only identifiable association is when the distal end of a ventriculoperitoneal shunt has perforated a hollow viscus, resulting in infection by mixed Gram-negative species. Infection by organisms usually associated with bacterial meningitis (*Haemophilus influenzae*, *Neisseria meningitidis* and *Streptococcus pneumoniae*) only cause about 5 % of shunt infections, although there is some suggestion that patients with shunts are more susceptible to these organisms [244].

Pathophysiology

Four mechanisms have been postulated by which shunt become infected.

Probably the most frequent cause of shunt infection is colonisation at the time of surgery. This is suggested by the fact that most shunt infections occur within a few weeks of surgery, usually with skin colonising organisms [245]. The initial step in shunt infection must be attachment of bacteria to the shunt material. Once bacteria have adhered to a catheter, they are not easily removed. Breakdown of surgical wounds or of skin overlying the shunt allows direct access of microbes to the shunt. Extension of tissue infections adjacent to the shunt are also included in this category. Hematogenous seeding of shunts is probably uncommon. Shunts with their distal end in the venous system (e.g. ventriculo-atrial shunts) are at continuous risk of infection due to bacteremia. Transient or asymptomatic bacteremia has not been definitively associated with shunt infection. It seems that sustained

bacteraemia, recent shunt surgery with the presence of devitalised tissue and haematoma is necessary. Even then, shunt infection in these circumstances is rare. Retrograde infection is usually associated with infection of externalised devices where organisms invade directly from the exit site.

Clinical Manifestations

Clinical presentation varies depending on age of the patient, causative organism and the type of shunt. Symptoms are usually caused by shunt malfunction secondary to infection, and include headache, nausea, lethargy and deteriorating mental status. Fever and pain are not uniformly present. Signs are related to the site where the infection originated. Proximal infection may cause shunt malfunction or obstruction. As the shunt lies within the CSF space, infection results in meningitis or ventriculitis. With ventricular shunts, meningitis is rare as there is usually no communication between the ventricles and the meninges. Distal infections usually have symptoms specific to the location of the end. Infected vascular shunts have associated bacteraemia. A complication of this may be shunt nephritis, which develops in about 4 % of infected vascular shunts [245]. It is an immune-complex mediated disease, similar to that seen in bacterial endocarditis. Infected shunts that terminate in the pleural or peritoneal space will usually present with failure of CSF absorption. In the peritoneum, encystment of the catheter and loculation of pockets of CSF (CSF-oma) can occur. These may become large and palpable, particularly in infants. If more severe, peritonitis may develop. Some shunt infections are insidious in onset, causing few symptoms. There may be only low-grade, intermittent malaise or fever. This is often the case when patients have received repeated courses of antibiotics for intercurrent infections.

Diagnosis

The main principle in the diagnosis of shunt infection is to have a high index of suspicion. Infection should be considered in any patient with a CSF shunt who develops fever, although only rarely will fever be caused by shunt infection. The diagnostic procedure of choice is direct culture of CSF from within or around the shunt. All other investigations, apart from blood cultures in the presence of an intravascular shunt, are indirect pointers of shunt infection. Most implanted devices have an access reservoir which can be sampled. The only risk of accessing these reservoirs is the introduction of infection. Any positive culture should be carefully evaluated. If the CSF is infected, a pleocytosis and variable biochemical changes may be found. In most shunt infections, culture of the tapped fluid is positive, even sometimes without a positive Gram stain, with a normal cell count and normal chemistry. The culture may take several days or even weeks to become positive, particularly in those with infection due to fastidious organisms, and the result may be confounded by prior antibiotic therapy. In distal shunt infection without shunt malfunction, the CSF may be completely normal. There may only be localised signs in the peritoneum, ranging from mild discomfort to frank peritonitis. In all cases, correlation of the clinical features, laboratory findings and culture must be made. Because of the often insidious presentation of shunt infection, any positive culture result should be taken extremely seriously.

Treatment

There are no published well conducted studies of any method of therapy for shunt infection. However, removal of the infected shunt is absolutely necessary for successful treatment [245]. Antibiotic therapy usually begins without positive bacteriological diagnosis. Coverage is selected for the most likely organisms. Most infections are due to staphylococci; therefore appropriate anti-staphylococcal therapy is necessary. Gram-negative aerobes are also relatively common, and may be suggested by a more severe clinical course. Bacteriological evaluation, with culture and sensitivities will allow therapy to be modified appropriately.

Vancomycin has been shown to be effective in therapy of staphylococcal shunt infection. Its efficacy is increased by the addition of rifampicin, which penetrates CSF well. Rifampicin should not be used alone as resistance to it develops rapidly.

For coverage for Gram-negative organisms, a third generation cephalosporin, such as ceftriaxone or ceftazidime penetrates inflamed meninges reasonably well. Aminoglycosides do not penetrate even inflamed meninges well, and their use should be restricted to Pseudomonas infection, where they should be used in combination with an antipseudomonal penicillin, or ceftazidime [243].

Direct instillation of antibiotics into CSF is achieved through a ventriculostomy or via a reservoir. The most commonly used intraventricular antibiotics are vancomycin and gentamicin, but detailed studies of efficacy and pharmacokinetics are not available, so dosage and frequency are empirical.

Treatment of an infected shunt should include parenteral antibiotic therapy, complete removal of the infected shunt at the beginning of treatment, and placement of an external ventriculostomy, which can also be used for antibiotic instillation. This may give a cure rate of >90 %. Duration of therapy is guided by the infecting organism, response to therapy and duration of positive cultures. Usually 7–10 days of therapy following the last positive culture and removal of the infected device is sufficient. Shunt revision is usually carried out following 72 h of observation off antibiotic therapy [246].

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Status Epilepticus

41

Robert C. Tasker and Ryan Wilkes

Abstract

The critically ill child with ongoing seizures refractory to treatment presents a challenge in neurocritical care. This chapter reviews the recent literature on refractory and super-refractory status epilepticus and summarizes the strategy regarding second-tier anti-epileptic drug therapies that can be used once initial anticonvulsants have failed. The pediatric experience of high-dose midazolam, barbiturate anesthesia, volatile anesthetics, hypothermia, ketamine and ketogenic diet for uncontrolled status epilepticus is summarized and evaluated.

Keywords

Status epilepticus • Super-refractory status epilepticus • Intensive care • Midazolam • Anesthesia • Barbiturates • Hypothermia • Ketamine • Ketogenic diet

Introduction

Status epilepticus (SE) is the most common neurologic emergency of childhood [1] and is associated with significant morbidity and mortality [2]. In the United States alone, some 42,000 deaths per year occur among the estimated 152,000 cases of SE, and mortality rates in various case series range up to 25 % [2–4]. Children have a lower mortality rate, up to 6 % [2, 5–8], but survivors may develop lifelong cognitive and neurodevelopmental problems, and epilepsy [5, 9]. Much of the morbidity associated with SE is found in those with seizures persisting despite standard anticonvulsive medication [9–12], so-called refractory status epilepticus (RSE).

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The pediatric critical care physician is usually involved in the treatment of children presenting SE after the fact. The child has had emergency treatment during pre-hospital transport, or in the emergency department, and we are then faced with three possible clinical pathways:

1. The previously well child now requiring tracheal intubation and mechanical ventilation because of respiratory depression complicating treatment, or the acute disease that has produced the seizure.
2. The child with a known seizure disorder on multiple anti-epileptic drugs (AED); checking and optimizing AED pharmacokinetics is now required.
3. The child who is mechanically ventilated child with ongoing RSE that now requires special intensive care AED therapies.

In current practice, a protocol-driven approach to acute seizure care [1, 13, 14] of children in the first two pathways now means that we no longer see the classic end-stage of SE with disruption in systemic physiology and metabolism leading to hyperpyrexia, exhaustion and death [15–18]. However, there is a risk that rather than too little medication being given too infrequently, overaggressive benzodiazepine use and overdosing leads to tracheal intubation, mechanical ventilation and short stays on the pediatric intensive care unit

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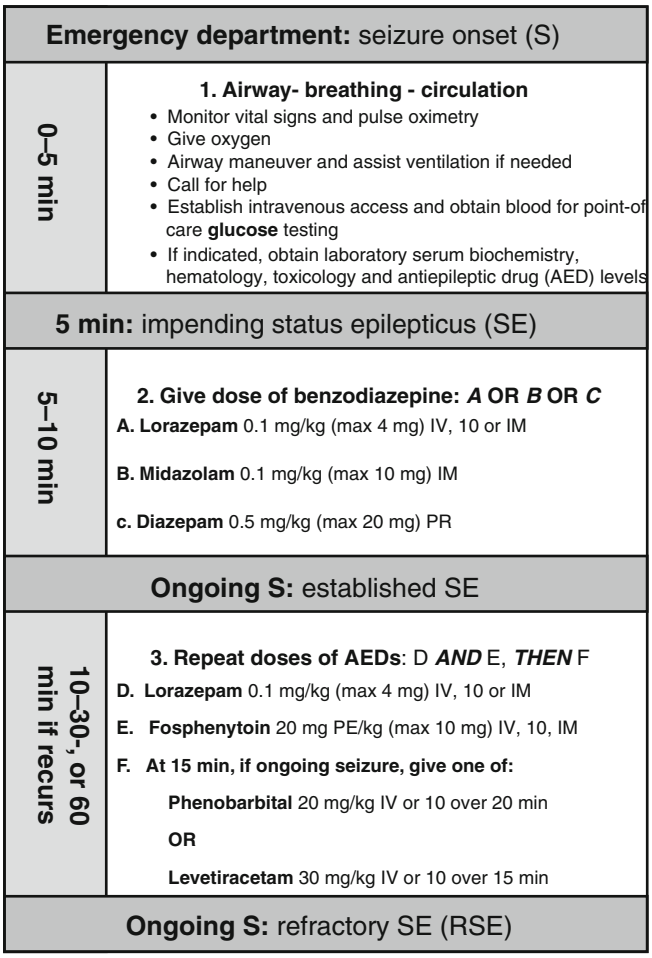


Fig. 41.1 Initial treatment of uncontrolled seizures

(PICU) [19–21]. We assume that readers will be familiar with standard emergency department guidelines for acute care and the respiratory management of children in the first two pathways (Fig. 41.1). Hence, the focus of this Chapter is how we approach seizure control and investigation for children in the third pathway, during their PICU admission [22].

Definitions

The point in time when a prolonged seizure becomes labeled as an episode of SE has changed over the last 20 years [23]. There is no consensus as to when 'usual' seizure duration has been surpassed and the transition to a state where there is failure in intrinsic mechanisms that bring about seizure cessation has been reached (i.e., onset of SE). SE was once defined as seizure activity, either continuous or episodic without complete recovery of consciousness, lasting for at least 30–60 min. In PICU practice we now use an operational definition starting with 5 min of seizure activity, and think of episodes in relation to their response to therapy. Hence terms such as *Impending SE*, *Refractory SE* and *Super-Refractory SE* are now frequently used in the literature.

Impending Status Epilepticus

One proposal for the definition of convulsive tonic-clonic SE is seizure activity lasting at least 5 min [24, 25]. In adults, this definition is based on videotape-telemetry studies that show mean duration of generalized convulsive seizures range from 62.2 s (n = 120) to 52.9 ± 14 s (n = 50) for the behavioral manifestations and 59.9 ± 12 s for the electroencephalographic (EEG) manifestations [26, 27]. Since none of these seizures lasted 2 min, an operational definition of SE as 5 min of continuous, generalized convulsive activity would reflect an episode lasting some 20 standard deviations (SD) above the norm, making it a 'rare' event. It might, however, be even more appropriate to terminate an episode with intravenous AEDs after 4–5 SDs above the norm (i.e., after 2 min) [26].

In emergency practice in children there is little difference between 2 and 5 min since it takes at least 5 min to administer an intravenous AED [28]. Hence a definition of 5 min of continuous seizure activity is a pragmatic solution to the question of definition of SE – it uses a duration that is consistent with practice in the emergency department and, it places the definition of SE far outside the norm for seizure duration. Some authors have chosen to call these 5 min episodes *impending SE*, since a significant proportion of patients will stop seizing spontaneously in the next few minutes [29]. Therefore, *impending SE* is defined as "continuous seizures lasting more than 5 minutes, or intermittent clinical or EEG seizures lasting over 15 minutes without full recovery of consciousness between seizures" [30]. This definition recognizes the need to treat such patients with intravenous AEDs and applies to adults and children over 5 years of age. Separating *impending SE* from other definitions of SE also helps to better define subpopulations for morbidity and mortality statistics, outcome measures, and clinical trials of AEDs [31, 32].

Another approach to making a decision about when a seizure episode has become SE is to consider the form of the seizure. This approach is often used in the PICU in patients with epilepsy. Typically, at baseline, these individuals may have a number of seizures each day. It is counterproductive to their ongoing management and return to baseline care to use the seizure protocol shown in Fig. 41.1, every time a 5-min event occurs. In this instance the clinical question is "how likely is it that this new seizure will extend into SE?" Table 41.1 provides a summary of the different forms of seizure types and SE. There is some evidence in adults that seizure duration differs for the various seizure types. For example, in a study of 599 seizures in 159 adults, seizures

Table 41.1 Forms of seizures in SE

Forms	Seizure	Behavior and autonomic	Medication
Convulsive			
Generalized tonic-clonic (GTC)	Increased seizures in epilepsy	Obtunded	1st: Lorazepam
	Duration of each seizure shortens	Salivation, bradypnea	2nd: Fosphenytoin
	May have abnormal cranial nerve exam	Cyanosis, hypotension	
Generalized clonic	Waxing and waning for hours	Variable behaviors	1st: Lorazepam
	Post-ictal hemiplegia	Consciousness preserved	2nd: Fosphenytoin
		Less autonomic than GTC	
Generalized tonic	Serial tonic episodies	Increased bronchial secretions and respiratory irregularity	1st: Lorazepam
	In epilepsy precipitated by benzodiazepines	Eye deviation	2nd: Fosphenytoin
	May last days with serial seizures		
Focal motor	Epileptic disorder or acute insult (AI)	Some impairment of consciousness	1st: Lorazepam
	AI develop secondary GTC seizures	Some autonomic features	2nd: Fosphenytoin
	Restricted distribution in epilepsy		
Myoclonic	Repetitive myoclonic jerks	Seen postanoxia in coma	1st: Lorazepam
	AI and epilepsy		2nd: Fosphenytoin or valproate
Non-convulsive			
Absence	Petit mal status epilepticus (SE)	Variable impaired consciousness	1st: Lorazepam
		Complex automatisms	2nd: Valproate
Complex partial seizure (CPS)	Psychomotor SE	Cycling from unresponsive to partial response	1st: Lorazepam
	Can present with recurring partial seizures	Reactive automatisms	2nd: Fosphenytoin
Classic form and SE in Coma	Prolonged altered in consciousness or CPS	Seen in epilepsy (Landau-Kleffner	1st: Lorazepam
	EEG changes from pre- to ictal state	A form occurs in coma/AI	2nd: Fosphenytoin or anesthesia
	Improved EEG/state with treatment		

with partial onset spreading to both hemispheres had the longest duration [33]. Secondarily generalized tonic-clonic seizures lasted longer than complex partial seizures, which lasted longer than simple partial seizures. Secondarily generalized tonic-clonic seizures were unlikely to last more than 11 min, complex partial seizures more than 10 min, and simple partial seizures more than 4 min. This gradation is likely related to activation of different neuronal networks at the onset and during propagation of seizures. So, from a practical perspective, a working definition of SE based on these limits in timings has been proposed for patients with a seizure disorder.

Refractory Status Epilepticus

Over the last 10 years there has been increasing use of the term RSE as a description of an episode of SE that persists despite treatment with adequate doses of multiple AEDs. There are many definitions in the literature and there is considerable variation in the duration required for an episode to reach so-called refractoriness [34]. In contrast to the definition used to describe *impending SE*, the features used to characterize RSE are duration as well as response to AEDs and electroencephalographic (EEG) features. The latter is particularly important since there is both experimental and clinical evidence to show that the EEG during the course of generalized convulsive SE in adults follows a predictable sequence with five identifiable patterns: I, discrete seizures; II, merging seizures with waxing and waning amplitude and frequency of EEG rhythms; III, continuous ictal activity; IV, continuous ictal activity punctuated by low voltage "flat periods"; and V, periodic epileptiform discharges on a "flat background" [35, 36]. The significance of this staging is apparent when duration and seizure response to treatment is examined in the experimental model. Stage I EEG represents a treatment-responsive state to combination therapy with diazepam and phenobarbital, whereas stage III is a treatment-refractory state even though there is overlap in absolute duration of SE in both patterns [37]. When diazepam alone is used to treat seizures, stage I EEG again represents a treatment-responsive state, whereas treatment in stages II-V has increasing likelihood of conversion to subclinical non-convulsive SE or EEG SE [35].

A commonly used definition for RSE is a state that meets the following criteria: clinical or EEG seizure lasting longer than 60 min despite treatment with at least one first-line AED (i.e., benzodiazepine) and one second-line AED (i.e., phenytoin, phenobarbital, or valproate) [11, 34]. In children, such episodes are frequent and occur in 25–50 % of patients in case series of SE [11, 38, 39]. In one study of 154 children with SE, 45 % of the RSE cases had non-convulsive SE [39], which is much higher than the 27 % seen in adults [34]. One possible explanation for the refractoriness is that in contrast to seizures that rapidly generalize and stop spontaneously, seizures that do not readily generalize and involve the motor cortex may be associated with more severe underlying brain pathology, and hence may be more refractory to therapy. Taken together with the previous discussion (see above), the EEG is a vital sign in those patients who do not arouse after acute control of motor seizures, particularly in those patients with acute structural lesions and at higher risk for non-convulsive episodes.

Super-Refractory Status Epilepticus

Super-refractory SE is a new descriptive term in the literature, first appearing in 2011 in the summary of the Third London-Innsbruck Colloquium on SE [40]. Of course *super-refractory SE* is not a new entity as we have seen the condition before 2011, but giving it a name better helps to clarify an approach to therapy in this difficult clinical situation. *Super-refractory SE* is a stage of RSE characterized by unresponsiveness to initial anesthetic therapy, and is defined as "SE that continues or recurs 24 hours or more after the onset of general anesthesia, including those cases in which SE recurs on the reduction or withdrawal of anesthesia." In adults it is generally seen in two distinctive clinical situations: in patients with severe acute brain injury; and, in previously healthy patients who have no apparent cause for SE, so called *new-onset* RSE (NORSE) [41]. The pattern of presentation is similar in children, but rather than talking about NORSE, authors have focused on specific age of occurrence and fever as an apparent triggering factor for the second entity. Fever might even have preceded the onset of neurologic symptoms and no longer be present at the time of presentation. Two conditions have been described in younger age groups: in school-aged children, febrile infection-related epilepsy syndrome (FIRES) [42]; and, in infancy, idiopathic hemiconvulsion-hemiplegia syndrome (IHHS) [43]. Whether the diagnosis of NORSE, FIRES and IHHS represents distinct pathophysiologies or a spectrum of acute encephalopathy with inflammation- and immunology-mediated SE, or some genetic or acquired channelopathy is, at present, unknown [44, 45].

Second-Tier Intravenous Anticonvulsants for Refractor SE

The hierarchy in escalation of AED treatment should be considered in relation to the continuum in time that starts with the recognition of *impending SE* (5 min), through to the determination of RSE (60 min), and later *super-refractory SE* (after 24 h). The protocol for treating *impending SE* is shown in Fig. 41.1 and occurs long before arrival to the PICU. The second-tier AEDs include some combination of fosphenytoin and phenobarbital, although levetiracetam and valproic acid are also frequently given. Last, in recent years, matching the continuum in seizure duration with escalation to high-dose midazolam has become an option.

Fosphenytoin

Fosphenytoin is a disodium phosphate ester of 3-hydroxymethyl of phenytoin developed as a replacement for standard injectable phenytoin sodium. The water-solubility of this pro-drug of phenytoin is 75,000 mg/L versus 20 mg/L for phenytoin sodium. The parenteral preparation of phenytoin sodium (50 mg/mL) is a hydroalcoholic mixture of 40 % propylene glycol, 10 % alcohol, and 50 % water, with the pH adjusted to 12. Phenytoin is associated with a higher risk of arrhythmias and hypotension. In addition, since it is dissolved in propylene glycol and ethanol (pH 12), it can cause a severe extravasation injury, known as "purple glove syndrome". Fosphenytoin is rapidly converted enzymatically to phenytoin (conversion half-life is 3 min in dogs and 1 min in rats). Fosphenytoin slows the rate of recovery of voltage-activated sodium channels and causes an activity-dependent inhibition of action potential firing. Doses are calculated as phenytoin equivalents and typical intravenous boluses are 15–20 mg/kg over 20 min. Continuous cardiac monitoring is recommended even though arrhythmias and hypotension are far less common with fosphenytoin, than phenytoin. Peak levels are not reached until 20 min after the infusion because of the time required for conversion of fosphenytoin to phenytoin, but it is not uncommon for seizures to stop some time before the infusion has finished. Also, in regard to AED monitoring, it is important to follow free phenytoin levels, since phenytoin is highly protein bound and in patients with hypoalbuminemia or on valproic acid (which displaces phenytoin from albumin) free level may be high with prolonged use. Overall, a number of studies report that using fosphenytoin after a benzodiazepine is successful in seizure control, with rates of 89–100 % [46, 47]. Its relative lack of respiratory depression also makes this agent useful.

Phenobarbital

Phenobarbital is a weak acid (pKa 7.3) that is sparingly soluble in water (1 mg/mL). The sodium salt of phenobarbital has better water solubility than the free acid, and consequently is used in most parenteral preparations. Phenobarbital injection is not an aqueous solution but contains 20 % sodium phenobarbital in a mixture of 90 % propylene glycol and 10 % water at pH 10–11. Phenobarbital is mainly metabolized to two inactive primary metabolites: p-hydroxy-phenobarbital, which is excreted in the urine as free glucuronide conjugate; and, an N-glucoside conjugate of phenobarbital. Phenobarbital has a long half-life and is also considered to have greater intrinsic antiepileptic properties than other barbiturates (see below, pentobarbital). It is commonly used after two doses of a benzodiazepine and a dose of fosphenytoin. Its mechanism of action is via the GABA receptor, at a different binding site to that of the benzodiazepines and so, theoretically, is useful during treatment of prolonged seizures. Phenobarbital has slow entry into the brain, but during seizure activity cerebral uptake is increased and the drug may be concentrated near seizure foci [48].

The typical dose of phenobarbital is 15–20 mg/kg, infused at a rate of 2 mg/kg/min for children under 40 kg and 100 mg/min for those over 40 kg [49]. Repeat dosing of 5 mg/kg is given if seizures persist. (Some authors have recommended a very-high-dose strategy with repeated boluses of 10 mg/kg every 30 min until seizures stop [50]; although in our experience this dosing is likely to induce coma.) The onset of drug action is within 5 min, with peak levels occurring at 15 min. However, a course of intravenous doses can result in prolonged somnolence and recovery because the elimination half-life of ranges 50–150 h.

Overall, phenobarbital is an effective AED, but its main drawback is respiratory depression and hypotension. In brain-injured patients, tracheal intubation and mechanical ventilation should be anticipated if prior doses of benzodiazepines have been given, with or without the addition of fosphenytoin. It is the frequent need for airway and hemodynamic intervention that has led to the use of other agents that have much lower rates of respiratory depression and hypotension (e.g., valproic acid and levetiracetam).

Valproic Acid

The US Food and Drug Administration approved intravenous valproate in 1996. Since its introduction, several case studies and uncontrolled case series regarding its use in SE have been published [51], with promising safety data and efficacy results. Although the drug is not approved for SE, it is emerging as an option in refractory cases. For example, intravenous availability allows for rapid administration and, unlike phenytoin, at a more physiologic pH and with wider serum level therapeutic range. It also produces less sedation and respiratory depression (unlike benzodiazepines and phenobarbital) and no hypotension (unlike phenobarbital and phenytoin). Valproic acid works by modulation of sodium and calcium currents along with activating the GABA receptor [52]. The main advantages of valproate are its efficacy against a wide variety of seizure types. It has been used as adjunctive therapy in adults and children with RSE [53] and it may be particularly helpful in patients with myoclonic SE, absence SE, or Lennox-Gastaut syndrome. The dose is 20–40 mg/kg (infused at a rate of 6 mg/kg/min) followed by a continuous infusion at 1–5 mg/kg/h.

The main disadvantages of valproate are hepatotoxicity and hyperammonemia. 1-in-500 children under 2 years of age develop hepatotoxicity [52] and the risk is much higher in those with an inborn error in metabolism. Therefore, transaminase levels and liver function should be monitored. The other complications include pancreatitis, thrombocytopenia and coagulation disorders; the latter possibly due to decreased hepatic production of clotting factors.

Levetiracetam

Intravenous levetiracetam acts at glutamate and GABA receptors as well as calcium channels [52], but its exact mechanism of action is unknown. It is unique as an AED because of its linear pharmacokinetics, minimal drug-drug interactions, and minimal metabolism. The antiepileptic effects of levetiracetam start within 24 h of administration and in RSE its most attractive potential feature, like that of valproic acid, is the lack of cardiopulmonary depression. But, unlike valproic acid, levetiracetam does not have significant end-organ toxicity and drug-to-drug interactions.

Bolus dosing of levetiracetam ranges from 30 to 60 mg/kg in children and 500–2,000 mg in adults, and its role in RSE is unclear with only small case series being reported. For example, Wheless et al. performed a prospective, single-center study to evaluate the safety of a rapid loading dose in 45 patients aged 4–32 years (mean 13.6 years) and found that high serum levels can be achieved rapidly and safely in a small volume infusion [53]. In three other pediatric series, such rapid infusions have been used in the treatment of seizures and SE in various settings: to treat SE in the PICU [54]; to treat new onset acute seizures and SE either as monotherapy or as an adjunctive AED [55]; and, as an agent in those with serial seizures [56]. Most recently, McTague et al. undertook a 2-year observational study on their use of intravenous levetiracetam to treat in-hospital acute repeated seizures or convulsive and non-convulsive SE [57]. Forty-five

pediatric patients (aged 0.2–18.8 years) were treated with an initial dose of intravenous levetiracetam (mean 14.4 mg/kg, range 5–30 mg/kg). Twenty-three of 39 (59 %) patients with acute repeated seizures became and remained seizure free. Intravenous levetiracetam terminated SE in three of four patients with convulsive and the two patients with non-convulsive SE. The authors concluded that a randomized clinical trial was justified to determine whether intravenous levetiracetam should replace intravenous (fos)phenytoin as the first long-acting AED in the management of acute repetitive seizures and SE.

High-Dose Midazolam for Refractory Status Epilepticus

There is no evidence that one particular AED is better than any other in the treatment of RSE. We are therefore left with weighing the risks and benefits of each agent in a given clinical situation. Patients who are hemodynamically unstable, have responded well to benzodiazepines, or who have a relatively benign etiology may be candidates for high-dose midazolam by continuous infusion. The use of midazolam for RSE in children is a relatively new practice – the initial PICU experiences were reported in the early 1990s [58].

Midazolam injection contains 0.5 % midazolam hydrochloride in water for injection (buffered to pH 3.3–3.5). Midazolam undergoes a facile 1,4-benzodiazepine ring-opening in an acidic aqueous solution to form a benzophenone derivative. At high infusion rates, up to 200 mcg/kg/min, the acidic diluent can cause a severe hyperchloremic, non-anion gap metabolic acidosis and resultant hemodynamic compromise [59]. Its reverse cyclization reaction to midazolam occurs in vivo at physiologic pH 7.4, which creates a highly lipophilic structure accounting for its rapid penetration into the brain and rapid onset of action. This imidazobenzodiazepine has a short elimination half-life of 1.5–3.5 h, and little accumulation. These favorable pharmacokinetics allow for repeat bolus dosing, aggressive titration of an infusion and relatively fast recovery time. It causes little hypotension and vasopressors are usually only needed when very-high-doses of midazolam are used. Midazolam shares anxiolytic, muscle-relaxant, hypnotic and anticonvulsant actions with other benzodiazepines. Yet, given these similarities, an obvious question is 'Why should it be effective when other GABA agonists (e.g., phenobarbitone and diazepam) have failed to control RSE?'

Pediatric Critical Care Studies of High-Dose Midazolam

Up to June 2013, there had been nine English language reports of midazolam infusion to treat pediatric RSE, with a minimum of five patients [38, 46, 60–67]); four prospective and five retrospective, for a total of 521 patients (Table 41.2). In these studies, the definition of RSE differed: failure to gain seizure control after two-, three- or five-doses of anticonvulsant drug was used in four, three and two studies

Table 41.2 Midazolam for RSE in children

Study [ref]	Prospective or retrospective (cases)	Midazolam protocol	Control: Time to control Proportion (%)
Rivera et al. [60]	Prospective (n = 24)	Mean 2.3 mcg/kg/min	Mean 47 min
		Maximum 18 mcg/kg/min	24/24 (100 %)
Igartua et al. [61]	Retrospective (n = 8)	Mean 14 mcg/kg/min	Mean 78 min
		Maximum 24 mcg/kg/min	7/8 (88 %)
Singhi et al. [62]	Prospective (n = 21)	Mean 5.3 mcg/kg/min	Mean 16 min
		Maximum 10 mcg/kg/min	18/21 (86 %)
Koul et al. [38, 63]	Retrospective (n = 51)	Mean 2 mcg/kg/min	Mean 35 min
		Maximum 7 mcg/kg/min	50/51 (98 %)
Brevoord et al. [46]	Retrospective (n = 45)	Mean 4 mcg/kg/min	Mean unknown
		Maximum 13 mcg/kg/min	32/45 (71 %)
Ozdemir et al. [64]	Prospective (n = 27)	Mean 3 mcg/kg/min	Mean 65 min
		Maximum 5 mcg/kg/min	26/27 (96 %)
Morrison et al. [65]	Prospective (n = 17)	Mean 9 mcg/kg/min	Mean 18 min
		Maximum 24 mcg/kg/min	15/17 (88 %)
Hayashi et al. [66]	Retrospective (n = 306)	Mean 4.3 mcg/kg/min	Mean unknown
		Maximum 20 mcg/kg/min	203/306 (66 %)
Saz et al. [67]	Retrospective (n = 22)	Mean unknown	Mean unknown
		Maximum 1.2 mcg/kg/min	21/22 (96 %)

respectively. The inclusion of seizure duration in the definition of RSE varied and ranged from 10 to 60 min.

Efficacy

The majority of the studies used cessation of convulsion as the endpoint for treatment. The study by Saz et al. gave no definition for seizure control [67]. The report by Hayashi et al. defined seizure control as the cessation of convulsions for at least 24 h after stopping the infusion [66]. In the other seven studies, seizure control was defined in relation to the period of time since treatment started (ranging 30 min to 48 h), where no convulsion was evident. Only two studies used continuous EEG (cEEG) to monitor for subclinical seizures and to treat cEEG-endpoints [61, 65]. In six studies the weighted, mean time from beginning midazolam to seizure control was 271 min [38, 60–65]. However, when excluding the seven patients in the Igartua et al. study [61], the weighted mean (including 133 patients) falls to 37 min. In the nine studies, seizure control occurred in 396/521 (76 %) patients. The four prospective studies [60, 62, 64, 65] showed higher proportion of cases with seizure control compared with the findings in the five retrospective studies (93 % versus 72 %, $P<0.001$). Eight studies used an algorithm with combined efficacy 193/215 (90 %). The one study that did not describe a treatment algorithm [66], reported the experience of 16 pediatric hospitals in Japan and included 306 patients treated with midazolam infusion and achieved seizure control in 203/306 (66 %). Two studies reported on the duration of midazolam infusions. Igartua et al. reported a mean duration of 192 ± 120 h [61] while Hayashi et al. reported a mean of 108.6 ± 175.5 h [66].

Dosing

The combined, mean dose required for seizure control was 3.2 mcg/kg/min. The Igartua et al. [61] study used the highest mean dose of midazolam (14 mcg/kg/min). In this study, seizure control was defined as a seizure-free period of 48 h and cEEG monitoring was used in all eight patients. The study by Morrison et al. [65] used the highest maximum dose of midazolam (24 mcg/kg/min).

Electroencephalography to Guide Therapy

cEEG use was reported in two studies. Igartua et al. [61] used cEEG in all eight patients and Morrison et al. [65] used cEEG monitoring in 13 of 17 patients. In both studies midazolam was titrated to cessation of both clinical and EEG seizure activity. The combined mean dose used to achieve seizure control in these studies was 10.7 mcg/kg/min. Four studies reported on intermittent EEG to confirm seizure control and the mean dose for seizure control was 2.8 mcg/kg/min [38, 60, 62–64], which appears to be much less than the mean doses used when applying cEEG during treatment [61, 65].

Breakthrough Seizure and Recurrences

Breakthrough and recurrent seizures are variably defined and inconsistently reported in studies. In general, breakthrough seizures refer to seizures that occur after initial seizure control. Recurrent seizures describe seizures occurring during or after infusion tapering. Both of these terms imply initial seizure control (by some predetermined criterion). Koul et al. [38, 63] described 5 of 51 patients with "recurrent status epilepticus, mostly related to drug default". Morrison et al. [65] reported 5 of 15 initial responders with breakthrough seizures and 1 of 15 initial responders with recurrent seizures. Singhi et al. [62] reported 12 of 18 initial responders with breakthrough seizures, and four responders had recurrent seizures after stopping the infusion. The combined total for breakthrough seizures and recurrent seizures was 52 % (17/33 patients) and 12 % (10/84 patients), respectively.

Hemodynamic Instability

Seven studies gave information about hemodynamic instability. Three studies reported no instability attributable to midazolam [38, 60, 63, 64]. In the patients reported by Hayashi et al. [66], 37 had "circulatory distress"; however, in none of these cases was the midazolam considered to be a contributory factor. In the study by Igartua et al. [61], which used the highest mean dose of midazolam out of all nine studies, no inotrope was needed for their patients despite a 5 mm Hg decrease in mean arterial pressure between pretreatment and peak midazolam dosing. Saz et al. reported 3 of 22 patients requiring fluid boluses [67]. Singhi et al. reported 5 of 21 patients with hypotension that required inotropes [62]. When combining these eight studies, the number of patients reported to have hypotension or require inotropes is 5/215 (2.3 %).

Strategy When Using High-Dose Midazolam

Taken together, all nine pediatric critical care studies involving midazolam for RSE used this agent as the first line of therapy for [38, 46, 60–67]). It is clear that when using an algorithm the rate of seizure control was high (90 %), the interval to seizure cessation was short (37 min) and there was little need for vasoactive agents (2 %). This combination of high efficacy, ability to be rapidly titrated to seizure control and relatively benign hemodynamic profile supports its use as the initial agent for RSE. However, in the literature, there is an apparent difference in the doses of midazolam used with and without cEEG. On average, considerably higher dosing is used when cEEG monitoring is used (2.8 mcg/kg/min vs. 10.7 mcg/kg/min), which raises the concern that non-convulsive seizures and SE may be undertreated when cEEG monitoring is not used [68]. Table 41.3 summarizes the dose escalation strategy for midazolam based on the algorithms presented in the literature.

Table 41.3 Strategy for high-dose intravenous midazolam in RSE

Timing from start of this strategy	Midazolam dosing	Steps
0 min: Initial bolus	Give 0.5 mg/kg	A
0 min: Start continuous infusion	Start at 2 mcg/kg/min (0.12 mg/kg/h)	B
5 min: If seizure persists 5 min after bolus (step A)	Give 0.5 mg/kg Increase infusion to 4 mcg/kg/min (0.24 mg/kg/h)	C
10 min: If seizure persists or recurs 5 min after step C	Give 0.1 mg/kg Increase infusion by 4 mcg/kg/min (0.24 mg/kg/h)	D
15 min: If seizure persists or recurs 5 min after step D	Repeat step D	E
20–45 min: If seizure persists or recurs 5 min after step E, then continue to repeat step D every 5 min until a maximum infusion rate is achieved	Maximum infusion rate of 36 mcg/kg/min (1.92 mg/kg/h)	F (five cycles of D-to-E may be needed)
45 min: By the completion of step F an EEG should be available to confirm seizure control or otherwise. If seizure is not controlled then consider this episode as ***treatment failure*** and move to step H	Maintain dose of continuous infusion that achieves clinical and EEG seizure control and 24–48 h later move to step I	G
45–60 min: ***Treatment failure***	Discontinue midazolam infusion and start general anesthesia with pentobarbital or isoflurane	H
24–48 h: If patient is free of clinical and EEG seizures then start to wean the infusion	Reduce infusion by 4 mcg/kg/min every 6–8 h	I
48–84 h: Continued EEG monitoring to observe for breakthrough seizures	Plan to discontinue infusion after optimizing other AEDs. If seizures recur then consider step K for ***weaning failure***, alternatively this episode may be in the category of super-refractory status epilepticus	J
Weaning failure	Consider re-bolus of 0.1 mg/kg and increase infusion by 4 mcg/kg/min AND/OR Consider alternative AEDs	K

General Anesthesia for Refractory Status Epilepticus

If seizures persist despite second-tier AEDs, then most protocols end with the phrase "refer to anesthesiologist for anesthesia." In the PICU there are two established choices – intravenous pentobarbital, a short-acting barbiturate, or an inhalational anesthetic such as isoflurane. Propofol has been used increasingly in the adult population over the last 10 years. However, the risk of propofol infusion syndrome in children is unacceptable and, therefore, not recommended for use on the PICU in a number of countries [69].

Pentobarbital

Pentobarbital penetrates the central nervous system rapidly, allowing for rapid titration to EEG burst suppression. It has multiple actions: activation of the GABA receptor in a way that is different to the benzodiazepines; inhibition of N-methyl-D-aspartate (NMDA) receptors; and, alteration in the conductance of chloride, potassium and calcium ion channels. These multiple mechanisms of action explain the drug's potential effectiveness in RSE that is resistant to benzodiazepine therapy [70]. Prolonged infusion of pentobarbital results in a transition from the usual first-order elimination kinetics seen with bolus doses, to the unpredictable zero-order kinetics and a prolonged elimination half-life because of distribution in lipid. This phenomenon makes recovery time very prolonged and the drug effect can last days, even with short infusion periods of 12–24 h [71].

Pentobarbital causes a reduction in cerebral metabolic rate for oxygen ($CMRO_2$) and, to a lesser degree, a matched fall in cerebral blood flow (CBF). A consequence of the fall in CBF is a reduction in level of intracranial pressure (ICP), which may be an advantage in patients with cerebral swelling [72]. Theoretically, pentobarbital may also be neuroprotective because of its inhibition of NMDA receptors, and reduction in $CMRO_2$. Anesthesia is induced by giving a bolus dose (range 5–15 mg/kg), usually over 30 min to an hour. The onset of drug action is within a few minutes and the peak effect is seen within 15 min. In order to achieve EEG burst suppression in a timely manner, it is best to repeat small (5 mg/kg) boluses while monitoring EEG and the hemodynamic state [73–75]. Simply giving a single bolus and adjusting the infusion typically causes an unnecessary delay in achieving therapeutic goals. The continuous infusion rate that many authors use is 1-5 mg/kg/h. When patients

Table 41.4 Barbiturate anesthesia for RSE in children

Study [ref]	Barbiturate (cases)	Anesthesia Protocol Time to anesthesia Duration of anesthesia	Findings: Midazolam failures (%) Responders (%) Mortality
Kim et al. [76]	Pentobarbital (n = 23)	Bolus (B) 5 mg/kg; Infusion (I) 1 to 3 mg/kg/h	7/23 (30 %)
		Median 24 h	17/23 (52 %)
		Mean duration 5.7 (range 0.5–27) days	Mortality 10/23 (43 %)
van Gestel et al. [77]	Thiopental (n = 20)	B to achieve blood level of 20 mg/mL at 6 h	20/20 (100 %)
		Data not given	11/20 (55 %)
		Mean duration 8.6 (range 2–33) days	Mortality 8/20 (40 %)
Sakuma et al. [78]	Barbiturates (n = 22), most commonly Pentobarbital (n = 15)	Mean effective dose 4.2 mg/kg/h	22/22 (100 %)
		Data not given	16/22 (73 %)
		Mean duration 52.3 (range 3–312) days	Unknown
Barberio et al. [73]	Pentobarbital (n = 30)	B 5.4 mg/kg; I mean maximum 4.8 (range 1.5–10) mg/kg/h	Not given but 37 % received benzodiazepines
		Median 35 (range 4–192) h	22/30 (73 %)
		Mean duration 6.9 (range 6–22) days	Mortality 3/30 (10 %)

receive prolonged treatment with pentobarbital they will develop tolerance to the sedative effect, but tolerance to the anticonvulsant effect should not occur, which explains why tachyphylaxis is less common with pentobarbital that with midazolam infusions [70].

Pediatric Critical Care Studies of Pentobarbital for Refractory Status Epilepticus

Up to June 2013 there had been four retrospective studies using barbiturate coma alone for RSE in pediatric patients, in the English language literature, for a combined total of 95 patients [73, 76–78]. These studies of barbiturate coma lacked explicit definitions for RSE, seizure control, breakthrough seizures and seizure recurrence during treatment (Table 41.4). In three studies [76–78], continuous infusion of midazolam had failed in 49 of the 65 cases (75 %). In the other study 37 % had received benzodiazepines before barbiturate anesthesia [73]. In the midazolam failure cases, 32/49 (65 %) responded to barbiturate anesthesia [76–78]. Two studies reported the duration of SE before barbiturate anesthesia was used; the median time was 24 and 35 h [73, 76].

Overall, there was some degree of treatment success, either induction of EEG burst suppression or seizure control was obtained in 66/95 (69 %) patients in the four studies [73, 76–78]. Two studies commented on the achievement of burst suppression. Baberio et al. [73] found 30/30 (100 %) patients, at least transiently, reached this goal while Sakuma et al. [78] found 17/22 (77 %) patients obtained burst suppression. The study by Kim et al. [76] reported the period before pentobarbital was used as 24 (2.5–48) h (median [interquartile range]). Baberio et al. [73] also reported the time a patient remained in RSE before starting pentobarbital, which varied widely with a mean time of 49.6 ± 47.4 h (median 35, range 4–192 h). This study also reported a mean time of 22.6 ± 17.5 h from beginning pentobarbital therapy until seizure control and/or burst suppression. Two studies provided information on the pentobarbital infusion rate to obtain seizure and/or burst suppression. The mean maximum dose was similar in the studies reported by Sakuma et al. [78] and Barberio et al. [73], 4.98 and 4.8 mg/kg/h respectively. A maximum hourly infusion rate of pentobarbital was reported in one study and was 10 mg/kg/h [73]. Barberio et al. reported the occurrence of breakthrough seizures in 20/30 (67 %) patients, even after achieving burst suppression [73]. Kim et al. found that seizures recurred in 5/23 (22 %) patients after stopping pentobarbital [76]. The weighted mean duration of barbiturate treatment in all four studies was 17.5 days [73, 76–78].

Last, in regard to the hemodynamic tolerance of prolonged barbiturate therapy, two studies reported on the use of vasoactive support. Baberio et al. [73] found that 28/30 (93 %) patients required vasoactive support (16/30 needed two agents) and van Gestel et al. [77] found that all 20/20 (100 %) of their patients needed vasoactive support. None of the studies reported that hypotension limited the dose of barbiturate anesthesia.

Strategy When Using Pentobarbital Anesthesia for Refractory Status Epilepticus

Overall, in spite of the undesirable pharmacokinetics and side effects of pentobarbital, it remains a very reliable drug for inducing anesthesia and stopping RSE [79]. Burst suppression is usually maintained for 24–48 h, although some authors argue that longer periods are associated with lower rates of recurrent seizures [74, 75, 80]. Despite its tissue

accumulation and long elimination half-life, breakthrough seizures can occur from abrupt discontinuation of the infusion, and so tapering the dose during weaning is recommended [76]. Hypotension should be anticipated in all patients receiving pentobarbital [73]. It is caused by drug-related dilation of venous capacitance vessels, which results in reduced cardiac preload and output. The total systemic vascular resistance changes little, and there should be not be any myocardial depression. One use of cEEG monitoring is to ensure the minimum infusion rate of pentobarbital – necessary to induce burst suppression – is given, thereby avoiding over-treatment and the hemodynamic risks. It is also advisable to make sure that the patient has adequate preload, and that vasopressors are readily available [81]. Last, it is worth noting that pentobarbital causes white blood cell dysfunction and is associated with increased rate of nosocomial infection, especially pneumonia. Patients may also be at risk of significant abdominal complications because these patients invariably develop ileus [82].

Inhaled Anesthetics

The inhaled anesthetic isoflurane has been used for the treatment of RSE for over 20 years. More recently, desflurane has also been used. Unlike other anesthetic therapies for RSE (e.g., high-dose midazolam or pentobarbital), inhaled anesthetics provide almost immediate control of seizure activity regardless of seizure chronicity or type. These medications are considered a last line of therapy since there are technical difficulties with safe administration outside of the operating room and concerns over potential toxicity with long-term use. The mechanism by which the inhaled anesthetics control seizure activity likely involves multiple receptors including GABA-, nicotinic- and glycine-receptors, and potassium-gated ion channels. It is difficult to determine what role the volatile anesthetics should have in the treatment of *refractory*- and *super-refractory SE*. Many protocols mention the use of these agents as a last resort. However, at this stage, permanent neurological damage is likely to have already occurred and advocates argue that initiation sooner would yield better outcomes. Overall, the anesthetics are a reliable method for controlling seizures and inducing EEG burst suppression. These therapeutic goals are achieved within minutes and breakthrough seizures are rare, and hypotension is almost never dose-limiting. The inhalational anesthetics can be readily titrated in a way that intravenous pentobarbital cannot. In PICU practice this means that long-term AEDs can be started and blood levels optimized while the patient is in EEG burst suppression. However, each PICU should decide who is able to initiate, supervise and monitor such therapy.

Isoflurane and desflurane produce a powerful dose-dependent suppression of EEG activity. Typically, volatile anesthetic potency is described in MAC (minimum alveolar concentration) units. The MAC is defined as the concentration of vapor in the lungs at one atmosphere that prevents the reaction to a standard surgical stimulus in 50 % of subjects. When comparing vapors, the unit is actually a median value and a lower MAC represents a more potent volatile anesthetic. Isoflurane has a MAC of 1.15. Other uses of MAC terminology include MAC-BAR (1.7–2.0 MAC), which is the concentration required to block autonomic reflexes to nociceptive stimuli, and MAC-awake (0.3–0.5 MAC), the concentration required to block voluntary reflexes and control perceptive awareness. The MAC value for EEG burst suppression is 1.5–2.0. Given this potency of the central nervous system depression, it means that induction of burst suppression and control of RSE occurs at dosing used in the operating room, and normally under the supervision of an anesthesiologist.

Isoflurane for Pediatric Refractory Status Epilepticus

The use of volatile anesthetics for RSE is limited to small case series and reports, predominantly in adults [83–85]. However, one of these series did include the use of isoflurane in five pediatric patients with RSE [83]. In all five patients seizure control and/or burst suppression was achieved. Four of the patients had failed treatment with pentobarbital. The isoflurane administration ranged from end-tidal concentrations of 0.5–2.25 %. The median duration of RSE prior to treatment with inhaled anesthetic was 7 days.

Strategy When Using Isoflurane Anesthesia for Refractory Status Epilepticus

Isoflurane is given via an anesthetic machine with end-tidal monitoring of isoflurane concentration. Initially, the concentration of the anesthetic is gradually increased until adequate suppression of the seizure and background EEG activity has occurred, and this dose is maintained. Then, at regular intervals, the minimum dose of anesthetic needed to achieve EEG burst suppression should be determined. We also follow the total anesthetic exposure by calculating the MAC-hours of treatment (i.e., the hourly end-tidal percentage concentration of isoflurane divided by 1.15 is summed for each hour of treatment).

The anesthetic agents cause non-linear decrease in $CMRO_2$, and once burst suppression occurs there is no further decrease in cerebral metabolism. Hence there is little value in going beyond EEG burst suppression and inducing electrocerebral silence. It also means that monitoring cEEG is the only technique by which to recognize that minimum necessary anesthetic dosing is being given. The anesthetic agents also decrease cerebrovascular resistance, thereby causing increase in CBF and, potentially, ICP – this complication is seen with isoflurane, and to a lesser degree with desflurane. This increase in ICP is typically mild, transient,

and only of major significance in patients with evidence of preexisting intracranial hypertension [72, 83].

Both isoflurane and desflurane produce a dose-dependent predictable fall in arterial blood pressure via lowering of systemic vascular resistance and, to a much lesser degree, negative inotropy. As a consequence, a compensatory increase in heart rate is frequently seen when starting these agents. Occasionally, rapid changes in the delivery of the anesthetics cause an increase in heart rate and blood pressure secondary to sympathetic stimulation.

Last, there are some concerns that the volatile anesthetics may be neurotoxic when used for prolonged periods in the treatment of SE [85]. The first cases of adverse neurology associated with prolonged isoflurane in the PICU population were reported in 1993 by Arnold et al. [86]. Isoflurane was used for sedation and bronchodilation and it proved to be effective, without significant cardiovascular, hepatic or renal toxicity. However, 5 of 10 patients developed a syndrome of extreme agitation and non-purposeful movements after stopping the isoflurane. All five patients were less than 5 years old and received at least 70 MAC-hours of volatile anesthetic. Other reports reflect a similar experience of psychomotor disturbances after stopping the anesthetic abruptly [87–90]. Therefore, it is unclear whether these symptoms are the result of a withdrawal syndrome or a direct neurological insult, but typically the symptoms are transient and self-resolving.

General Anesthesia for Super-Refractory SE

General anesthesia allows us to control seizure activity and maintain a patient's homeostasis. This state, however, is not an end in itself; rather it provides an opportunity to develop a strategy for mid- to long-term management, and AED therapy – for example, establishing the cause of the episode of *refractory* or *super-refractory SE* by following a protocol for investigation that is appropriate when usual causes have been ruled out (Table 41.5). In 2006, the American Academy of Neurology and the Practice Committee of the Child Neurology Society provided an evidence-based practice parameter for diagnostic assessment of the child with SE [91]. The field, however, is changing rapidly and expert neurologic opinion should always be sought [92].

Table 41.5 Diagnostic considerations in patients presenting with RSE

Diagnostic steps
1. Clinical assessment
General assessment
Acute cause: meningoencephalitis, sepsis, febrile infections (FIRES), electrolyte disorder, hypoglycemia, stroke, demyelinating disease, trauma, intoxication
Detailed neurologic assessment
Non-acute cause: cortical malformation, neurocutaneous syndromes, brain tumor, autoimmune disorder, monogenic epileptic encephalopathies, chromosomal abnormalities, metabolic disease
2. Laboratory testing to consider
Complete blood count and differential; coagulation work-up
Inflammatory markers: C-reactive protein, erythrocyte sedimentation rate, von Willebrand factor antigen
Metabolic/genetic: pyridoxine dependency, beta-ureidopropionase deficiency, DNA polymerase subunit gamma-1 (POLG) mutations, mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS), protocadherin 19 (PCDH19),sodium channel protein type 1 subunit alpha (SCN1A)
Infectious work-up: bacteria, fungal and viral cultures and serology
Testing for oligoclonal banding
Testing for antibodies, including neuronal and ion-channel antibodies (Hashimoto thyroiditis, lupus, paraneoplastic panel)
3. Neuroimaging
Brain MRI with gadolinium, fluid attenuation inversion recovery (FLAIR) sequences, diffusion-weighted imaging and angiography (MRA)
White matter/basal ganglia: MELAS, Wilson, Adrenoleukodystrophy, POLG mutations
Conventional angiogram for microvasculitis
4. Lumbar puncture and cerebrospinal fluid (CSF) analysis
Measurement of opening pressure
CSF cell count and differential, protein and glucose
Bacterial (Q fever, Chlamydia, Tuberculosis), parasites/fungal, and viral (HHV6, HHV7, Influenza A, Adenovirus, Echovirus, Mycoplasma, Rotavirus, Respiratory syncytial virus, Parvovirus B19, West Nile virus, Epstein-Barr virus, other encephalitides) cultures and serology
Testing for oligoclonal bands
Testing for neuronal and ion-channel antibodies
5. Brain biopsy
Consider if normal angiogram, as diagnostic of microvascular vasculitis

In the PICU, the diagnostic process is best exemplified in our approach to FIRES that leads to immunotherapy (see below) and our approach to potential small-vessel central nervous system vasculitis [93, 94] or type II focal cortical dysplasia [95–97] that leads to diagnostic brain biopsy. Concurrent with this investigational process, there is also the need to optimize AED therapy (i.e., rationalizing choice of new and old medication and the potential for pharmacokinetic interactions) and their blood levels. General anesthesia provides a period when transitions can be carried out. It is not 'magic' and should not be considered as therapy that is successful or unsuccessful; what is considered successful is whether the choices of long-term AEDs bring about control or not, or whether appropriate and effective immune therapy has been used. As already stated, the approach to these choices is multidisciplinary and, often times, there is little in the way of evidence-based information to help inform decision-making. New ideas are constantly being developed and clinical trials are needed in this area of intensive care. For example, there is an association between prolonged SE and increased drug

resistance. This phenomenon may be related to increased expression of drug-efflux reporter genes and proteins, e.g., P-glycoprotein (P-gp) and multidrug-resistance-proteins) [98–100]. Early in the episode, efflux transporter genes expression is low because of down-modulation by increased levels of pro-inflammatory cytokines, but later this relationship is reversed and drug resistance occurs. Verapamil can act as a P-gp inhibitor and there are two case reports of its use in patients RSE [101, 102]. Further basic research and clinical trials are needed to prove the effectiveness of P-gp inhibition by co-administration of verapamil during AED therapy for SE.

Duration of Anesthesia

Having induced anesthesia and achieved steady state EEG burst suppression with the minimum dose necessary, one question is 'how long should the patient remain in this state?' There is not an evidence-based answer to this question. However, if one considers that categorization of *super-refractory SE* is important, then at 24-h after starting anesthesia, it should be lightened so as to ascertain whether breakthrough seizures occur or not. Abrupt weaning may lead to breakthrough seizures and so the speed of weaning should occur slowing. It will be longer with intravenous anesthesia (pentobarbital) than volatile anesthetics, and it is reasonable to wean over 24 h (but may be much longer with pentobarbital). In our practice we initially maintain patients in an anesthetized EEG burst suppression state for 48 h and then lighten the depth of anesthesia over a further 24 h. This 3-day interval allows us time to make choices about AEDs and optimize drug levels. If seizures recur, then a repeat cycle of anesthesia is re-established and the duration of individual cycles of anesthesia is increased, often for 3- to 5-days. There is no time limit or the number of cycles of general anesthesia. Rather, the limit comes down to setting of goals and deciding at what point the therapeutic target should change from total seizure control to accepting a particular seizure frequency in a patient. For example, in the literature there is one example of an 18 year old with a flu-like prodrome and *super-refractory SE* who had pentobarbital-induced EEG burst suppression for over 7 weeks while other AEDs were tried [103]. In our practice, making decisions about choice of AEDs, duration of drug-induced coma and setting realistic therapeutic targets is a multidisciplinary process between the PICU, anesthesiology, and epileptology/neurology teams. Figure 41.2 summarizes our approach in the transition and escalation of AED therapies for RSE and super-refractory SE.

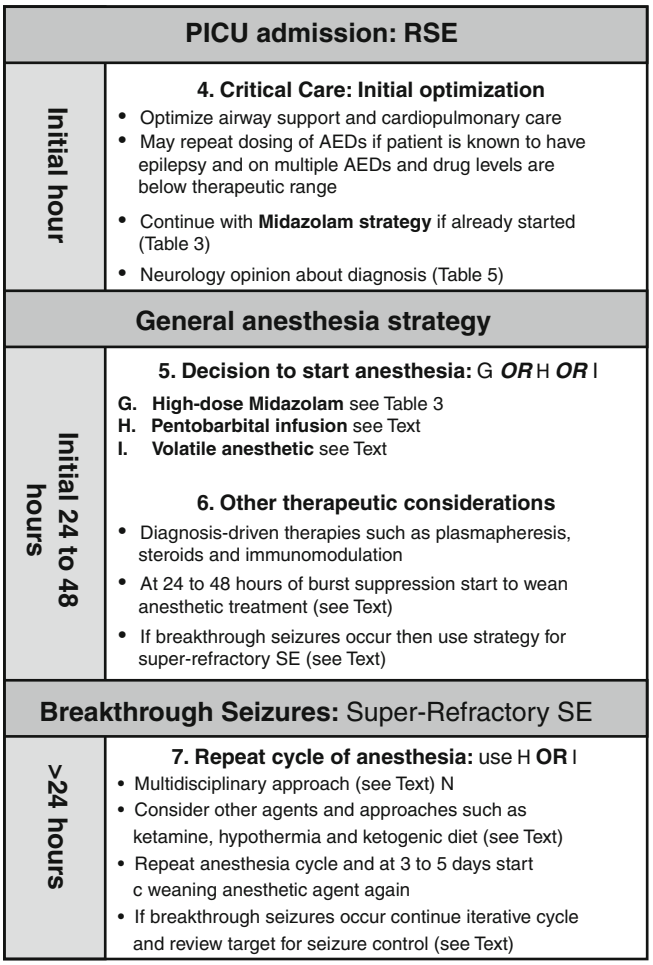


Fig. 41.2 Intensive care treatment of refractory- and super-refractory SE

Other Medications and Approaches During Anesthesia

The other AEDs that have been used for control of *refractory-* and *super-refractory SE* include propofol, ketamine, and topiramate. There are too few data to make an evidence-based assessment about such treatment and prolonged propofol infusion is not recommended in PICU practice in many countries because of the risk of propofol infusion syndrome [69]. Some patients may benefit from surgical corpus callosotomy, lobar resection or hemispherectomy for discrete, localized seizure foci [104]. This approach is only available in epilepsy-surgery centers. The other therapies that have been used or tried include ketogenic diet, hypothermia, and immunomodulation [105].

Ketamine

Prolonged seizures are accompanied by a decline in sensitivity to GABA agonists, but not to NMDA-receptor antagonism. Since ketamine is an NMDA-receptor antagonist that is not associated with cardiorespiratory depression, it is a potential option for treatment of RSE. Up to June 2013, two pediatric case series of intravenous ketamine for RSE have been reported. One single-center study reported its use in nine children with RSE who had all failed to respond to midazolam, and half had also failed to respond to barbiturate

anesthesia. Rosati et al. [106] used a ketamine infusion of 36.5 (range 10–60) mcg/kg/min after a median of 6 (range 2–26) days of RSE along with midazolam (to prevent emergence reactions) and found that six of nine patients had their seizures controlled. Another study of 58 cases from North America and Europe reported use of ketamine in 12 children after a median of 9 days of RSE (range 0–122 days), although the analysis of the pediatric data was not separated from the adult data [107]. Ketamine was not universally effective in controlling SE (at best 57 % in the whole population with a mortality of 45 %) – the authors commented "likely response was not observed when infusion rates were lower than 15 mcg/kg/min; ketamine was introduced at least 8 days after SE onset; or after failure of seven or more drugs." Of note, one-third of the whole series developed complications while receiving ketamine, most commonly sepsis, shock, organ failure and pneumonia. There was no relationship between the dose or duration of exposure to ketamine, but complications were higher when more than one other anesthetic drug was used concurrently. Taken together, the collective experience of ketamine in North America and Europe is small and its role in super-refractory SE requires further investigation.

Therapeutic Hypothermia

Therapeutic hypothermia (TH) has been used to treat *refractory*- and *super-refractory* SE for many years. In 1984 Orlowski et al. reported three children with SE successfully treated with a combination of TH (30–31 °C) and thiopental [108]. Since then, in the English language literature there have been other pediatric cases reported where TH has been combined with other anesthetic agents, or bumetanide [109, 110]. In the Japanese literature there is more extensive reporting of hypothermia for RSE. For example, Nakagawa et al. used successfully the combination of hypothermia for 48–72 h with midazolam (2 children) or barbiturates (10 children) after 2.5 (range 0.9–10.2) hours of RSE [111], personal communication].

Taking these reports together, it seems that TH may help control ongoing SE, but its efficacy is transient and, like other 'anesthetic' approaches, it should be considered as a temporizing measure while other therapeutic options are explored. At the time of writing this review, there is one prospective randomized study of therapeutic hypothermia in convulsive SE in adults in intensive care registered with ClinicalTrials.gov – the HYBERNATUS study NCT01359332 is still recruiting participants.

Ketogenic Diet

The ketogenic diet is a high-fat, low-carbohydrate and adequate protein diet used widely to treat refractory epilepsies in children. It has also been tried as an acute treatment for *refractory*- and sup*er-refractory* SE in children [112–119]. The enteral diet is administered through a gastrostomy tube and most reports use a 4:1 or 3:1 ketogenic ratio (grams of fat to protein and carbohydrate combined) with total avoidance of glucose initially. The diet is started after 24 h of fasting, and successful screening to exclude underlying biochemical, metabolic, or mitochondrial disease, including β-oxidation deficiencies. The short-term side effects of the diet include acidosis, hypoglycemia, weight loss, and gastroesophageal reflux, which can obviously complicate the care of a critically ill patient. Adequate nutrition needs to be assured. In the initiation phase, blood glucose should be measured at least every 3 h for the first 3 days and then, if appropriate, every 6 h thereafter. Glucose is given if blood sugar falls below 45 mg/dL. Once ketosis is achieved, urinary ketones and serum β-hydroxybutyrate should be measured daily. Later on, the frequency of the serum testing can be changed to weekly. During the diet, glucose needs to be severely restricted and total fluid intake should be monitored closely. Since steroid administration may inhibit the development of ketosis, use of this agent should be avoided [114]. In rare instances ketogenic parental nutrition has been used successfully in children with epilepsy [120], and there is now a recent proof-of-concept case report in an adult with *super-refractory* SE [121].

Table 41.6 summarizes the pediatric cases and case series that have examined the ketogenic diet in *refractory*- and *super-refractory* SE [112–119]. Out of 34 children in the literature that we have identified 25 (proportion 74, 95 % confidence interval 59–89 %) who responded to ketogenic diet within 19 days of initiation of treatment. Over half of this

Table 41.6 Studies examining ketogenic diet or modified Atkins diet for RSE

Study [ref]	Age range (cases)	Seizure-free cases	Time to response	Etiology
Villeneuvre et al. [112]	1–10 year (n = 5)	4 of 5	1–10 days	Cryptogenic (2), Sturge-Weber, encephalitis, hypomelanosis of Ito
Kumada et al. [113]	5 year (n = 2)	2 of 2	5–10 days	Frontal lobe epilepsy, heterotopias
Nabbout et al. [114]	5–8 year (n = 9)	7 of 9	4–6 days	FIRES
Kramer et al. [115]	4–9 year (n = 4)	1 of 4	1 day	FIRES
Nam et al. [116]	4–14 year (n = 4)	4 of 4	3–19 days	Suspected viral meningoencephalitis
Vaccarezza et al. [117]	1–14 year (n = 5)	4 of 5	2–3 days	FIRES (3), refractory partial epilepsy (2)
Caraballo et al. [118]	9.5–12 year (n = 2)	1 of 2	Unknown	FIRES
Sort et al. [119]	3–11 year (n = 3)	2 of 3	1–7 days	Hemiconvulsion-hemiplegia-epilepsy syndrome, mitochondrial disorder, FIRES

population suffered FIRES. Taken together, it should be noted that there are no prospective studies of ketogenic diet in *refractory*- and *super-refractory* SE. We do not know the likelihood of it working in an individual case. At the time of writing this review, there is one prospective randomized study of ketogenic diet for RSE in adults in a neurointensive care unit registered with ClinicalTrials.gov (NCT01796574 is still recruiting participants).

Electroencephalography and Non-convulsive Seizures

The discussion so far has focused on the intensive care treatment of mechanically ventilated patients with ongoing RSE that requires special intensive care AED therapies. As discussed in previous sections cEEG is used in these patients once high-dose or anesthetic therapies are used. In contrast to this population, with a known seizure and RSE, there is a very different population that we also need to discuss, i.e., the comatose child with no apparent clinical seizures – either because these are subtle events or because neuromuscular blocking agents are being used – who on undergoing cEEG monitoring has electrographic seizures (ES) and electrographic SE (ESE) identified.

Many North American centers now monitor cEEG in comatose patients in order to detect ES and ESE activity [122]. However, to date, the clinical significance of ES and ESE remains largely unknown, including, for example, whether the relationship of such activity to outcome is independent of underlying etiology, or even whether treatment is advisable. Topjian et al. [123] reported that in a single-center PICU series of 200 patients undergoing cEEG monitoring during acute encephalopathy, the presence of ESE rather than ES alone was associated with increased mortality and worsened neurologic outcome at discharge. The authors defined an ES as an abnormal paroxysmal event that differed from background activity "lasting longer than 10 seconds with a temporal-spatial evolution in morphology, frequency, and amplitude, and with a plausible electrographic field." ESE was defined as "either a single 30 minute ES or a series of recurrent independent ES totaling more than 30 minutes in any one hour." Cases were grouped into the ESE category if they met the criteria for ESE at any time during cEEG monitoring. Taken together with all of the recent PICU series of cEEG monitoring in comatose patients, ES has been identified in 7–46 % of cases and ESE in 18–35 % of cases [123–135]. This prevalence is confirmed by a recent multicenter study reviewing the experience in 11 North American sites, with 550 consecutive children undergoing cEEG in the PICU, where ES occurred in 162 of 550 subjects (30 %), of whom 61 had ESE – 36 % of those with ES and 11 % of the whole series [135]. The wide range in prevalence of ES and ESE likely reflects the case mix in different series. For example, groups at high risk for ES are patients with epilepsy [131, 135], central nervous system infection [128, 133], structural brain lesions [126, 132], encephalopathy after cardiac arrest [123, 130], and traumatic brain injury.

There remains debate about the significance of ES and ESE in comatose, sedated, and paralyzed, possibly postictal patients [136] and, as a consequence, there is substantial variation in treatment in the PICU [122]. Topjian et al. [123] showed that ESE, rather than ES alone, is associated with worsened outcome. The authors' practice was to "aim to terminate ES and ESE when identified." Hence, the relationship between ESE and outcome was present despite treatment, and they have reported elsewhere that over half of the subjects received multiple AEDs [137]. The lack of relationship between ES and outcome may have been because of a confounding effect of treatment. The presence of ESE may merely serve as a biomarker of disease pattern, with the link between severity of underlying pathology having the major effect on outcome. Kirkham et al. [133] described that larger numbers and total duration of ES/ESE was related to worsening outcome in their population of 204 critically ill comatose children. The recent large multicenter study [135] found that subjects with ESE had greater odds of in-hospital death, even after adjusting for EEG background and neurologic diagnosis category. Among subjects with an acute structural disorder (e.g., stroke, CNS inflammation or autoimmune disorder, traumatic brain injury and hypoxic-ischemic encephalopathy), death occurred in 37 % (10 of 27) with ESE and 18 % (40 of 218) without ESE ($P = 0.02$). Among subjects with an acute non-structural neurologic disorder (e.g., sepsis, metabolic, pharmacologic sedation, toxin, paralytic administration), death occurred in 33 % (4 of 13) with ESE and 12 % (15 of 129) without ESE ($P = 0.04$).

Instituting cEEG monitoring in the PICU, so as to identify ES and ESE, requires significant manpower resources and out-of-hours activity. For example, in August 2011, 58 North American pediatric centers were surveyed and the scale of the potential work was demonstrated by the common indications for cEEG: altered mental state after a seizure or SE (97 %), altered mental state of unknown etiology (88 %), or altered mental state with an acute primary neurologic condition (88 %) [138]. In addition, in 37 % of these centers specialist physicians reviewed the cEEG twice per day, and there was variability in technologist availability for citing the monitoring. Clearly, it is not cEEG monitoring per se that improves outcome, but possibly our interventions guided by this technology. To date, however, there is little evidence that titrating AED therapy against a particular cEEG end point improves patient outcome and a prospective randomized controlled trial of cEEG monitoring and AED treatment is definitely needed.

Fever-Induced Refractory Epileptic Encephalopathy and FIRES

These conditions have multiple labels in the literature including: FIRES, fever-induced refractory epileptic encephalopathy in school-aged children, IHHS, acute encephalopathy with inflammation-mediated status epilepticus (AEIMSE), acute encephalitis with refractory repetitive partial seizures (AERRPS), NORSE and devastating epilepsy in school-age children (DESC) [41–45]. In the following text we will group these conditions together since the diagnostic evaluation fails to show any specific cause. These conditions also best exemplify the therapeutic approach in the intensive management of RSE and super-refractory SE. From the perspective of non-AED management, it is critical to establish whether the condition is consistent with some autoimmune disease (e.g., glutamate-receptor subunit R3 antibodies, NMDA-receptor antibodies, voltage-gated potassium channel antibodies, other paraneoplastic antibody) since early plasmapheresis and immunomodulation may have a role (Table 41.5, Fig. 41.2). Thereafter, the PICU-specific AED treatments are much as we have discussed, but with the following caveats.

General Anesthesia

First- and second-tier AEDs are universally ineffective at providing sustained seizure control in FIRES cases [115], and barbiturate anesthesia also seems to be disappointing [139]. For example, in a series of 77 patients with FIRES, 46 underwent drug-induced EEG burst suppression for a median duration of 7 days (mean 14.3 days). Nine patients died, and 66 out of 68 survivors developed severe refractory epilepsy. The authors found that induction of EEG burst suppression was not associated with an increased risk of death, but a longer duration of this state was associated with worse long-term cognitive outcome [115, 139]. However, it is also possible that these patients had more severe disease [140].

In a multicenter report of AERRPS, Sakuma and colleagues described their experience with pentobarbital and midazolam in 29 patients, age range 1–14 years [78]. Of the 22 patients treated with intravenous barbiturates 13 had a "complete" response, while 3 had an "excellent" and 4 had a "good" response. None of the patients had a "poor response". The maximum dose of pentobarbital was 4.98 ± 2.06 mg/kg/h and the mean duration of infusion was 52 ± 72.6 days. Midazolam was given to 25 patients and only three had complete seizure control; 5 others had a "good" response and 17 were judged to be "poor" responders. The maximum midazolam infusion dose rate was 0.47 ± 0.33 mg/kg/h, which is not as high as the high-dose strategy described by Morrison and colleagues (see above discussion [58, 65]). These findings suggest that midazolam, at least at the doses used in this study, is inadequate at producing enough neuronal suppression in this malignant process.

Other Therapies for FIRES

Immunomodulatory therapy does not appear to work in cases of FIRES. Ketogenic diet, however, may have some role (see discussion above and Table 41.6). For example, Nabbout et al. reported nine children who received 4-to-1 ratio of fat to combined protein and carbohydrate ketogenic diet [114]. The diet was started between 4 and 55 days after the presentation with FIRES. In seven of eight patients reaching ketonuria (the ninth patient was unable to reach ketonuria because of use of steroids) seizure activity stopped within 2–4 days of reaching ketonuria, and within 4–6 days of starting the diet. One of the seven responders was taken off the diet and experienced abrupt return of *refractory SE*, and died 10 days later. For the six responders who were kept on the diet, isolated seizures returned within a few months. These seizures were considered mild, with a frequency of up to two seizures per week.

Conclusion

When a child with ongoing SE is admitted to the PICU, there is an inadequate evidence-base from randomized controlled trials for what AED-strategy we should use. To date, therapy has been based on case series with a dearth of open data, and this lack of information compromises optimal therapy. This review and presentation of information in Tables and Figures is one approach. Figure 41.3 summarizes the key data from the pediatric studies reviewed in this Chapter, and it forms the basis for our current strategy to refractory- and super-refractory SE in children. There is a hierarchy in approach that most authors take in controlling RSE. The studies indicate that in the acute setting of RSE (level 1), midazolam achieves seizure control at a mean of 37 min after starting an infusion. When midazolam has failed, barbiturate anesthesia (level 2) is used at a mean of 66 h after RSE onset. When both midazolam and barbiturates have failed, isoflurane or ketamine anesthesia (level 3) is used at a mean of 10 days after RSE onset. At present, we do not use TH or ketogenic diet in our 'routine' strategy for refractory- and super-refractory SE, but this may change as experience from randomized studies become available.

Finally, it is our view that since cases of truly *refractory-* and *super-refractory SE* are seen infrequently at any given institution, the first way of improving the quality of evidence is to develop national and multinational case registries of existing practice.

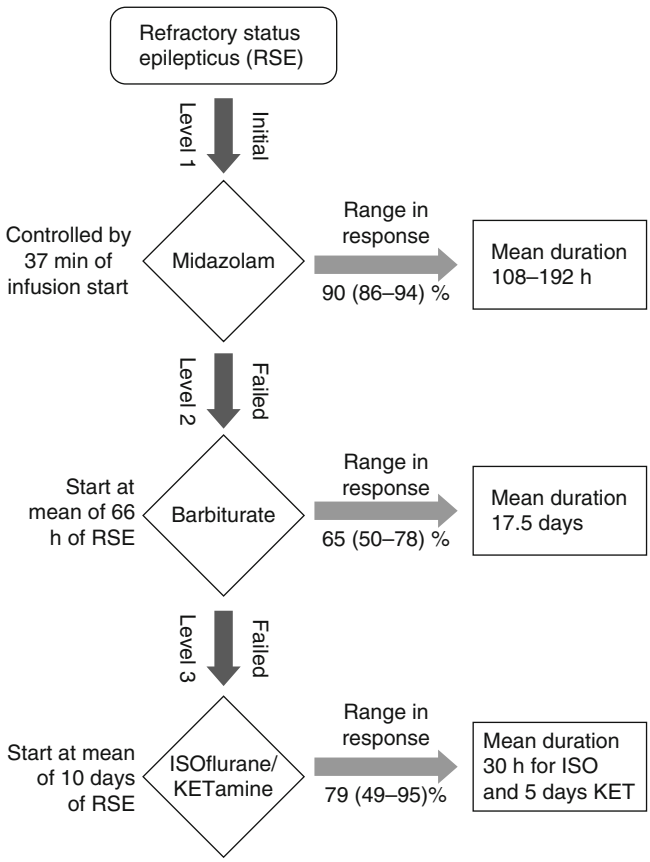


Fig. 41.3 Approach to RSE based on the studies reviewed in this chapter

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Diseases of the Peripheral Nervous System

42

Matthew Pitt

Abstract

The disorders of the peripheral nervous system become important in the ICU either as a cause for the child to be admitted or as a complication during the time they are there. EMG is an essential diagnostic tool in the management of such cases. The conditions affecting children can be divided according to anatomical location that is, anterior horn cell, peripheral nerve, neuromuscular junction and muscle. They can be further subdivided into those that are acquired and those that are hereditary. Within the acquired conditions, poliomyelitis or poliomyelitis like syndromes, the Guillain Barre syndrome, botulism, and acute myositis are amongst some of the most important. In the hereditary conditions spinal muscular atrophy with respiratory distress (SMARD), congenital hypomyelinating neuropathy, congenital myasthenic syndromes, and myotonic dystrophy, feature most prominently. The conditions that children acquire while in the ICU include critical illness neuropathy and myopathy, but these are relatively rare but receiving greater interest in the recent literature. Of the mononeuropathies that may occur, the sciatic nerve is more affected than other nerves in the leg or arm. Analysis of cases referred for EMG in the author's hospital also highlight the importance of bulbar palsies, failure to wean from ventilation in addition to those conditions already described.

Keywords

EMG • Peripheral nervous system • Guillain Barre syndrome • Myopathy • Neuropathy • Botulism • Spinal muscle atrophy • Critical illness neuropathy and myopathy

Introduction

Diseases of the peripheral nervous system (PNS) become important to pediatric intensive care specialists in one of two ways. First, there are those children who come to the intensive care unit (ICU) as a result of disease of the peripheral nervous system, which has affected their ability to sustain respiration or protect their airway. The next group of children, who may be in the ICU for other reasons, develop diseases of the peripheral nervous system, which often affect their ability to recover. The most well known of these are critical illness myopathy and neuropathy, which are generalized disturbances, but also even in the best managed intensive care units, unfortunately, children may develop pressure palsies. Finally, the recent use of electromyography (EMG) in our ICU is discussed, which gives an indication of some of the more difficult cases that are seen.

When considering the PNS conditions it is easiest to classify them anatomically into those that affect the anterior horn cells, peripheral nerve, neuromuscular junction, or muscle itself. These constitute the lower motor neuron (LMN).

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Conversely, any condition which affects the spinal cord above the anterior horn cell or the spinal sensory pathways above the dorsal root ganglia is considered an upper motor neuron (UMN) disturbance and will not be the subject of discussion in this chapter.

The diagnosis of peripheral nerve disease in children in the ICU is most difficult, as the usual clinical methods, so valuable when diagnosing neurological conditions, are severely restricted. It is for this reason that the role of Electromyography (EMG) is of crucial importance to the intensive care specialist [1, 2]. EMG has a primary role in the diagnosis of all neuromuscular disease, but more so in the ICU than perhaps anywhere else. Despite this, there are many ICUs, certainly in the United Kingdom, that do not have readily available access to EMG. It is, of course, possible to send off investigations without prior EMG but even in conditions which are obvious, such as spinal muscular atrophy (SMA), confirmation that this is the condition by EMG is a much more efficient way to plan investigation. There are other conditions, like Congenital Myasthenic Syndromes (CMS), where the condition may not even be suspected unless EMG is performed. For these reasons, before discussing the conditions in the two groups already identified, a brief introduction to EMG is presented and details of how it is performed in our unit (as one example of how this could work in other ICUs) described.

Electromyography in the Intensive Care Unit

EMG in this chapter encompasses not only needle electromyography, but nerve conduction studies and is the convention in United Kingdom. In the United States, electrodiagnostic examination (EDX) is a more commonly used term. The environment in the pediatric ICU presents particular difficulties to the electromyographer. EMG machines are exceptionally sensitive and in any hospital the ICU most probably has more equipment and more potential for electrical interference than in any other unit, with the possible exception of the operating room suites. It is essential that all the cabling through the walls is shielded, without this it is sometimes near impossible to do EMG, particularly when trying to record sensory potentials or electromyography. It is fortunate that modern equipment that will populate the ICU such as ventilators and monitors, syringe pumps, etc are usually built to a high standard and the quality of grounding, which is so important, excellent. Strangely, the major source of artifact comes from unexpected areas such as the motors to the ICU beds. From time to time, other machines are introduced, which unexpectedly produce difficulty, the most recent being hemofiltration units used for renal replacement therapy.

When performing EMG studies in the ICU it is absolutely essential to have specialized equipment such as single use



Fig. 42.1 The left ulnar nerve being stimulated in a neonate with recording electrodes over the abductor digiti minimi muscle

stick on recording electrodes, which can be cut down to any size. Most stimulating electrodes are reusable usually having saline soaked felt pads, which make the contact between the stimulator electrode and the skin surface. The ideal construction is one that allows the limb to be encircled at the same time as the stimulations are given and an option for an inter-electrode separation of 1.5 cm (normal is 3.0 cm) is essential for neonates and infants. In addition, the actual stimulation area in these electrodes is much smaller, allowing a far more precise localization of stimulation point (Fig. 42.1).

The EMG examination of a child with a suspected peripheral nerve disturbance follows a set routine. First sensory nerves are tested – over 3 or 4 years old the superficial peroneal is used, below this age, the medial plantar. An arm nerve is tested if there is abnormality in the leg, the author's preference being Palm to wrist median nerve stimulation. Motor nerve conduction follows. In the smallest of children the tibial nerve is used, recording from abductor hallucis, with the proximal stimulation behind the knee not as difficult as in adults. In older children the peroneal nerve is used. In the upper limb, in children the ulnar is preferred to the median because proximal stimulation is easier. F waves can be useful particular for the diagnosis of proximal nerve involvement in Guillain Barre Syndrome (GBS).

If the sensory nerve findings are normal it is possible to rule out a sensorimotor neuropathy. Even if the sensory studies and the motor studies showed no abnormality, it is obligatory to then do electromyography of at least one muscle. In situations where there is a disturbance of the motor neuron, sometimes the reinnervation of denervated muscle fibers may be so complete that disturbances in the compound muscle action potential (CMAP) amplitude itself are not observed. In this situation the needle EMG will show easily recognizable changes with high firing, large amplitude, long

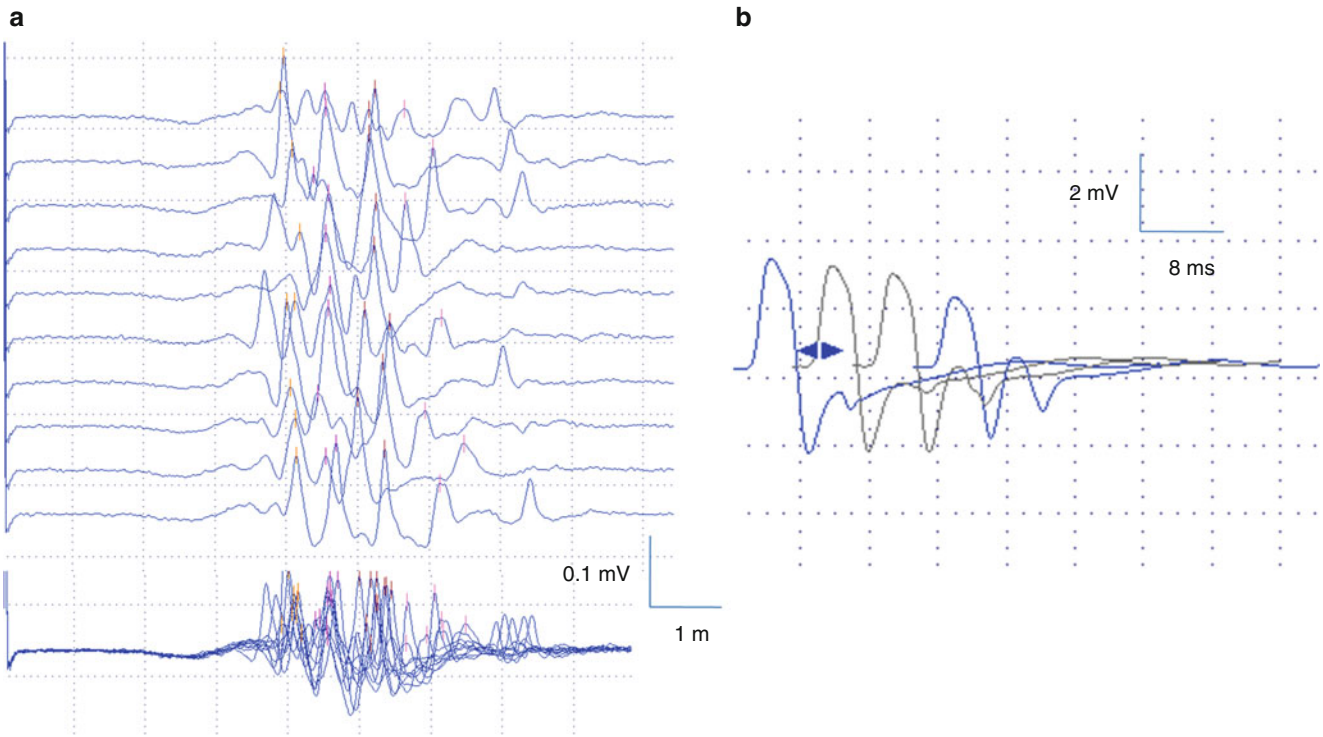


Fig. 42.2 Traces from a study of a child with fast channel syndrome congenital myasthenia. (**a**) recordings of successive traces using stimulation of the facial nerve and recording from the left orbicularis oculi. The increased jitter causing successive recordings not to overlap is demonstrated further when the traces are superimposed in the bottom trace. (**b**) repetitive nerve stimulation from extensor digitorum commonest at 3 Hz from same child

duration units that indicate that the motor unit has been reorganized with larger, more dense units replacing those that were denervated. Tibialis anterior (TA) is the muscle to study as it will show abnormality even in conditions affecting proximal muscles more than distal, such as SMA, and is easily activated by the examiner tickling the sole of the foot. Activation of the quadriceps, in contrast is very difficult even in conscious children. Iliopsoas is a muscle that is occasionally recommended but it is relatively inaccessible and there is little information about the normal pattern to be seen.

In our experience, if no EMG abnormality has been found by this stage examination of the neuromuscular junction is then undertaken using Stimulation single fiber electromyography (StimSFEMG). This is more sensitive, although perhaps less specific, than repetitive nerve stimulation and is performed on orbicularis oculi [3]. We have a very large experience with the use and interpretation of StimSFEMG [3–6]. It is preferred as the first line investigation disorders of the neuromuscular junction rather than repetitive nerve stimulation (RNS). While it is acknowledged that RNS is easier to perform in the ICU than elsewhere because the children are sedated and concerns about the discomfort that it causes can be reduced, children still will experience discomfort and almost invariably move the limb during the stimulation, making accurate interpretation difficult. That being said, we use RNS in those children where there is an abnormality of StimSFEMG because if it is positive there is a high likelihood that the condition is myasthenia if the effects of prolonged neuromuscular blocking agents can be excluded (Fig. 42.2).

Peripheral Nerve Diseases Resulting in ICU Admission

Clearly there will be instances where children who have known disorders of the peripheral nervous system, become unwell and need admission to ICU. For example, a child with severe muscular dystrophy with significant scoliosis may be particularly prone to respiratory infection and therefore may be admitted for its treatment. This is not the purpose of this section, which will concentrate on those children who are presenting to ICU de novo, weak or hypotonic with no diagnosis. Many of these patients will be very young, even in the neonatal period. Instead of dividing the clinical conditions, according to the age range [7], comments will be directed mainly towards the youngest children, and where the condition occurs in significant proportions in older children this will be brought to the reader's attention. The conditions are divided into acquired and hereditary.

Acquired Disorders

Anterior Horn Cell Disease

Historically the most common infection causing anterior horn cell disease was poliomyelitis, caused by the poliovirus. With widespread vaccination this condition has been eliminated from most parts the world. Indeed, there was a time when the most common reason for poliovirus infection was vaccine related. Now that the vaccine has been changed from the live, attenuated virus to the killed vaccine in areas where the risk of native infection is negligible, even this no longer occurs. However, the poliovirus is not the only member of the enterovirus genus (Picornaviridae) to cause poliomyelitis syndrome, with Coxsackie and Echoviruses as well as other newer enteroviruses implicated [8]. The predominant virus causing these varies in different parts the world, although enterovirus 71 is implicated perhaps more than others [9–19], particularly in Southeast Asia, one of the areas of the world where there are epidemics of acute flaccid paralysis (AFP) [11, 20–22]. West Nile virus is one of the most important mosquito borne flaviviruses to cause anterior horn cell inflammation [8]. Other important viruses of this genus causing a similar acute flaccid paralysis include Japanese encephalitis [23], Murray Valley encephalitis [24], St Louis encephalitis, Russian Spring encephalitis and also other tickborne encephalitis [25]. When encountering AFP in such an epidemic, recognition of the likely cause of the anterior horn cell disease seen is straightforward. Some children may need ICU.

Diagnosis is more difficult in sporadic cases seen outside of epidemics and is often overlooked. One such example was a 7 week old child who was admitted to the ICU of another hospital with a severe chest infection. The child was proven to have a Coxsackie infection and was on the ventilator for several weeks. Previously having fed normally on return home the child was unable to feed and often had periods of aspiration. There was also some generalized weakness. The child then was seen in many different hospitals including those specializing in respiratory disease and other neurological centers before being referred for electromyography. The EMG showed the classical changes of patchy denervation particularly prominent in the bulbar muscles and a diagnosis of post enteropathic motor neuron disease or poliomyelitis syndrome was made. Not all cases have such a clear relation to an infection and sometimes even though one suspects it, proving that there has been an infection with a virus known to be associated with this complication may be difficult. However, when a child is seen who gives this history of deterioration following an upper respiratory infection or gastrointestinal infection and is found to have patchy anterior horn cell disease it is certainly important to consider this within the differential diagnosis. These cases do not deteriorate. This is an important diagnostic pointer and one which is useful to separate these cases from the initial presentation of a neurometabolic disorder, whose onset maybe precipitated by infection, but who will show in inexorable deterioration.

Disorders of Peripheral Nerve

Acute inflammatory demyelinating polyneuropathy (AIDP) or GBS is seen in children [26–29]. It is less common than in adults and is very rarely seen in infants. It has different forms, the most common being demyelinating. The acute axonal form is found in certain countries more commonly, such as China [30]. Classically, the disorder presents with a respiratory or gastrointestinal prodrome (*Campylobacter jejuni* is often implicated), followed about 2 weeks later by the onset of weakness usually in an ascending manner and starting in the legs. Pain may be severe and is one of the characteristic features in children, which is seen less in adults. Sometimes this may be the only abnormality. The children often are systemically unwell and very irritable. On examination the classical clinical finding is weakness with loss of reflexes. Sometimes the condition may present with an external and internal ophthalmoplegia, before the more generalized abnormalities present. This is the Miller Fisher variant and is associated with antiGQ1b antibodies [29].

Diagnosis is aided by EMG. A variety of abnormalities can be detected. There may be changes of the distal motor latency, absence of F reflexes, slowing of conduction velocity of the main trunk of the motor nerve, and most characteristically of all temporal dispersion or block when a proximal part of the nerve is stimulated (Fig. 42.3). There is no particular pattern that is more common in children and variations of all of these findings can be found. It is also the experience of most neurophysiologists that some children may present with a clinical story that is striking and yet have very little by way of neurophysiological abnormality. In these circumstances abnormalities of the F wave, sometimes difficult to obtain even in normal children, maybe the only proof of the condition. Diagnosis is secured by findings of raised CSF protein in the absence of pleocytosis (increased cell count), but this may take a few days to develop (i.e., hyperproteinorachia). Anti-ganglioside antibodies may also be found.

Prompt treatment with immunoglobulin has reduced the number of children needing ICU. Also, irrespective of the effects of treatment, the condition appears to be more benign than in adults. The management of those children who do reach the ICU presents no particular problems, although the autonomic disturbances that can occur may need attention.

There are occasions when the onset of GBS is so sudden and severe that a diagnosis of a central nervous system catastrophe arises with considerations of brain death. There is an adult literature showing an association with closed head injury [31–34], which might be explained by the fact that the sufferers were weakened by GBS before they sustained the head injury itself. Our patient was different. She was a

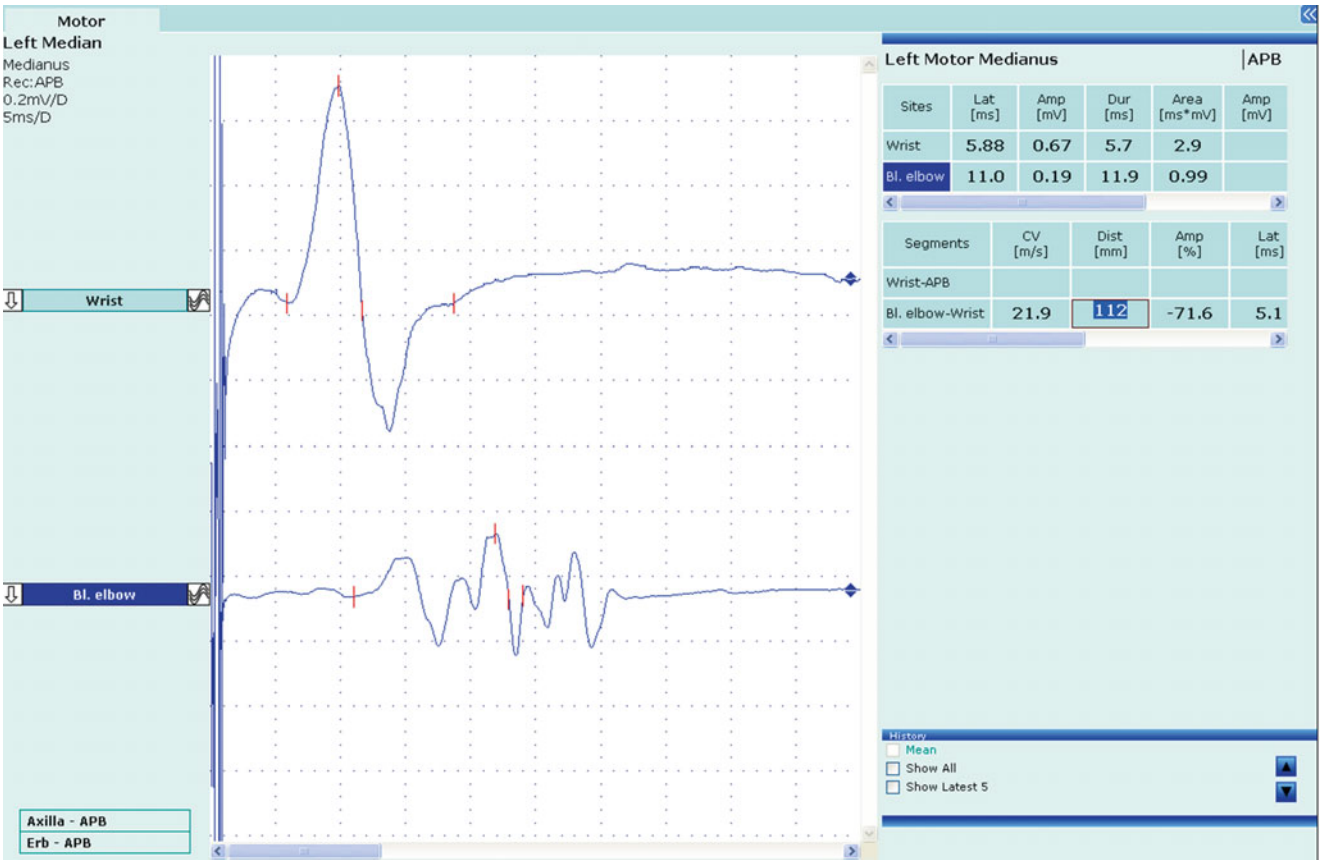


Fig. 42.3 Motor nerve conduction studies in a child with Guillain Barre syndrome showing prolongation of the distal motor latency, slowing of conduction velocity, and temporal dispersion of the compound muscle action potential when stimulating proximally

14-year-old girl with acute lymphoblastic leukemia, who had developed an abscess in her buttock and rapidly became completely paralyzed [35]. The first investigation performed was an EEG, which was requested from a fear that a catastrophic cerebral event had taken place, but this showed normal brain activity for a child at this age. EMG showed the changes of a severe demyelinating polyneuropathy but she went on to make a full recovery.

Chronic inflammatory demyelinating polyneuropathy (CIDP) is even more rare in children [36]. It has many different forms and may even present at birth [37, 38]. However, it has not been the author's experience that any child has ever needed ICU care.

Neuromuscular Junction Abnormalities

Botulism

There are several different forms of botulism [39]. The most important to the pediatric ICU physician is infantile botulism, which usually occurs in children under the age of 6 months and is due to an overgrowth of the intestinal flora by *Clostridia botulinum* [40]. This change in the gut flora results in production of the toxin. The first sign of its effect is constipation followed by a descending weakness with bulbar muscles (shown by ptosis and papillary changes) affected before limbs, the reverse of what happens in GBS with which it is sometimes confused. Children can rapidly deteriorate and require admission to the ICU within a few days of the first symptoms.

Although *Clostridium botulinum* is found in almost all parts of world, infantile botulism is rarely reported in many areas, partly maybe, but not the complete explanation, because the diagnosis is missed [40]. There are certain areas, where climatic and soil conditions are optimal, where its incidence is higher, such as in California and Utah [41] where there may be seasonal variation [42, 43]. Sometimes there is relationship to times when building construction work is performed in the location [43]. Presumably when the spores are released into the atmosphere there is an increased incidence of children who are exposed. It is likely that the levels of colonization of the intestine is higher than the number of symptomatic cases as on occasion the organism has been identified in the stool of asymptomatic normal children [42, 44]. There is no easy explanation for why some children appear to develop the condition while others do not. It appears that

timing is of great importance and often it occurs when there has been a change from breastfeeding to first formula feeding [43]. Presumably at this time the intestinal flora may change and perhaps be more susceptible to replacement by *Clostridium botulinum*. Honey appears to be a potent source of the spores but often the source is unknown [45].

Whatever the exact mechanism for the development of infantile botulism its diagnosis in areas where it is epidemic presents little if any difficulty. Most clinicians are able to identify it without any further investigation other than confirmation of presence of the spores in stool sample [45]. The classical findings on clinical neurophysiology – namely, a small compound muscle action potential and an increment on faster rate repetitive nerve stimulation [46] or a reduction of jitter at faster rates of stimulation [47] can be seen in some cases, but not in all in the author's experience. The neurophysiological changes depend considerably on the exact point in the time course of the condition when the child is seen [48].

In areas where the condition is not epidemic such as the United Kingdom the diagnosis can be very challenging. That said, the most important single factor is to think of the diagnosis, and consider it in all children presenting with weakness under the age of 6 months, particularly if they had had a period of preceding constipation. The first case diagnosed in our hospital was in 2004 and this was the first seen in London for 12 years. Interestingly, no sooner had this case been diagnosed than another case was diagnosed in the following months [49] – we now have a total of four proven cases. None of them demonstrated the full classical neurophysiological findings but those tested all showed an abnormality of neuromuscular transmission (NMT) demonstrated by StimSFEMG.

Not all cases of infantile botulism are caused by the more virulent forms. One of our cases came from Greece where it is likely that the child has developed the condition from contamination of Camomile given to her when she developed a gastrointestinal upset, while visiting her grandparents in Greece. The child never was paralyzed but was significantly weak following a period of constipation. Ptosis was prominent. Around 6 weeks after this presentation she still demonstrated neuromuscular transmission disorder on StimSFEMG and this was the pointer to the diagnosis. When the study was repeated a few weeks later there had been an improvement.

The importance of early diagnosis of infantile botulism relates to the effective treatment that can be given in the form of botulinum immunoglobulins (BIG). Studies in the United States have shown that if BIG is administered within the first few days of the start of the symptoms it will significantly reduce the length of time spent in the ICU [50, 51]. Once botulinum toxin has bound onto the neuromuscular junctions they are irreversibly blocked and only by regrowth of new neuromuscular junctions is muscle activity restored. This may take up to 3 months and is the normal period of time that paralysis may persist in the child untreated. When BIG is administered early, it essentially "mops up" free botulinum toxin preventing its irreversibly binding to the neuromuscular junctions. The problem in countries where it is not often seen is that the diagnosis is often delayed compared to the time taken in epidemic areas and therefore use of BIG is less effective.

The other forms of botulism such as food poisoning or wound botulism can occur in any age group and children are not immune to this. However, the classic food poisoning scenario is of adults eating contaminated shellfish rather than children. Such is the lethal nature of the infection that not all cases make it to ICU. Wound botulism is most common in the drug addict population and again, while some children may be affected, it is rare.

Tick Paralysis

Ticks are obligate hematophagous ectoparasites of various animals, including humans, and are abundant in temperate and tropical zones around the world. Paralysis from the toxins produced by ticks is a well recognized veterinary disease but ticks are second only to mosquitoes as vectors of pathogens causing human disease [52]. Tick paralysis in humans appears to occur only in certain parts of the world [28, 53]. However, in areas where paralysis frequently occurs from tick bites it is a sound rule to never make a diagnosis of GBS without searching assiduously for the parasite [54]. Its removal immediately restores normal motor function. Like the situation with botulism where the condition is frequently seen it should present little or no diagnostic difficulties. Easy to say for someone who has never seen a case perhaps and it must be difficult to avoid a certain degree of triumphalism if you are the one who finds the tick and magically restore the child to full strength when you remove it!

Autoimmune Myasthenia Gravis (AIMG)

Whether the development of an autoimmune condition such as myasthenia gravis is the result of a hereditary predisposition or an acquired phenomenon is debatable. However, for the purposes of this discussion we will consider it under the acquired conditions affecting the peripheral nervous system. AIMG may present as a congenital form where the mother is a sufferer of myasthenia gravis and the transmission of the antibodies across the placenta causes a transient disturbance of neuromuscular transmission (NMT). The baby is born with weakness, which may necessitate a brief period in the ICU but which gradually improves. There are occasions when a mother with asymptomatic myasthenia gravis will produce a child with arthogryposis and the Pena-Shokeir phenotype [55]. The antibodies causing both presentations are against the adult form of the Acetyl choline receptor (ACHR) and

specifically its epsilon subunit. The fetal ACHR only differs from the adult by the presence of a gamma subunit instead of an epsilon subunit. Occasionally the mother will produce antibodies against this gamma subunit only and the antibodies may not be detected when the usual AIMG antibodies are sought. These children may also present with arthrogryposis rather than typical picture suggestive of myasthenia gravis [56, 57]. It is not uncommon for the mother to have had several affected stillbirths before a live infant is born and any surviving baby is highly likely to need ICU. It is only when antibodies against this foetal subunits are tested that the correct diagnosis is made.

AIMG either due to antibodies against ACHR or against the MuSK receptors does occur in children and may represent as acute weakness. The youngest age that we have seen AIMG is 14 months. It is however, uncommon for children to be so weak at their presentation as to need intensive care. However, one of the scenarios we have come to recognize as an indicator of this condition is when a child takes a disproportionate amount of time to recover from neuromuscular blocking agents (NMBA). In one such instance the child returned from the operating room to ICU having been given pancuronium for intubation and yet still was weak 3 h afterwards. StimSFEMG at that time showed clear evidence of disturbance of NMT and initially pancuronium was implicated. However, 2 days later when the NMT disorder was still present it became not tenable as the diagnosis and later on antibodies to the ACHR were found.

Acute Muscle Disease

There are very few instances where acquired muscle disease, such as myositis, is sufficiently severe to cause the child to need respiratory support. These usually present little diagnostic difficulty with high CK the most prominent feature. These conditions are very rare. A child in our ICU did develop rabdomyolysis following serious burns, which severely delayed recovery but the burns were the initial reason for the admission into the ICU, not the rhabdomyolysis.

Hereditary Conditions

Anterior Horn Cell Disease

Spinal muscular atrophy (SMA) due to mutations of the 5q chromosome is the most important of anterior horn cell diseases seen in childhood and is the most common genetic neuromuscular disorder [58–60]. SMA is classified by numerical system with SMA 0 the worst and SMA 3 the least affected. The condition is confirmed by finding the SMN gene deletion. It is only the most severe forms of this condition that will present as the floppy baby and require the attention of the ICU. The most common situation for neurologists is to be presented with a child with a typical clinical picture, usually encompassing proximal weakness and intercostal muscle weakness but preserved diaphragmatic function. Children are usually very aware and alert. In many parts of the world the first investigation is to determine the presence of the SMN deletion. This can be made available very quickly in most, well-financed health services. In the past when a delay of maybe 10 days might be expected before the results could be obtained, it was not uncommon as an electromyographer to be asked to study such children to confirm the clinical impression. The major concern to the clinicians in these situations was that the child might deteriorate in the period between presentation and the return of the investigation confirmed the diagnosis and a decision whether to ventilate or not might have to be made without a clear diagnosis. Unfortunately, paradoxically the EMG can sometimes, particularly in those children, who are severely affected, be difficult to characterize as indicating acute neurogenic change and give full support in the diagnosis. Interestingly, the same difficulty of diagnosis also was found by histopathologists during the time when they were also doing muscle biopsies early in the condition. This fortunately is now only a distant memory and it is uncommon as an electromyographer now to be referred cases at all. However, this is not a situation with the most severe forms of SMA, types 0 and early presentations of type 1, who can present as very floppy infants and need ventilation from birth. Just as it was difficult to diagnose more clinically ambivalent children with SMA when they presented regularly to the laboratory so these difficulties when they are seen on the ICU will remain. One difficulty is that SMA 0 may have involvement of the sensory nerves as well as the motor neurons [61]. This is because of an associated dorsal root ganglionopathy, which appears very similar from a clinical standpoint to a severe sensorimotor neuropathy. However, conduction velocities are usually not severely reduced although they may be below what is expected at the age of presentation and therefore confusion with hypomyelinating congenital neuropathy should not occur. To some people the presence of fibrillation potentials is a particular pointer towards the diagnosis but in the author's experience these changes can be seen in many different conditions and are not specific for that diagnosis. The important point when faced with the child who has some of the characteristics electromyographically that would suggest SMA is that there should be no hesitation in sending the necessary genetic confirmation. The test itself is widely available and not unduly expensive and will immediately resolve any diagnostic difficulty. In some parts of the world when children with SMA reach a point in their life when they need ventilation, this can be achieved with an ambulatory system preventing their long-term ventilation on ICU. It is not every parent's desire for this to take place and care is discontinued and child allowed to pass away peacefully [62, 63].

Spinal Muscle Atrophy with Respiratory Distress (SMARD)

Infants presenting with a very severe weakness after a normal perinatal period have been recognized for some time. This condition had been variously described as a severe infantile neuropathy or distal spinal muscular atrophy [64] but both conditions share the immunoglobulin mu-binding protein 2 (IGHMBP2) gene abnormality identified in SMARD.

The clinical presentation of children with this condition is quite striking. We recently reported 13 cases of infants with this condition, all of which were small for dates (usually below the third centile), but all had been born normally and were able to breathe and feed sufficiently to be sent home. However, before 3 months old all presented with respiratory distress and were found to have either an isolated unilateral diaphragmatic paralysis or bilateral diaphragmatic paralysis. Many went to surgery for plication of the diaphragm in the mistaken belief that this was a diaphragmatic eventration, but on surgery it was observed that the muscle appeared very thin. EMG showed a striking pattern of findings. In the legs, sensory nerve responses were often absent and motor nerve responses present but with very significant reductions in the conduction velocity, within the demyelinating range. Strangely, when studying the arms the conduction velocity was normal, which is most unusual in a demyelinating peripheral neuropathy. To add further confusion EMG showed clear evidence of neurogenic change, usually the associated feature of axonal neuropathy. EMG of the diaphragm [65] (Fig. 42.4), when done, invariably shows marked denervation and may be a key to the diagnosis. Nerve biopsy of a sensory nerve showed a loss of large diameter fibers and this was thought, if it had occurred in the motor nerves as well, to explain the changes of conduction velocity. Initially the nerve biopsy findings were thought to be characteristic of this condition but we later found other children with unrelated conditions, who had similar patterns of abnormality.

The clinical characteristics of our patients, namely that they were low birthweight and then presented with diaphragmatic weakness before the age of 3 months, is seen in a large proportion of children with SMARD. However with increasing use of the genetic marker there is an emerging recognition that that SMARD may present with different phenotypes [66–70]. There are some children who present later and are not as weak and may, with some respiratory support, have independent lives. Of note, all of the children in our series died.

Disorders of the Nerve

The most common hereditary condition that affects the nerve is Charcot Marie Tooth disease type I. However, this is never severe enough to cause a patient to need ventilation unless a significant weakness is provoked by such a patient being exposed to a neurotoxin such as vincristine [71–73]. Even



Fig. 42.4 EMG study of the diaphragm approached via the chest wall

then the need for ventilatory support is unlikely. Mutations of the genes responsible for CMT 1 are also associated with the more severe forms; Dejerine Sottas disease and congenital hypomyelinating neuropathy [74, 75]. The classical presentation is that the baby is born floppy. If the mother is experienced she may have noted reduced fetal movements in the last trimester. The child needs immediate intubation and ventilation and appears completely flaccid. Diagnosis can be challenging particularly in the congenital hypomyelinating form, in whom it is not uncommon to find no response whatsoever in either the sensory or motor nerves. There are two important maneuvers that allow the diagnosis to be made. First is to give very high levels of stimulation, often the highest the EMG machine is capable of delivering such as 100 mA at 0.5 ms duration. The next is to increase the time base. It is not unknown for the initial response to have a distal motor latency exceeding 20 ms and may be missed. Conduction velocities of 1 or 2 meters per second are not unknown. Sometimes even with the maneuvers described, there is still no response even when stimulating the face. In a recent case, an infant of 36 weeks gestation had been ventilated and paralyzed for a period of 9 days. Four days after the paralysis was discontinued concerns were raised because of the lack of movement. In the first examination it was felt that there was a small sensory response but no motor response was obtained. EMG showed profuse fibrillation and a few poorly formed units. On first examination a diagnosis of the prolonged effects of vecuronium was entertained or even possibly a disorder of NMT such as CMS. The presence of fibrillation potentials usually means axonal discontinuity but it is recognized in functional denervation as in

Table 42.1 The differing genetic abnormalities identified in children with congenital myasthenic syndrome from four centres (as shown), presented at 186th ENMC workshop 24–26 June 2011, Naarden, the Netherlands

	Index Cases				
	Mayo	Munich	French network	Oxford	Total
Pre-synaptic defects					
Choline acetyltransferase deficiency	17	15	4	8	44
Lambert-Eaton sydrome like	1				1
Other presynaptic defects	1				1
Synaptic basal lamina-associated defects					
Endplate AChE deficiency (COLQ)	43	38	19	20	120
Postsynaptic defects					
Primary kinetic abnormality of AChR	53	11	10	39	113
AChR deficiency	109	147	40	138	434
AChR mutations with unclear effects		1	19	1	21
Rapsyn deficiency	48	43	28	71	190
β2-laminin deficiency	1				1
MuSK deficiency		1	3		4
Na channel myasthenia	1		1		2
Agrin deficiency			1		1
Plectin deficiency	2				2
DOK7 deficiency	31	31	28	67	157
GFPT1	2	12		4	18

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neuromuscular blockade. However, when the study was repeated after a week there had been no improvement. EMG when repeated again showed fibrillation potentials. A diagnosis of prolonged neuromuscular blockade was untenable. A hypomyelinating neuropathy was the most likely explanation.

Neuromuscular Junction Disorders

The congenital myasthenic syndromes (CMS) are disorders that affect both pre-and post-synaptic regions of the neuromuscular junction, in addition some affect the speed of depolarization [4, 76–80]. In any series the most common abnormality is mutations in the epsilon unit of the ACHR. The different congenital myasthenic syndromes were the subject of a European neuromuscular center workshop held at Naarden in the Netherlands in June 2011. Table 42.1 shows the published results of the different centers participating in a workshop with the numbers of cases shown against the genetic or other defect identified [81]. Of the known CMS some are less likely to present as diagnostic problems in the ICU than others. The most common abnormality, mutations of the epsilon ACHR, is usually relatively benign and more commonly present in older children and even adults [82]. These are not the conditions likely to be associated with sufficient weakness to require ventilation, certainly not from birth. Those conditions associated with apnea, which can be fatal, may cause patients to present to the ICU. These include CMS with episodic apnea or what used to be termed Infantile Myasthenic Syndrome, which is associated with an abnormality of Choline Acetyl transferase (CHAT), a presynaptic enzyme responsible for production of acetylcholine in the presynaptic region [83]. Some mutations of Rapsyn [84] may also be associated with episodic apnea. More recently we have identified that stridor, which can be a very serious perinatal complication requiring intubation and protection of the airways can be associated with an abnormality of Dok7 [85]. Mutations of the ColQ [86], part of the endplate acetylcholinesterase molecule responsible for the breakdown of acetyl choline molecules in the synaptic cleft can also present with significant weakness early on.

Muscle Disease

Myotonic Muscular Dystrophy

Children who present with myotonic dystrophy and are sufficiently weak to require ventilation from birth always will have inherited it from the mother [87]. It is not uncommon for the mother to be undiagnosed, but when examined clearly will show the clinical features of the condition. One of the diagnostic difficulties with babies suffering from myotonic dystrophy is that they will not demonstrate myotonic discharges on EMG. In larger children and adults these are always present and easily found. One technique to bring out the myotonic discharges is to give a prolonged muscular stimulus up to 1 s duration and this will provoke a train of discharges [88]. Unfortunately, not all EMG machines allow this length of stimulus to be administered. Fortunately, myotonic dystrophy is one of several known trinucleotide repeat disorders in which certain areas of DNA have repeated sequences of two or three nucleotides, in this instance cytosine-thymine-guanine (CTG) repeats and whose detection is routine. Consequently, the diagnosis can quickly be established both in the parent and the baby. The likelihood of survival is inversely correlated with the duration of ventilation in the ICU [87].

Other Myopathies

Nemaline rod myopathy and X-linked myotubular (Centronuclear) myopathy are amongst the few congenital myopathies that are so devastating in their weakness as to present with inability to sustain respiration [89, 90]. EMG will show a myopathic pattern without any particular characteristics that allow one to advance the diagnosis, this is achieved by biopsy and genetic testing.

Peripheral Nerve Diseases Acquired in the ICU

Critical Illness Neuropathy and Myopathy

Weakness in the context of critical illness can be due to one of three causes; critical illness neuropathy, critical illness myopathy or a combination of the two, critical illness polyneuropathy and myopathy (CIPNM), and it might affect up to 85 % of adult patients [91]. The high incidence seen in many studies in adults may be because of case selection bias with only those with sepsis, multiorgan failure or prolonged ICU admission being selected. When unselected cohorts are studied the incidence is much lower – between 0.2 % and 0.5 % [92, 93]. The neuropathy is an axonal neuropathy in which the motor nerves are affected more than the sensory, on the basis that the CMAP is markedly reduced, which is the reverse of most neuropathies. Once present it may be very difficult to treat and be responsible for prolonged ventilation. Reports vary as to the incidence of CIPNM in children [94–96]. Certainly personal experience would suggest that the condition is really quite rare, supported by a prospective study [97] showing only approximately 1.7 % of children would be troubled by muscle weakness in the ICU sufficient to cause difficulty weaning from mechanical ventilation. Over 20 years experience the author is only confident that he had seen perhaps two or three cases and these have been in children usually over the age of 12.

There is perhaps more convincing evidence of the entity called critical illness myopathy than critical illness neuropathy. This originates from work using stimulation of the nerve endpoint and noticing the difference in the evoked action potentials according to whether you are stimulating the muscle itself, direct muscle stimulation (DMS), or the terminal nerve branches [98–100]. Furthermore, it is possible to demonstrate slowing of muscle fiber conduction velocity as well as altered muscle-fiber excitability [101]. Unfortunately very little work of this kind has been done on this condition in children, perhaps because of its invasive nature. However, the finding that muscle fiber conduction corresponds with duration of the CMAP [101, 102] offers the potential of a screening technique that could be widely applied. There may be a variety of reasons why the incidence of both of these conditions may be less in children. Any explanation is speculative but it may not simply be that that they have not been investigated adequately. Adult patients have considerably more susceptible nervous systems than those presenting in the first 2 years of life. Children undoubtedly have a greater capacity for recovery than adults and also the number of children who are exposed to prolonged intensive care stays is perhaps less than those in adults.

Mononeuropathies Which Develop in ICU

Mononeuropathies seen in our ICU have all been the result of either pressure or direct damage to the nerve. All nerves that have pressure points are susceptible to damage in the ICU. Those in the upper limb are rare and of those likely to be affected the ulnar nerve is particularly susceptible as the nerve passes around the olecranon. In the lower limb foot-drop is not uncommon and often clinically diagnosed as being due to a common peroneal palsy. However, neurophysiological examination often shows this is not the case and the area of pressure is found higher up affecting the sciatic nerve itself. This is seen particularly in children who are cachectic. We have seen this in a child, who had experienced very serious infection and complications following heart transplantation and in another child, who had severe pancreatitis. The neurophysiological findings showing identifiable abnormality in the territory of the tibial nerve branch of the sciatic

nerve will characterize the condition as being due to a sciatic nerve palsy rather than the peroneal palsy. These findings may take the form of sensory disturbance with or without changes in the motor nerve and accompanied by EMG abnormalities in the muscles supplied by the tibial nerve. Even if the tibial nerve is not affected neurophysiologically you may still not be able to identify any focal abnormality in the peroneal nerve particularly around the fibular head. This preferential involvement of the peroneal branch of the sciatic nerve is well recognized as being due to the fasicular representation of the nerve, which extends all the way back to the sciatic notch. The peroneal fascicle is much more susceptible to pressure than the tibial. This differential susceptibility of certain fascicles in a nerve, to pressure, trauma or infection, is equally well seen in the brachial plexus as in the lumbar plexus. For example, the anterior interosseous nerve may be affected in the brachial plexus, in such conditions as neuralgic amyotrophy, and yet present with an apparent focal isolated mononeuropathy [103, 104]. This has important implications when using EMG to localise the site of the abnormality. When studying the sciatic nerve in adults it is always recommended that you sample extensively in the hamstrings trying to identify the lower limit of the involvement. We do not do this. If there is abnormality above the fibular head, indicated either by finding abnormalities in the medial gastrocnemius, which implies involvement of the tibial component or by looking at short head the biceps, whose nerve supply originates from above the popliteal fossa, imaging is ordered which will be focused from the knee to the sciatic notch. MRI is the imaging of choice.

The only other mononeuropathy we have experienced has been a femoral nerve neuropathy as a consequence of venous cannulation. This is a particular danger in the cardiac ICU where large cannulae are required to be inserted for profusion of the Berlin heart. This allows the diseased heart to be bypassed and is invaluable in the treatment of children with such conditions such as infective myocarditis keeping them alive until either the myocarditis recovers or a heart transplant becomes available.

Our Recent Experience Using EMG in the ICU

What has been discussed so far presents the most well known of peripheral nerve complications related to the ICU. In many ways the conditions described are no different from those previously identified in other reviews of the subject of peripheral nerve disease in the pediatric ICU [1, 2, 7, 29, 105]. It has been further illustrated with particular personal examples seen in our ICU over the years. However, it has been our experience more recently that we are being asked to study children in the ICU with suspected neuromuscular abnormalities much more commonly. Also we seem to be identifying abnormalities, which are not well recognized or even recognised at all. We reviewed the referrals in the last 4 years to our Department from the ICU. Results are presented from 2007 until the current year. 143 cases were studied in the ICU during which time a total of around 3000 EMGs have been performed in the unit overall, amounting to just under 5 % of all work. Of course the referrals for EMG did not accurately reflect the number of children with peripheral nervous disorders, who were seen in the ICU, as if the condition is already known there is no need for a referral. As a consequence we tend to see the very young children. 107 or 75 % of the cases were under 1-year of age and therefore seen mainly in the neonatal intensive care unit. Eighty-six of these 107 were under 6 months. At the other end of the age range only 22 cases were over 3 years of age. The sexes were approximately equally represented.

There were a wide range of reasons for referral for EMG. A big proportion – around 40 referrals – were for suspected neuromuscular disorder. Sometimes in the very youngest the child will present as a floppy baby and need to be ventilated, on other occasions the child may have been admitted for something different and then the suspicion that there might be an underlying neuromuscular disorder arises as time goes on. Another cohort of around 25 referrals was specifically for the identification of bulbar palsy. A particular impetus to referral is when the child does not seem to wean from paralyzing agents as quickly as anticipated, a further 32 referrals.

Very few EMGs were normal. Motor neuronopathy was a common finding, seen in nearly a third of all cases, sometimes isolated only to the bulbar region, demonstrated by finding denervation in the tongue, (Fig. 42.5) and thought possibly to represent some perinatal event when seen in babies, but more commonly found to affect the whole motor neuron pool, that is both the cranial motor nuclei and anterior horn cells, even though the clinical suspicion might only suspect bulbar muscle involvement. Not all of these were due to SMA. One case was later found to be Brown Vialetto van Laere syndrome [106, 107], others, Spinal muscular atrophy with pontocerebellar hypoplasia (SMA-PCH, also known as pontocerebellar hypoplasia type 1 [PCH1]) [108–114] or SMARD, but a significant proportion remained undiagnosed. With increasing use of EMG generally our neurologists are recognizing that many neurodegenerative conditions thought to involve the brain only also involve the anterior horn cells as well, a fact that only recognized by referral for EMG.

There were a few peripheral neuropathies, even fewer myopathies, one case of botulism and scatterings of focal neuropathies and diaphragmatic palsies. Three patients were referred suspected of having CMS and all three had abnormalities of NMT. Not all have been characterised genetically. The 32 children who were slow to wean from ventilator, deserve special mention. While a few were found to have a neuromuscular disorder such as a myopathy or even anterior

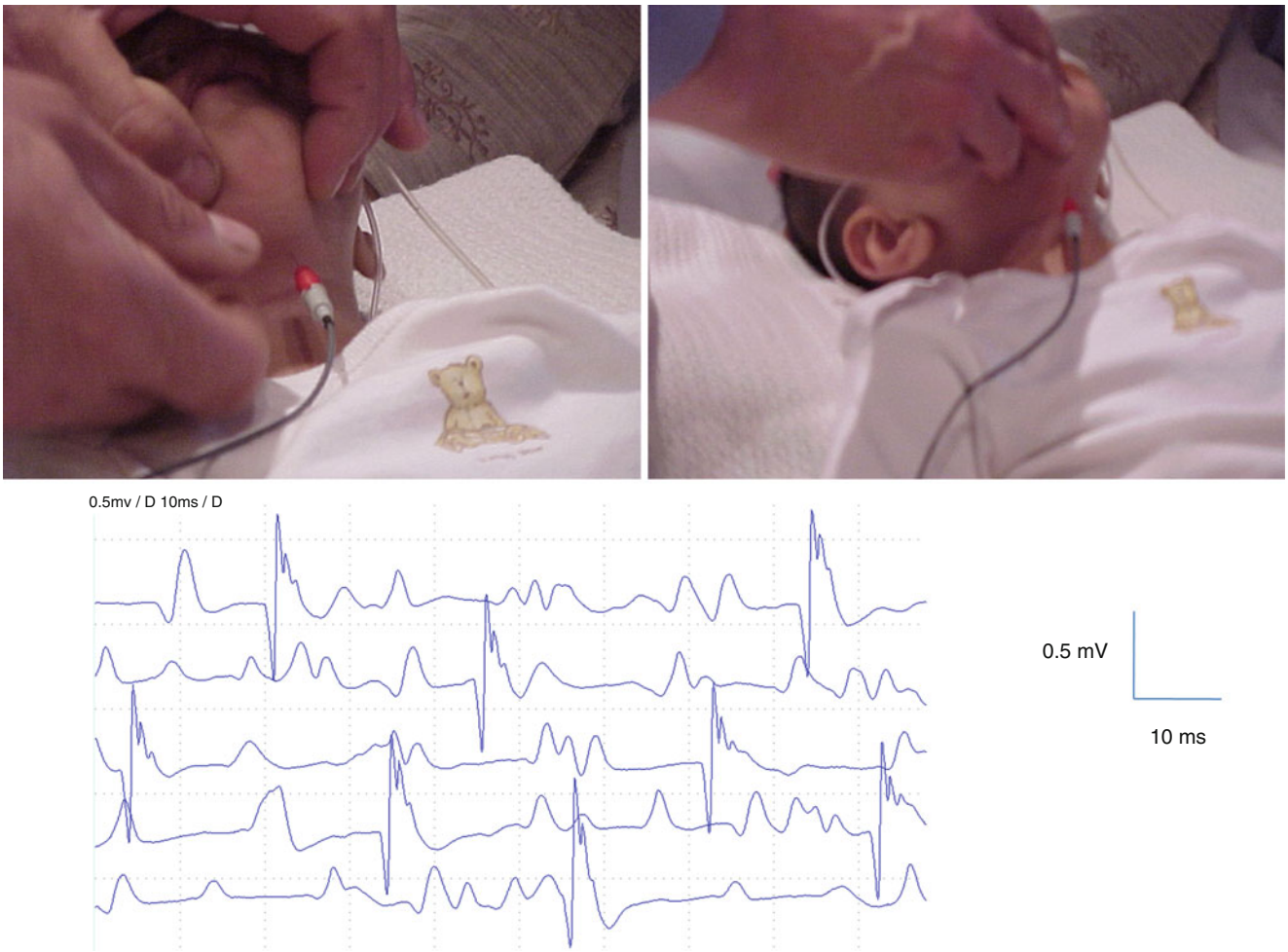


Fig. 42.5 EMG of the tongue demonstrated being approached from sub-mental route and with an EMG recording showing a pattern indicative of chronic denervation and re-innervation

horn cell disease the great majority were found to have abnormalities in neuromuscular transmission, often without any other abnormality on the EMG, something that has not been previously recognised. Vecuronium is the non-depolarizing NMBA used almost exclusively in our ICU. Prolonged paralysis after NMBA is nothing new. Almost as soon as the medication was introduced reports were a made of prolonged paralysis [115–125]. This could be explained in the situation when there is impairment of renal function [126], or perhaps when magnesium which has effects on neuromuscular transmission is administered [127]. Other cases have been reported where there was a pre-existing or undiagnosed neuromuscular disorder such as myositis [128] or Charcot Marie Tooth disease [129]. There is also a recognition of the influence of the steroids on the development of this paralysis [130, 131]. One grouping for such cases divides them into those where the paralysis can be explained by increased levels of vecuronium persisting from pharmacokinetic reasons and those in which there is a myopathic process [124]. The latter group are described as having myopathic potentials on EMG and where muscle biopsies are performed there is evidence of loss of thick myofilament demonstrated on electron microscopy [132]. Our difficulty is that while some of the patients are undoubtedly manifesting altered pharmacokinetics of vecuronium, in particular delayed excretion, and make a complete recovery, there still remain a group of children who do have some residual weakness but do not have the myopathic changes described above, but show EMG evidence of NMT disorder, demonstrated with StimSFEMG. We do not know whether these interesting cases with prolonged persistence of abnormalities of NMT do represent CMS. Paralysis with NMBA can unmask unsuspected AIMG [133–135] but little is known about whether a similar mechanism occurs with CMS. We recognised a lethal congenital form of CMS when we saw several babies who were born completely flaccid with EMG abnormalities of NMT but these were seen before any paralysing agent had been administered [136]. No genetic abnormality was identified.

Of course the lack of a genetic abnormality does not disprove that the EMG findings indicating NMT disorder are due

to CMS, as the full extent of the genetic abnormalities involved in the production of neuromuscular junction abnormalities is only just beginning to be completely unravelled and there yet be more to be discovered. It is sanguine in this regard to imagine if a child suspected of CMS had been identified in 1995 mutations in ACHR epsilon subunit [82] were the only ones known and the diagnosis would be unproven. Since that time successively there have been discoveries of other subunits abnormalities in 1996 [137] including those causing slow channel syndrome [138]: followed then by discovery of the disorders of ColQ (1998 [86]), choline acetyltransferase (CHAT) abnormalities (2001 [83]), Rapsyn mutations (2002 [139]), sodium channel mutations (SCN4A) (2003 [140]), MuSK antibodies (2004 [141, 142]), Dok7 (2008 [143]), Agrin (2009 [144]) and most recently mutations in GFPT1 (2011 [145, 146]). It is difficult to predict whether more mutations will be discovered and therefore if confident that there is a disturbance of NMT and this is not due to paralysing agents, it might be worth considering treating these children as CMS. Unfortunately not all do well with pyridostigmine and conditions such as Dok7 will do better with salbutamol or ephedrine [4, 147–149]. So even a lack of response to pyridostigmine, the standard therapeutic trial for myasthenia, will not completely solve the mystery. Of all groups of patients seen in the ICU these are perhaps the most diagnostically challenging.

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Movement Disorders in the ICU

43

Dragos A. Nita and Teesta B. Soman

Abstract

Despite significant advances in pediatric neuro-critical care, movement disorders are often an under-treated and under-recognized entity in the intensive care unit (ICU). The goal of this chapter is to discuss the clinical features of the most common hyperkinetic and akinetic-rigid- movement disorders that can be seen in the ICU setting and that represent medical emergencies. Diagnostic considerations as well as management principles are reviewed, along with appropriate pathophysiology where relevant.

Keywords

Dystonia • Acute dystonic reaction • Chorea • Athetosis • Balismus • Post pump chorea • Myoclonus • Tremor • Drug-induced movement disorders • Neuroleptic malignant syndrome • Serotoninergic syndrome

Introduction

The movement disorders that are usually seen in the pediatric intensive care unit (PICU) setting can either be due to aggravation of a pre-existing movement disorder in a child or as a result of the new-onset of abnormal movements in a critically ill child. Movement disorders are conditions which include involuntary motor movements that are abnormal in initiation, implementation, velocity, frequency or posture. They can be classified broadly into two categories: hyperkinetic disorders (e.g. dystonia, chorea, myoclonus, and tremor) and rigid-hypokinetic disorders (e.g. parkinsonism). They can be primary movement disorders, or secondary to a variety of pathological processes, often secondary to medication (Table 43.1). The key to diagnosis is the qualitative appreciation of the movement and the pattern recognition for the presentation [1].

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Hyperkinetic Movement Disorders

Hyperkinetic disorders are characterized by abnormal excessive involuntary movement. These movements can be regular and rhythmic, as in tremor; more sustained and patterned, as in dystonia; brief and random, as in chorea; or jerk-like as in myoclonus.

Dystonia

Dystonia is a movement disorder characterized by involuntary, sustained muscle contractions that result in twisting and repetitive movements or abnormal postures. Primary dystonia is defined as dystonia without any additional neurologic signs and without a history of possible acquired causes. There are now over 20 genetic subtypes of dystonia. Secondary dystonias have either a history of possible acquired causes (toxin and drug exposure being the most common) or additional neurological signs. Neurodegenerative dystonias are a heterogeneous group of inherited, progressive conditions, often untreatable (Table 43.2). There are no consistent neuropathologic findings in primary dystonia. In secondary dystonia lesions of the basal ganglia are often

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Table 43.1 Drug induced movement disorders in children

Movement disorder	Common drugs	Less common drugs
Dystonia	Neuroleptics	Dopamine agonists
	Antiemetics	Valproic acid
	L-dopa	Phenytoin
	Lithium	Carbamazepine
		SSRIs
		TCAs
Chorea	Neuroleptics	Estrogen (oral contraceptives)
	L-dopa	Phenytoin
		Valproic acid
		Cocaine and amphetamines
		Anticholinergics
		Antihistaminics
		Lithium
Tremor	Alcohol	Lithium
	Sympathomimetics	Opiates
	Neuroleptics	Immunosuppressants (tacrolimus)
	Valproic acid	Hypoglycemic agents
	Corticosteroids	Antibiotics and antiviral agents
	Xanthenes	Anticonvulsants
	Thyroxin	Antiarrhythmics
		Antidepressants
Myoclonus	SSRI	TCAs
		Lithium
		MAO inhibitors
		Carbamazepine
		Penicillins and cephalosporins
		Cocaine
		Opiates
		Amantadine
		L-dopa
		Bromocriptine
Parkinsonism	Neuroleptics	Flunarizine
	Anti-emetics (metoclopramide)	Cinnarazine
		TCAs
		Chemotherapeutic agents
		Carbamazepine
		Phenytoin
		Valproic acid
		Lamotrigene
		Melatonin

MAO monoamine oxidase, *SSRIs* selective serotonin reuptake inhibitors, *TCAs* tricyclic antidepressants

identified on MRI and on autopsy. The assessment of atypical and/or secondary dystonia is usually extensive and includes neuroimaging, inflammatory work-up, as well as metabolic and toxic screening.

Trihexyphenidyl (and other anticholinergic agents), baclofen and clonazepam are the most commonly used drugs to treat dystonia. Dantrolene is less commonly used. Often a combination of agents is needed for severe cases. Trihexyphenidyl is a centrally acting anticholinergic drug and is usually well tolerated in children. It can be used in doses up to 40–80 mg per day (occasionally higher) as tolerated until a beneficial effect is seen. It must be started at a low dose (1 mg) and gradually titrated upwards over a period of many weeks to months. Common side effects which limit its use are sedation, dryness of mouth and eyes, constipation and altered personality. Some patients may also get an allergic rash. Oral baclofen is useful in children especially with spasticity or as an adjunct to trihexphenydyl. It is started at 5–10 mg/day and gradually titrated upwards as tolerated. Adverse effects are sedation and hypotonia. Clonazepam and other benzodiazepines can be helpful, but sedation is a limiting factor for their use. Surgical therapies such as baclofen pump or deep brain stimulation are used for medically intractable dystonias.

Acute Dystonic Reactions Secondary to Drugs

Drugs are the most common cause of acute focal or generalized dystonia that may present as a medical emergency if the airway or breathing are adversely affected [2]. It may also present as oculogyric crises, laryngeal dystonia, blepharospasm, torticollis, trismus or dysarthria with onset within 24 h of drug exposure [3]. Neuroleptics (dopamine antagonists) and antiemetics are by far the most commonly implicated medications (Table 43.1). Neuroleptic drugs are more likely to cause acute dystonic reactions in younger patients and tardive dyskinesia or parkinsonism in older patients. Acute dystonic reactions are usually not severe and self-limited. The medication causing dystonia must be immediately discontinued. When severe, patients require anticholinergic therapy such as benztropine 1–2 mg IV. It is common for the dystonia to return as the effect of the parenteral medication wears off and for this reason oral anticholinergic therapy should be continued for few days in a tapering dose after acute therapy [4].

Spasmodic Dysphonia/Adductor Laryngeal Breathing Dystonia (ALBD)

ALBD is a rare task-specific dystonia in which the vocal cords undergo adductor spasm during inspiration but not other activities such as speaking [5]. The clinical presentation is with severe stridor, and there is a risk of life-threatening respiratory obstruction. Botulinum toxin injections into the overactive thyroarytenoid muscles is effective treatment in most patients and may avert the need for tracheostomy [2].

Table 43.2 Classification of dystonia by etiology

Primary dystonia	Secondary dystonia	Neurodegenerative (secondary)
Primary genetic dystonia:	*Structural lesion:*	*Amino acids/organic acids:*
DYT-1 (9q34)	Cervical cord lesions	Glutaric acidemia
DYT-2 (unknown)	Head trauma	Propionic aciduria
DYT-3 (Xq13.1)	Tumors	Isovaleric acidemia
DYT-4 (unknown)	*Vascular lesion:*	Methylmalonic aciduria
DYT-5a (14q22.1)	Perinatal cerebral injury	*Lysosomal storage disorders:*
DYT-5b (11p)	Basal ganglia stroke (putamen)	Neiman-Pick type C
DYT-6 (8p21)	*Infectious / post-infectious:*	GM1 gangliosidosis
DYT-7 (18p)	Retropharyngeal abscess	GM2 gangliosidosis
DYT-8 (2q33)	Encephalitis lethargica	Krabbe
DYT-9 (1p)	*Inflammatory* :	NCL
DYT-10 (16p11.1)	CNS vasculitis	Pelizaeus-Merzbacher
DYT-11 (7q21)	Antiphospholipid syndrome	Metachromatic leukodystrophy
DYT-12 (19q)	*Demyelination*:	*Mitochondrial disorders:*
DYT-13 (1p36)	Pontine myelinolysis	MERRF
DYT-14 (unknown)	MS	MELAS
DYT-15 (18p)	*Drug induced* (see also Table 43.6):	LHON plus dystonia
DYT-16 (unknown)	D2 antagonists (neuroleptics/antiemetics)	*Trinucleotide repeat disorders*
	Intrathecal baclofen withdrawal	Machado-Joseph disease (SCA3)
	Toxic:	DRPLA
	Carbon monoxide	*Other:*
	Methanol	Wilson
	Organophosphates	Molybdenum cofactor deficiency
	Cyanide	Glucose transporter defects
	Psychiatric/psychogenic dystonia	

CNS central nervous system, *DRPLA* dentatorubral-pallidoluysian atrophy, *LHON* Leber's hereditary optic neuropathy, *MELAS* mitochondrial encephalomyopathy lactic acidosis and stroke, *MERRF* myoclonic epilepsy with ragged red fibers, *MS* multiple sclerosis, *NCL* neuronal ceroid lipofuscinosis, *SCA* spinocerebellar ataxia

Status Dystonicus

Status dystonicus is a serious and potentially life threatening disorder which occurs in people who have primary or secondary dystonia, who rarely can develop a life-threatening disorder of unremitting, severe generalized dystonic spasms. Status dystonicus can arise after intercurrent infection, alteration in medications, sudden depletion of intra-thecal baclofen or for no obvious reason [6]. Patients are at risk of respiratory compromise, but also of acute renal failure from secondary rhabdomyolysis. The response to conventional drug treatment is often poor. Benzodiazepines, levodopa, benzhexol, tetrabenazine, pimozide, haloperidol, baclofen, propanolol, and anti-epileptic agents such as carbamazepine have been used with limited benefit [7]. Triple therapy with oral tetrabenazine, high-dose benzhexol, and a dopamine blocker such as haloperidol was found to be useful in a few cases [6]. Patients may require sedation and muscle paralysis to prevent the secondary complications mentioned above.

Sudden Withdrawal of Intrathecal Baclofen

Intrathecal Baclofen therapy is used for the management of severe spasticity. A life-threatening syndrome can be precipitated by the sudden withdrawal of this drug, when the catheter tip becomes dislodged. Clinically patients present with high fever, altered mental status, and severe dystonia and spasticity that may progress to rhabdomyolysis [8]. Treatment includes giving high doses (up to 120 mg/day in divided doses) of oral or enteral baclofen. Benzodiazepines and dantrolene have also been used [8, 9].

Chorea, Athetosis and Ballismus

Chorea is defined as an involuntary movement which is brief, irregular, non-rhythmic, non-purposeful that flows from one body part to another in a random fashion. The movements typically last longer than myoclonus, and are briefer than dystonia (although dystonia may be combined with chorea in some patients). Athetosis consists of nonpatterned, writhing movements that represent a form of "slow chorea". Ballismus is a form of severe, coarse chorea; it is usually unilateral (hemiballismus) and often results from a lesion in the contralateral subthalamic nucleus and adjacent structures. An etiologic approach to chorea is presented in Table 43.3.

Chorea usually develops gradually and is rarely disabling or life-threatening, especially early in the course.

Table 43.3 Classification of chorea by etiology

Primary chorea	Secondary chorea	Neurodegenerative (secondary)
Physiological chorea of infancy	*Structural lesions:*	*Huntington's disease*
Benign hereditary chorea	Tumors	*Huntington's disease like illness 3*
	Vascular lesions:	*SCA17*
	Post pump chorea	*Mitochondrial*
	Stroke	*Lesch-Nyhan syndrome*
	Moya-moya disease	
	Perinatal cerebral injury	
	Infectious:	
	Encephalitis (EBV, HIV)	
	Bacterial and tuberculous meningitis	
	Inflammatory:	
	Antiphospholipid antibody syndrome	
	CNS vasculitis	
	SLE	
	Sydenham's chorea	
	Anti-NMDA receptor encephalitis	
	Demyelination:	
	ADEM	
	Drugs: (see Table 43.6)	
	Toxins:	
	Manganese	
	Methanol	
	Carbon monoxide	
	Bilirubin (kernictrus)	
	Metabolic:	
	Hyperthyroidism	
	Hypoparathyroidism	
	Hyper- and hyponatremia, hypomagnesemia, hypocalcemia	
	Hypo- and hyperglycemia (latter may cause hemichorea, hemiballism)	
	Nutritional (e.g., beriberi, pellagra, B12 deficiency in infants)	
	Pregnancy (Chorea Gravidarum)	

CNS central nervous system, *SLE* systemic lupus erythematosus, *NMDA* N-Methyl-D-aspartate

Occasionally, the onset can be acute and severe. Cerebral imaging, with computed tomography and magnetic resonance imaging are recommended to exclude cerebral hemorrhage or infarction, as well as to examine the basal ganglia for signal abnormalities. Biochemical testing is important to exclude hyper- or hypoglycemia. Serological testing is required to exclude autoimmune disease. Post pump chorea may be seen after cardiac surgery in a small number of children. The estimated frequency is 10 % (0.6–18 %) per procedure, but the incidence appears to be decreasing over time, presumably as a result of changing operative techniques. Risk factors include more time on pump, deeper hypothermia (<36°), and circulatory arrest [10]. Symptoms begin 3–12 days postoperatively. Neuroimaging studies and EEG are normal.

Mild chorea often does not require treatment. The first line of treatment for disabling or exhausting chorea involves dopamine receptor blockade by typical and atypical neuroleptics [1]. Neuroleptics may cause tardive dyskinesia, which can be difficult to differentiate from the primary disease, as well as be more disabling and treatment resistant. Thus, these medications should be used with caution and generally only for short courses. Clozapine has not been reported to cause tardive chorea, but it is not clear that this agent is useful in suppressing chorea. Another pharmacological class that can be used are presynaptic dopamine depletors, that include reserpine (no longer available in the US) and tetrabenazine used at 25–200 mg/day. Glutamate antagonism with amantadine may be somewhat useful. Valproic acid is particularly useful in Sydenham's chorea. An attempt should be made to periodically wean symptomatic treatment as chorea can often fluctuate in severity or resolve spontaneously.

Myoclonus

Myoclonus is defined as a brief, shock-like, jerky involuntary movement involving one muscle or a group of muscles.

Table 43.4 Classification of myoclonus by etiology

Primary and physiologic myoclonus	Secondary myoclonus (non-epileptic)	Epileptic myoclonus
Essential myoclonus	*Structural lesions:*	*Epileptic fragments:*
Hereditary (AD)	Tumors	Epileptic myoclonic jerks
Sporadic	Post hypoxic (Lance-Adams)	Epilepsia partialis continua
Physiologic myoclonus	*Vascular lesions:*	Stimulus-sensitive myoclonus
Benign neonatal sleep myoclonus	Stroke (thalamus VL, VPL, brainstem)	Myoclonic absences
Hypnic jerks/myoclonus	Subdural hemorrhage	*Childhood myoclonic epilepsy:*
Hiccups	CSVT	Benign myoclonic epilepsy of infancy
	Infectious:	Infantile spasms (West syndrome)
	Encephalitis (arboviruses, HSV, HIV)	Severe myoclonic epilepsy of infancy (Dravet syndrome)
	SSPE	Lennox-Gastaut syndrome
	PML	Myoclonic astatic epilepsy (Doose syndrome)
	Inflammatory/autoimmune:	Juvenile myoclonic epilepsy (Janz syndrome)
	Anti-Hu encephalitis	*Familial cortical myoclonus with epilepsy*
	Opsoclonus-myoclonus	AD cortical myoclonus and epilepsy
	Demyelination:	Familial cortical myoclonic tremor
	MS	Familial essential myoclonus and epilepsy
	Drugs: (see Table 43.6)	*Progressive myoclonic epilepsy*
	Toxins:	Unverricht-Lundborg disease
	Bismuth	Lafora body disease
	Heavy metals	NCL
	Methyl bromide	
	DDT	
	Metabolic:	
	Hepatic and renal failure	
	Hyponatremia	
	Metabolic alkalosis	
	Vitamin E deficiency	
	Other neurodegenerative disorders not defined by occurrence of seizures	
	Spinocerebellar degeneration (progressive myoclonus ataxia, ataxia-teleangiectasia, Friedreich ataxia)	
	Basal ganglia degeneration (Wilson disease, torsion dystonia, PKAN)	

AD autosomal dominant, *CSVT* cerebral sinus venous thrombosis, *DDT* dichlorodiphenyltrichloroethane, *MS* multiple sclerosis, *NCL* neuronal ceroid lipofuscinosis, *PKAN* pantothenate kinase-associated neurodegeneration, *PML* progressive multifocal leukoencephalopathy, *SSPE* subacute sclerosing panencephalitis, *VL* ventrolateral thalamic nucleus, *VPL* ventroposterolateral thalamic nucleus

In addition to the etiologic classification myoclonus can be approached based on the localization of the pathological mechanism that generates it [1]. With cortical myoclonus, a focal discharge from the primary sensorimotor cortex causes a myoclonic jerk after a time interval required for corticospinal transmission. It is commonly seen with neurodegenerative disorders, but may also occur with reflex sensory stimulation. Cortical-subcortical physiology is the major mechanism for myoclonic seizures that occur in primary generalized epileptic syndromes. Segmental myoclonus is generated at a particular segment or contiguous segments of the brainstem and/or spinal cord. Peripheral myoclonus arises as a consequence of a peripheral nervous system lesion producing hyperactive motor discharges to its muscle. An etiologic approach to myoclonus is presented in Table 43.4.

The initial steps in the evaluation of a patient with myoclonus are the history and examination. The findings should identify which major clinical and etiologic classification (physiologic, essential, epileptic, or secondary myoclonus) best reflects the circumstances of the patient. Ancillary

Table 43.5 Classification of tremor by etiology

Primary and physiological tremor	Secondary tremor	Pseudotremor
Primary:	*CNS Pathology:*	*Other rhythmic movement disorders:*
Essential tremor	Parkinsonism	Head bobbing
Idiopathic palatal tremor	Wilson disease	Spasmus nutans
Orthostatic	MS	Hereditary chin quivering
Enhanced physiologic tremor:	Fragile X permutation	
Metabolic (hyperthyroidism, hyper parathyroidism, hypoglycemia)	Midbrain tremor (Holme's tremor)	
Drugs (caffeine, theophylline, amphetamines, valproic acid, beta-agonists, benzodiazepine withdrawal)	*Peripheral neuropathies:*	
Other (fever, sepsis, anxiety, stress, fatigue)	Hereditary neuropathies	
	Recovery phase of GBS and CIDP	
	Psychogenic	

CIDP chronic inflammatory demyelinating polyneuropathy, *CNS* central nervous system, *GBS* Guillain-Barre syndrome

testing should include electrolytes, renal and hepatic function tests, drug and toxin screen, brain/spine imaging, and CSF analysis. Clinical neurophysiological testing (EEG, EMG) should be able to distinguish between the different physiologic mechanisms. Uncommon and rare genetic diagnoses should be considered if a clear cause is not identified.

A large number of medications, mainly anticonvulsants, have been used to treat myoclonus. Evidence from uncontrolled observational studies suggests that levetiracetam and valproic acid are effective for various types of cortical myoclonus. Clonazepam may also be helpful for subcortical-suprasegmental types of myoclonus. Limited evidence suggests that a number of other drugs are occasionally useful for myoclonus of various physiologic types: benztropine and trihexyphenidyl for essential myoclonus; carbamazepine and lamotrigine for cortical, segmental, and peripheral types of myoclonus; diazepam, tetrabenazine and topiramate for spinal segmental myoclonus; phenobarbital and primidone for cortical myoclonus, sumatriptan for palatal myoclonus, zonisamide for propriospinal myoclonus (a type of subcortical-suprasegmental myoclonus) [11]. Of note, phenytoin and carbamazepine may exacerbate myoclonus in some patients, particularly those with Unverricht-Lundborg disease, and may worsen myoclonic seizures [12].

Tremor

Tremor is defined as a rhythmic, sinusoidal involuntary movement, around a central point involving one or more body parts. Tremor can be broadly divided into rest tremor and action tremor. Tremor that is present when the limb is fully at rest, supported by gravity without any voluntary contraction of the involved muscles, is known as rest tremor. Tremor occurring during voluntary contraction of muscles is known as action tremor. Action tremor can be postural- when the limb is held in a certain posture, kinetic- when performing a movement or terminal (intention) - when exacerbated towards the end of a goal directed movement [1]. A classification of tremor by etiology is presented in Table 43.5 and causes of drug-induced tremor are summarized in Table 43.1.

Medications commonly used to treat essential tremor are beta-blockers and primidone. Among beta-blockers, propranalol is the most frequently used medication. Dosage of 40–80 mg/day can be used in children and up to 320 mg in adults. Atenelol, a selective ß1 anatgonist is not effective in treatment of tremor. The common adverse effects are exacerbation of preexisting asthma and hypotension, which may limit its use. Primidone is also effective in suppressing tremor. Dosage of 50–100 mg/day is used in children and up to 750 mg in adults. It is particularly useful in children with tremor and epilepsy. The major side effect is sedation, and must be increased gradually. Other drugs that are used for treatment of tremor include benzodiazepines like alprazolam or clonazepam, gabapentin and topiramate [1].

Akinetic-Rigid Movement Disorders

Akinetic-rigid disorders are characterized by reduced activity or bradykinesia. They are not seen frequently in the pediatric population. Primary bradykinetic movement disorders frequently are accompanied by rigidity, postural instability, and loss of automatic associated movements. The bradykinetic disorders reviewed here are juvenile Parkinson disease, juvenile Huntington disease, Wilson disease and neurodegeneration with brain iron accumulation. The drug-related conditions that present with rigidity and stiffness and represent medical emergencies are discussed separately. Diagnosis of the specific condition depends primarily upon careful observation of the clinical features. In all these conditions, patients could be admitted to the ICU due to rapidly progressive symptoms.

Table 43.6 Classification of akinetic-rigid movement disorders by etiology

Primary	Secondary	Neurodegenerative (secondary)
Genetic parkinsonism:	*Structural lesions:*	*Secondary parkinsonism:*
PARK2 – Parkin	Tumors	PKAN
PARK6 – PINK-1	Head injury	Wilson's disease
PARK7 – DJ-1	*Vascular lesions:*	Juvenile Huntington's disease
PARK9 – Kufor-Rakeb syndrome	Stroke	Mitochondrial
PARK 16 – PLA2G6	*Infectious:*	Nieman Pick Type C
	Encephalitis lethargica	GM2 gangliosidosis
	Tetanus	
	Rabies	
	Inflammatory / autoimmune:	
	CNS vasculitis	
	Stiff man syndrome	
	Drug induced (see also Table 43.6):	
	Neuroleptic malignant syndrome	
	Parkinsonism–hyperpyrexia syndrome	
	Malignant hyperthermia	
	Serotonin syndrome	
	Toxins:	
	Strychnine	
	Metabolic:	
	Hypocalcemia	
	Hypoparathyroidism	
	Psychiatric:	
	Lethal catatonia	

CNS central nervous system, *PKAN* pantothenate kinase-associated neurodegeneration

Primary and Neurodegenerative Akinetic-Rigid Movement Disorders

Juvenile Parkinsonism is defined as parkinsonism with onset at age 20 or less. Tremors, bradykinesia, rigidity, and postural instability occur, often symmetrically. Most cases of PD are sporadic, but genetic loci (Table 43.6) have been associated with autosomal dominant or recessive Parkinson disease or parkinsonism.

While Huntington disease (HD) typically presents during the fourth and fifth decades of life; onset occurs during childhood or adolescence in approximately 5–7 % of patients. HD is one of a number of disorders that are associated with expansion of unstable trinucleotide (CAG) repeats. Juvenile onset disease shows a major transmitting parent effect, as approximately 80 % of symptomatic patients inherit the mutant HD gene from their father.

Wilson disease (hepatolenticular degeneration) is a treatable cause of juvenile parkinsonism, dystonia, and multiple movement disorders. This rare disorder has an estimated prevalence of 30 per million. Wilson disease is an autosomal recessive defect of cellular copper export. The major abnormality in Wilson disease is reduced biliary excretion of copper that leads to its accumulation, initially in the liver and then in other tissues, particularly the brain. Tissue copper deposition causes a multitude of signs and symptoms that reflect hepatic, neurologic, hematologic, and renal impairment.

Neurodegeneration with brain iron accumulation (NBIA) is a rare progressive neurodegenerative syndrome that causes parkinsonism, dystonia, cognitive decline, and other neurologic deficits. NBIA is now considered a spectrum of phenotypically overlapping disorders, with several subtypes defined by differences at the molecular genetic level: pantothenate kinase-associated neurodegeneration (PKAN) caused by mutations in the gene encoding pantothenate kinase 2 (PANK2) formerly known as Hallervorden-Spatz disease; infantile neuroaxonal dystrophy caused by mutations in the PLA2G6 gene; or NBIA of unknown cause [13].

Secondary Akinetic-Rigid Movement Disorders

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is a life threatening neurologic emergency associated with the use of neuroleptic agents and characterized by a distinctive clinical syndrome of mental status change – 82 % of patients [14], rigidity, fever – 87 % >38°C and 40 % over 40°C [15], and dysautonomia – tachycardia 88 %, tachypnea 73 %, high blood pressure 61–77 % [16]. There is generalized rigidity, often

accompanied by akinesia, that can be so severe as to render the patient bedbound. Rhabdomyolysis and renal failure may ensue. NMS is most often seen with the "typical" high potency neuroleptic agents (e.g., haloperidol, fluphenazine). However, every class of neuroleptic drug has been implicated, including the low potency (e.g., chlorpromazine) and the newer "atypical" antipsychotic drugs (e.g., clozapine, risperidone, olanzapine) as well as antiemetic drugs (e.g., metoclopramide, promethazine) [15]. The diagnosis is made on clinical grounds. The differential diagnosis also includes lethal catatonia, serotonin syndrome, malignant hyperthermia, acute carbon monoxide poisoning, and salicylate, amphetamine, cocaine, and phencyclidine toxicity [2]. Treatment for mild cases involves the immediate cessation of all neuroleptic medications. For moderate to severe cases, treatment involves counterbalancing dopaminergic blockade with dopamine agonists (most commonly with bromocriptine) and reducing the muscle rigidity by blocking calcium release from the sarcoplasmic reticulum using dantrolene. Neither form of treatment has been validated by a controlled trial. Supportive measures such as muscle paralysis and ventilation may also necessary.

Parkinsonism–Hyperpyrexia Syndrome

Withdrawing dopaminergic medication in patients with Parkinson's disease can cause a syndrome indistinguishable from NMS, called the parkinsonism-hyperpyrexia syndrome [17]. Parkinsonism-hyperpyrexia can also develop after withdrawal of nondopaminergic drugs used to treat Parkinson's disease such as amantadine or anticholinergics. Treatment consists of reinstituting dopaminergic therapy and provision of supportive care until recovery takes place, which may take weeks.

Malignant Hyperthermia

Malignant hyperthermia is a rare syndrome characterized by the rapid onset of fever, fluctuations in blood pressure, hyperkalemia, and metabolic acidosis, followed by severe muscle rigidity and secondary rhabdomyolysis. The majority of cases are triggered by various halogenated inhalational agents and depolarizing muscle relaxants. The clinical syndrome results from uncontrolled calcium flux across skeletal muscle membrane. In over 50 % of families, there is linkage of the autosomal dominant trait to a gene encoding the skeletal muscle ryanodine receptor [18]. Treatment is supportive and includes discontinuation of the triggering agent and administration of dantrolene that is highly effective. Mortality, however, remains around 10 % [19].

Serotonin Syndrome

Serotonin syndrome is a potentially life-threatening condition associated with increased serotonergic activity in the context of therapeutic medication use, inadvertent interactions between drugs, or intentional self-poisoning [20]. The diagnosis of serotonin syndrome is made solely on clinical grounds. Mental status changes include anxiety, disorientation and delirium. Autonomic manifestations include diaphoresis, tachycardia, hyperthermia, hypertension, vomiting and diarrhea. Neuromuscular hyperactivity can manifest as muscle rigidity, myoclonus or tremor. Hyperreflexia and the presence of bilateral Babinski sign is common. Patients may startle easily. Most cases can be managed simply by discontinuation of the drug and supportive measures. In severe cases, cyproheptadine (an antihistamine and serotonin antagonist) may be administered. Benzodiazepines have also been used.

Tetanus

Tetanus is characterized by muscle spasms caused by the toxin-producing anaerobe Clostridium tetani. The exotoxin prevents glycine and GABA release in the spinal cord. Muscle spasms may be triggered by touch, visual, auditory, or emotional stimuli [21]. It can be associated with respiratory failure and autonomic instability. There is no diagnostic test, but a measurable titre of anti-tetanus antibody effectively excludes the diagnosis. Management in the ICU should involve neutralization of the unbound toxin with tetanus immune globulin, removal of the source of infection, and supportive therapy. Sedation with gamma-aminobutyric acid (GABA) agonists and avoidance of excessive sensory stimulation are important adjunctive therapies. Intravenous lorazepam or diazepam have been used, as well as baclofen, methocarbamol and dantrolene.

Strychnine Toxicity

Strychnine blocks spinal and brainstem inhibitory interneurons, resulting in marked muscle rigidity and changes in mental status. It is still found in pesticides, some traditional herbal remedies and contaminated heroin. Initially, it presents with a hyperalert state and confusion, followed by hyperreflexia with rigidity, severe muscle spasms, and opisthotonus. Unlike tetanus, muscle tone normalizes between spasms. The patient remains fully conscious. Sustained spasms cause respiratory hypoventilation and muscle necrosis, with death ensuing rapidly from asphyxia and cardiac arrest. A high index of suspicion is needed to make a timely diagnosis. Treatment with respiratory support, activated charcoal, benzodiazepines, and barbiturates needs to be instituted immediately.

Rabies

Rabies is the major virus of the Lyssavirus genus. The typical presentation is with pain or stiffness at the site of the infecting bite. It invariably evolves into a progressively worsening encephalopathy. Death is inevitable. Encephalitic rabies presents with the classic hydrophobia, aerophobia, pharyngeal spasms, and hyperactivity. This "furious" phase is followed by loss of all central and peripheral neurological function known as "paralytic" rabies with a presentation of quadriparesis with sphincter involvement. The diagnosis can be by the demonstration of antigen in nerve biopsy.

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