Neonatal Lung Diseases

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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 oximetry 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].

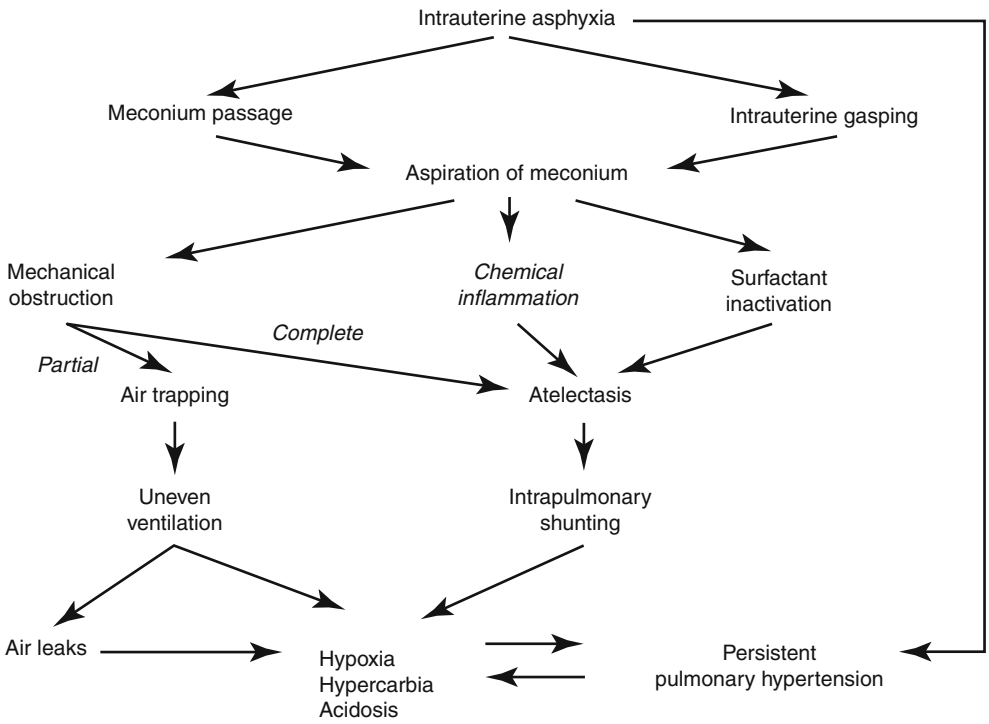

Fig. 14.1 Pathogenesis of meconium aspiration syndrome

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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