Pediatric Respiratory Physiology

11

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Contents

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Abstract

This chapter provides information about structural and biochemical lung development, which starts as early as the fifth week of gestational age but can last up to 4 years postnatally. During the intrauterine period, fetal breathing movements and lung fluid are essential factors for regular lung maturation and growth. Transition from intrauterine to extrauterine life is a critical phase, during which clearance of lung fluid and lung expansion due to air filling on the one hand and establishment of pulmonary blood flow due to a marked reduction of pulmonary vascular resistance on the other hand are the key features of this process. In contrast to older infants and adults, respiratory physiology of neonates is characterized by a relatively small airway diameter enhancing airway resistance, a higher chest wall compliance, and weakness of respiratory muscles, making the newborn much more vulnerable to respiratory failure. Dysfunctional transition may result in respiratory distress and persistent pulmonary hypertension, both of them still being important causes of morbidity and mortality. Their present-day management includes prenatal steroid treatment, intratracheal surfactant application, mechanical ventilation, and a differentiated medical therapy.

Keywords

Lung development · Surfactant system · Transition to extrauterine life · Neonatal respiratory physiology · Respiratory distress · Pulmonary hypertension

Introduction

Lung architecture consists of two multiple-branched, treelike systems, the airways, and the vasculature, which develop in a well-coordinated way from the primary lung bud to the final generation of millions of alveolar gas exchange units. In contrast to other organs like the brain or heart, which develop and begin their functions early in fetal life, the lung starts its process of differentiation and function during the second half of pregnancy. Whereas histological changes during lung development are well described, genetic and cellular mechanisms controlling lung development are complex and yet partially understood (Morrisey and Hogan 2010). Five phases of lung development are distinguished. The boundaries of these phases are not precise: at any time, there may be a substantial difference of development between distinct areas of the lung and, moreover, a significant variability between individuals. The subsequent description of lung development is illustrated in Fig. 1.

Embryonic Phase (Until Eighth Week of Gestation)

The respiratory system emerges from the ventral wall of the anterior foregut. Approximately on day 28, the two primary lung buds appear. At the same time the single foregut tube separates into a dorsal esophagus and a ventral trachea. The two primary lung buds extend into the surrounding mesenchyme and then start division. On day 32 five lobar buds (three on the right, two on the left side) exist which further develop into the mature lung lobes. The

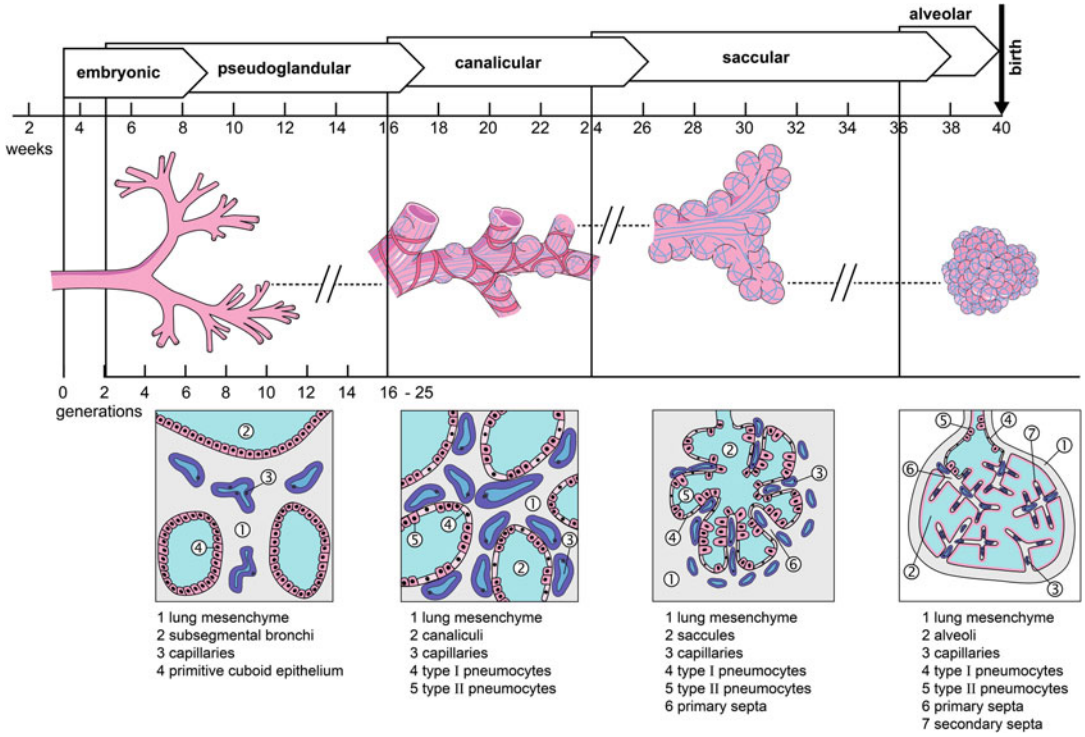


Fig. 1 The five phases of lung development

branching process proceeds, and by the seventh week of gestation, the subsegmental branches of the airways have already been established. At that time, the development of the vascular components of the lungs is initiated as well. The pulmonary arteries originate from the ventral part of the sixth aortic arch, and the pulmonary veins grow out of a dorsal bud of the commune atrium of the developing heart. During the further development, the pulmonary arteries always follow the airways, whereas the pulmonary veins will grow in the septa of the connective tissue.

Pseudoglandular Phase (5th–17th Week of Gestation)

Due to repeated dichotomous branching, conductive airways and the associated pulmonary arteries are formed, resulting in 16–25 generations of primitive airways at the end of this phase. Thereafter, additional growth occurs only by elongation and widening of existing airways, further branching does not happen. As the name suggests, the lung looks like a gland during the pseudoglandular phase. The tubules are coated with a single-layered epithelium. At the tenth week of gestation cartilages, smooth muscles and small glands appear in the walls of the bronchial tubes. The respiratory epithelium begins to differentiate, and cilia emerge in the proximal airways. In general, the airways differentiate in a centrifugal direction.

Canalicular Phase (16th–26th Week of Gestation)

The characteristic feature of the canalicular phase is the approach of epithelial tubuli and pulmonary capillaries. By vigorous growth of capillaries, the mesenchyme is penetrated by a network of canals, originally giving this phase its name. Today, the term is deduced from the widening of the tubuli into canaliculi. This process congests the

surrounding mesenchyme resulting in a close contact between canaliculi and capillaries. Simultaneously, differentiation of the primitive epithelial cells into flat type I (representing the blood-air barrier and being ultimately responsible for gas exchange) and cuboid type II pneumocytes (surfactant synthesis) starts. This phase of lung development is particularly important, because at the end of this period, the lungs are enabled to perform gas exchange to a limited extent giving the fetus the chance of viability.

Saccular Phase (24th Week of Gestation Until Birth)

During this phase a substantial increase of lung parenchyma and a remarkable change in the appearance of the lungs occur. Connective tissue becomes less prominent, the airspace increases considerably, and the airspace walls undergo a significant thinning. The distal airspaces divide into saccules which by and large are the last generation of the airway branch. The walls of the airspaces correspond to the primary septa. At the end of this phase, the first alveoli emerge. Usually, preterm infants born during the early saccular phase can be sufficiently oxygenated with some kind of ventilatory support. After 34 weeks of gestation, in most cases the infant is able to sustain itself with oxygen.

Alveolar Phase (36th Week of Gestation to 18 month–4 years Postnatal)

The development of alveoli starts – a process that will continue for months to years after birth. The alveoli emerge by further division of the primary septa into secondary septa, which form the barrier for gas exchange and are only a few nanometers thick. This barrier consists of three layers: the thin process of the type I pneumocytes, both the basal membrane of the pneumocytes and the endothelial cells of the capillaries, and the thin extensions of the endothelial cells. With ongoing maturation, each capillary is simultaneously attached to at least two alveoli.

At the time of birth, the lung does not consist of mature alveoli but of approximately 200 million terminal sacculi. These differentiate into the 300–600 million alveoli finally completing lung development.

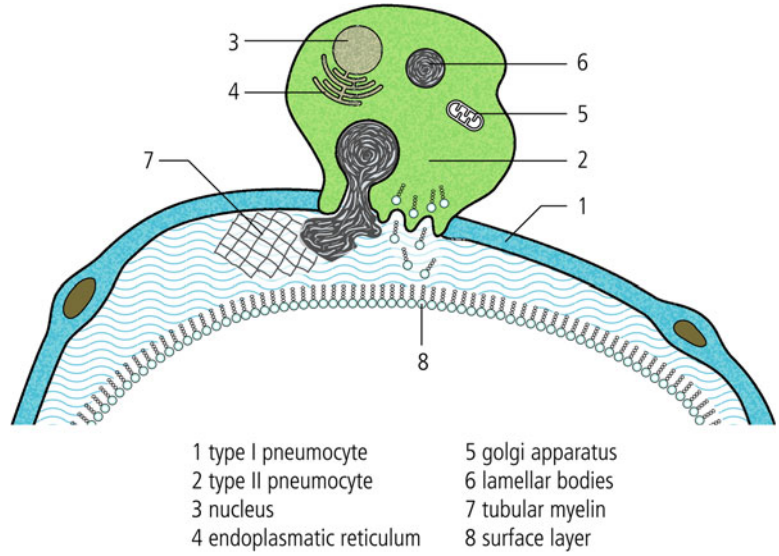
Prenatal Development of the Pulmonary Surfactant System

Pulmonary surfactant is a lipoprotein mixture, uniquely located at the air-liquid interface of the lung. Its functions include both reduction of interfacial surface tension depending on the lung volume to prevent lung collapse and to reduce work of breathing, as well as inhibiting and inactivating environmental pathogens.

Surfactant consists of 90% lipid components, mainly phospholipids (80–85%) and cholesterol, and 10% protein components (Haagsman and van Golde 1991). Phosphatidylcholine (PC) with its disaturated molecular species dipalmitoylphosphatidylcholine (DPPC) is the predominant phospholipid. The protein component contains four surfactant proteins: surfactant protein-A (SP-A), SP-B, SP-C, and SP-D. Surfactant is produced and secreted by type II alveolar cells. SP-A regulates the uptake of phospholipids into type II cells and surfactant secretion. Both SP-A and SP-B are responsible for the formation and the structural integrity of surfactant components. The hydrophobic proteins SP-B and SP-C interact intensively with the lipids and promote the formation of surfactant layers and their adsorption to the air-liquid interface. The hydrophilic proteins SP-A and SP-D are mainly responsible for the innate host defense system of the lung by both directly killing microorganisms or by enhancing the uptake of pathogens by phagocytes (Orgeig et al. 2010).

The phospholipids and the proteins are synthesized in the endoplasmic reticulum, then modified by the Golgi apparatus, and finally stored in the lamellar bodies (see Fig. 2). The lamellar bodies are released into the liquid lining the alveoli by exocytosis across the cell plasma membrane. Thereafter they morph into a grid structure called tubular myelin, which provides the lipids for the

Fig. 2 Surfactant synthesis



surface film. Due to the amphipathic nature of the phospholipid molecules (one hydrophilic and one hydrophobic end each), they adsorb to the air-liquid interface forming a surface layer that lowers the surface tension. Compression of that film results in further reduction of the surface tension, because the phospholipid molecules are insoluble and thus packed more densely, therefore facilitating an adequate regulation of surface tension. Approximately 90% of the secreted phospholipids are reabsorbed by the type II pneumocytes and reutilized for further surfactant synthesis.

The pulmonary surfactant system is one of the last systems to develop before birth (Orgeig et al. 2011). Both SP-B and SP-C proproteins and their mRNA are detectable in human lung tissue in the 25th week of gestation, SP-D and its mRNA even as early as the 16th week. In fetal lung tissue, lamellar bodies are sporadically found after the 20th week of gestation and regularly after the 24th week. DPPC appears at low levels in amniotic fluid between 24 and 28 weeks of gestation. The surfactant proteins SP-A and SP-B appear after 30–31 weeks for the first time. Although the surfactant system undergoes a maturation process until term at 40 weeks, preterm infants often have sufficient amounts of surfactant to warrant gas exchange as from the 24th week of gestation.

Maturation of the surfactant system is mainly controlled by mechanical forces and neurohormonal factors. Mechanical forces include lung distension by lung liquid and fetal breathing movements (see below), the most important neurohormonal factors are cortisol, thyroid hormones, and adrenergic agonists (Mendelson and Boggaram 1991).

In general, cortisol is the major regulatory hormone for terminal maturation of the fetus and prenatal preparation for birth. During the first and second trimester of pregnancy, the main source of fetal cortisol is the mother; while in the last trimester, the fetus is able to synthesize and release cortisol under fetal hypothalamic control which results in a considerable increase of cortisol levels.

With respect to surfactant maturation, cortisol specifically induces phospholipid synthesis. Furthermore, cortisol directly stimulates the type II pneumocyte to release surfactant, which drastically elevates the surfactant concentration in the alveolar compartment. This effect is utilized in case of imminent preterm birth.

As with cortisol, the levels of thyroid hormones and adrenergic agonists increase as term approaches. Regarding surfactant maturation, T_3 and T_4 act synergistically with glucocorticoids by particularly enhancing the lipid components of

surfactant and stimulating surfactant secretion of type II pneumocytes. Adrenergic agonists contribute to surfactant maturation by increasing the synthesis of SP-A, -B, and -C and enhancing choline incorporation into phospholipids resulting in increased surfactant phospholipid synthesis.

At term birth, the type II pneumocytes of the fetus contain much more surfactant than the adult lung, and this surfactant is provided for release at delivery. The initiation of breathing after birth causes mechanical stretch, thus deforming the type II cells, and this triggers surfactant release.

The Role of Lung Fluid and Fetal Breathing Movements in Lung Organogenesis and Growth

At the end of the nineteenth century, it became evident that the fetal lungs are filled with a fluid in utero. It was erroneously believed far into the twentieth century that the liquid was inhaled amniotic fluid. However, the following three findings led to the conclusion that fetal lung liquid is created by an active secretion of the lung itself (Olver et al. 2004): (1) the presence of lung fluid despite of congenital airway atresias, (2) the fact that the introduction of a radiopaque contrast medium into the amniotic cavity was not associated with its subsequent appearance in the fetal airways, and (3) the difference in the composition of lung fluid in comparison to amniotic fluid. Meanwhile, it is taken for sure that the production of lung fluid is induced by an active chloride transport into the lung lumen by alveolar type II cells. Sodium follows passively and fluid flows to balance the osmotic gradient. Lung liquid is more viscous than amniotic fluid, thus keeping the lungs free of the later. Lung fluid is present as early as the sixth week of gestation, and secretion reaches its peak in the third trimester (McCray et al. 1992). During the last weeks of gestation, the lung liquid volume reaches a level which is considerably greater than the analogous level of the functional residual capacity of the lung after birth. Shortly before birth a decline in lung liquid volume already occurs.

Human fetal breathing movements (FBMs) were first observed over 120 years ago once rhythmical fetal movements transmitted through the maternal abdominal wall were described and presumed to correspond to FBMs (Boddy and Mantell 1972). It was, however, only after decades that this phenomenon was proven when the technique of ultrasound became available.

FBMs are characterized by rhythmic contractions of the diaphragm, intercostal, and laryngeal muscles. FBMs intermittently reduce intrathoracic pressure hence expanding the fetal lung. They usually occur during the second half of pregnancy but have been detected as early as tenth week of gestation (de Vries et al. 1986). First, FBMs occur as single isolated movements and escalate to episodes of more clustered events later on. During gestation, intensity of FBMs increases. Normally, in the third trimester of pregnancy, FBMs are present within 50–70% of the time with a pronounced diurnal variation reaching a peak in the evening and a minimum in the early hours of the morning (Dawes 1974). With accelerating gestational age, both inspiratory and expiratory displacement of the fetal abdominal wall increases just as the inspiratory and expiratory velocities do. Despite of the age-dependent change of fetal breathing patterns, the frequency of FBMs does not vary over time and ranges between 40 and 70/min (Florido et al. 2005).

The changing pattern of FBMs with ongoing pregnancy is believed to result from maturation of the respiratory neural control. Since the possibility to study the human fetus is limited, most knowledge about prenatal respiratory control is derived from animal experiments. A restricted area of the medulla containing the pre-Bötzinger complex is necessary for generating respiratory rhythm in utero as well as later in life (Greer et al. 2006). Besides, fetal breathing is responsive to chemical stimuli and agents affecting postnatal breathing. Fetal breathing can be stimulated by high levels of carbon dioxide (CO_2) especially in a behavioral state which corresponds to REM sleep in children and adults. With ongoing pregnancy the threshold of CO_2 which stimulates breathing declines, thus preparing the fetus for breathing after birth. Another potent stimulus of

fetal breathing is external cooling. Therefore, the triggers for breathing after birth already work during fetal life (Darnall 2010).

In contrast to postnatal breathing, decreasing PO_2 inhibits rather than stimulates fetal breathing, a phenomenon which is called fetal hypoxic depression. In preterm infants the fetal response to hypoxia might persist leading to the well-known apnea of prematurity. It is presumed that the activation of adenosine receptors contribute to the hypoxic inhibition of fetal breathing. Therefore, the administration of adenosine receptor antagonists such as caffeine stimulates FMBs – a major treatment used in apnea of prematurity as well (Mathew 2011). Finally, fetal breathing is abolished or reduced by maternal anesthesia or sedation.

For adequate lung development and structural maturation, a high level of lung distension in the fetus is apparently necessary which is achieved by both the presence of lung fluid and FBMs.

Lung liquid is secreted against a resistance provided by the upper respiratory tract (URT), therefore generating a pressure which is 2–3 mmHg above amniotic fluid pressure and acting as an expanding force to stretch the lung and stimulate growth (Olver et al. 2004). There is evidence that change in volume is a more influential prerequisite for optimal lung growth than change in pressure. Changes in the resistance of the URT associated with FBMs play a major role in controlling the amount of lung fluid. The relatively high level of lung liquid volume is maintained because the pulmonary recoil pressure is opposed by the resistive effect of the URT during apnea and by rhythmic contractions of the diaphragm during FBMs, respectively (Harding and Hooper 1996). Reductions of lung expansion lead to lung hypoplasia, composed of reduced lung volume and structural impairment. Lung hypoplasia is based on a lack of FBMs, reduced intrathoracic space, or a combination of both of them. The reasons for diminished lung expansion include neuromuscular disorders, which cause respiratory muscle fatigue, pleural effusions, skeletal dysplasia, oligohydramnios, and congenital diaphragmatic hernia (CDH). The surgical procedure of fetal tracheal occlusion used in case of CDH results in an accumulation of lung fluid and subsequently lung expansion (Ruano et al. 2012). However, the effect is limited if further lung expansion is impossible because the available intrathoracic space is already occupied by herniated viscera.

In general, it is not completely clarified whether hypoplastic lungs will attain a normal structure during postnatal life, but there is quite some evidence that these lungs will be permanently impaired.

Besides the impact described above, FBMs affect pulmonary development by influencing lung epithelial cell differentiation. In fact, it is well known that mechanical stress generated by the fetus plays a role in how differentiating tissues respond to gene instructions. The expression of growth factors, as, e.g., platelet-derived growth factors (PDGFs), insulin-like growth factors (IGFs), and thyroid transcription factor 1 (TTF-1), which are relevant mediators of lung organogenesis, is upregulated by rhythmic mechanical stretch. In contrast, insufficient FBMs lead to reduced expression of these growth factors resulting in disturbed lung cell cycle kinetics, i.e., decreased cell proliferation and increased cell death. Besides, in the absence of FBMs, the type I pneumocyte is unable to flatten, thus hampering sufficient gas exchange, and type II pneumocytes are not able to compile, store, and release surfactant (Inanlou et al. 2005).

Physiology of Transition from Intra- to Extrauterine Life

Since the fetal lung is not at all concerned with gas exchange, only 10% of the right ventricular output pass through the lungs, the remainder being shunted to the left ventricle and the aorta via the foramen ovale and the ductus arteriosus, respectively.

Accordingly, the pulmonary vascular resistance (PVR) is high in utero. Therefore, establishment of functional residual capacity (FRC) and pulmonary blood flow are crucial for normal transition.

To establish FRC, the newborn has to accomplish three procedures: clearance of lung fluid, expansion of the lungs with air, and prevention of lung collapse.

The precise mechanisms of lung fluid clearance are yet incompletely understood, although fundamental factors seem to be clarified. With onset of labor, the clearance of lung liquid is induced by mechanical forces. The limited intrauterine space will cause a high pressure on the chest wall and increase transpulmonary pressure leading to a loss of lung fluid of approximately 50%. Furthermore, labor increases the release of cortisol, thyroid hormones, and fetal adrenaline, which cause a stop of the chloride depending fluid secretion by the alveolar type II cells and stimulates them to reabsorb fluid by activating Na + channels (Te Pas et al. 2008).

After delivery, an amount of 25–33% of lung fluid will be ejected through mouth and nose. The mechanism is presumably the high compression of the fetal chest during progression through the distal part of the birth canal, the so-called vaginal squeeze. When delivery occurs before onset of labor, i.e., in case of cesarean section, these mechanisms are virtually absent, resulting in greater liquid retention within the lungs and being the explanation for the increased respiratory morbidity seen in those infants.

Breathing undergoes a transition at birth from an intermittent process in the fetus to a continuous one in the newborn. Animal studies suggest that the initiation and maintenance of continuous breathing after birth is mainly due to a drop in body temperature and an elevation of PCO_2 after cord clamping (Kuipers et al. 1997). The first breath after birth usually appears within 10–18 s (range 0.5–72 s).

Because there is no elastic recoil of the chest wall after birth, only little passive inflation of the lungs appears, and the first breath requires an active effort of the infant, which mainly consists of a contraction of the diaphragm (Saunders and Milner 1978). Accordingly, the pressure gradient between oral cavity and alveoli provides the gas entry into the lungs. During first breath, the baby produces a large negative intrathoracic pressure (mean about 50 cmH_2O, range 28–105 cmH_2O) during inspiration and a marked positive pressure (mean about 70 cmH_2O, range 18–115 cmH_2O) during expiration by exhaling against a closed glottis (Vyas et al. 1986). This facilitates the establishment of the FRC. In healthy infants, the mean volume of the first breath is about 40 ml, and a considerable FRC with a mean of 10–15 ml is generated in this way, reaching the normal value of 30 ml/kg body weight within 2–3 h. Additionally, there is a post-inspiratory activity of the respiratory muscles, which counteracts the passive recoil of the lungs and the chest and therefore helps to maintain FRC. Simultaneously, recruitment of surfactant to the air-liquid interface reduces the surface tension, sustaining FRC and preventing lung collapse. The residual amount of lung liquid which still fills the airways after birth is cleared by the transpulmonary pressure generated by the first breath, which causes a shift of lung liquid from the airways into the interstitium and subsequent removal by the pulmonary circulation and lymphatic vessels. Moreover, the rise in alveolar PO_2 stimulates the activation of Na + channels resulting in further absorption of lung fluid.

The average respiratory rate immediately after birth is 60/min (range 24–106), remains constant for a few hours, and gradually declines to values of 40/min (range 32–48) after 1 day.

During fetal life, oxygen saturation (SpO_2) is about 60–70% and can drop to values as low as 30% during birth process without developing acidosis. Within the first minute after birth, SpO_2 is about 60% with a lower range of 30% even in healthy, term infants and increases steadily to values above 90% within 8 min (range 5–10 min) (Dawson et al. 2010). In infants born by cesarean section, saturations are 2–3% lower compared with infants born vaginally, and there is an almost 2 min delay in reaching a SpO_2 above 90%. This knowledge is important to avoid unnecessary administration of oxygen after birth. In the healthy newborn, the normal SpO_2 value, i.e., 97–100%, is reached within a few hours after birth.

Establishment of pulmonary blood flow is accompanied by dramatic changes in the circulatory system. Compared with small pulmonary

arteries in postnatal life, comparable arteries during fetal life have a more cuboidal endothelium and a pronounced medial smooth muscle coat in relation to the external diameter. This structural pattern is assumed to be responsible for the increased vasoreactivity and the high PVR of the fetus (Lakshminrusimha and Steinhorn 1999).

The mediator of this high pulmonary vascular tone is mainly a low oxygen tension (approximate 30–50 Torr, depending on gestational age and whether the oxygen tension is measured in the umbilical vein or umbilical artery (Nicolaides et al. 1989)) promoting synthesis of platelet-activating factor (PAF) and endothelial-released vasoconstrictors, the most important one being endothelin-1 (ET-1), a potent vasoactive peptide, which bonds with the ET_A receptor of the vascular smooth muscle cells. Anyway, vasoconstriction is achieved by elevating intracellular Ca^{++} concentration and sensitizing myofilaments to Ca^{++} (Gao and Raj 2010). Vasoconstriction is further maintained by low basal secretion of vasodilators like nitric oxide (NO) and prostacyclin (PGI_2) (see Fig. 3, left).

By clamping the cord, the infant is cut off from the low-resistance placental vascular bed. Accordingly, the systemic vascular resistance suddenly rises, hence facilitating closure of the foramen ovale. Cessation of the blood flow through the umbilical vein causes a collapse of the ductus venosus. The onset of air breathing is accompanied by a marked increase of oxygen tension leading to vasodilation of the pulmonary vessels on one hand and to a closure of the ductus arteriosus on the other.

Dilation of pulmonary vessels is achieved both by the NO-mediated system and the prostaglandin system in a complementary fashion. Endothelial nitric oxide synthase (eNOS) plays a decisive role in the transition of pulmonary circulation (Lakshminrusimha and Steinhorn 1999). In the presence of oxygen, eNOS converts l-arginine into l-citrulline and NO. At term gestation a maturational increase of the eNOS protein level occurs being crucial for a sufficient synthesis of NO, because NO is not stored in the cell. The release of NO is stimulated by oxygen both directly and indirectly by an increase of oxidative phosphorylation and release of ATP. NO itself initiates rapid vasodilation by stimulating the soluble guanylate cyclase in the smooth vascular cell and thus converting GTP into cGMP. The increase of intracellular cGMP induces a decrease of Ca^{++} influx and therefore a relaxation of the smooth vascular cell (see Fig. 3, right).

Prostacyclin (PGI_2) is the most potent of the prostaglandins and is generated by the enzyme cyclooxygenase (COX) from arachidonic acid. PGI_2 activates the enzyme adenylate cyclase, which converts ATP to cAMP. The increase of cAMP also results in a relaxation of the smooth muscle cells by decreasing the Ca^{++} influx (Gao and Raj 2010).

Pulmonary vasodilation leads to rapid structural changes of the pulmonary microvasculature with significant thinning of the vessel walls, a flattening of the endothelial cells, and a widening of the lumen. Later on, the dilation is followed by a reduction of the musculature, a process which continues over several weeks (Hall and Haworth 1987).

Pulmonary vasodilation results in a nearly tenfold increase of pulmonary perfusion within a few minutes. The enhanced pulmonary venous return with a rise of the left atrial pressure above the right atrial pressure further promotes closure of the foramen ovale. Increase of pressure in the systemic circulation on one hand and decrease of pressure in the pulmonary circulation on the other hand reverse the blood flow through the ductus arteriosus from right to left to left to right. The smooth muscle cells of the ductus arteriosus react to the increase of oxygen tension with constriction, leading to functional closure within 24–48 h after delivery with the result that the adult circulatory pattern is established. Later on, the anatomical closure of the ductus arteriosus will be achieved within the next weeks of life, being completed in more than half of the cases after 4 weeks of age and in 90% of the cases after 8 weeks. The high PVR declines continuously postpartum to about half of the systemic arterial pressure within 3 days. At the age of 2–3 months, pulmonary arterial pressure has further decreased to the normal level of about 15% of the systemic arterial pressure (Kliegmann et al. 2007).

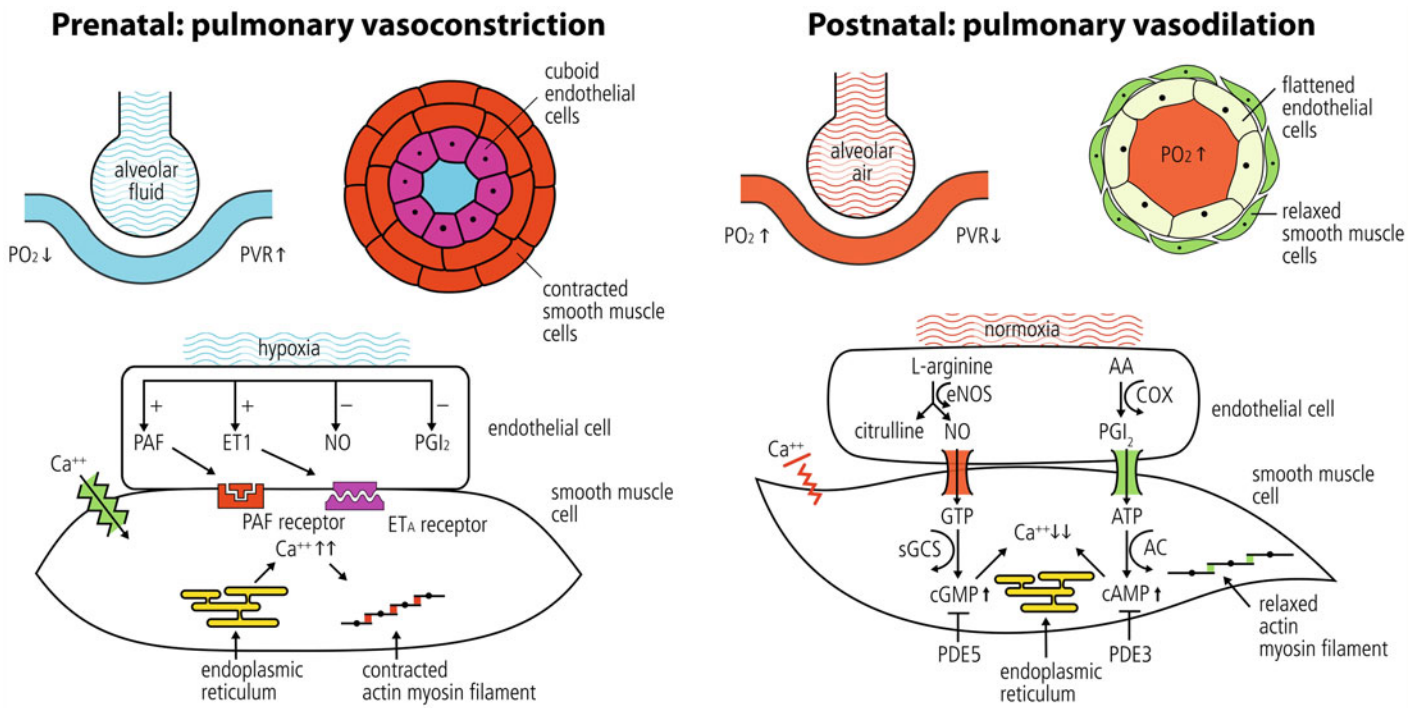


Fig. 3 Mediators of pulmonary vasculature tone regulation *PVR* pulmonary vascular resistance, *PAF* platelet-activating factor, *PAFr* PAF receptor, *ET-1* endothelin 1, *ETA* endothelin-1 receptor a, *NO* nitric oxide, *eNOS* endothelial nitric oxide synthetase, *AA* arachidonic acid, *COX* cyclooxygenase, *PGI2* prostacyclin, *IP* prostacyclin receptor, *GTP* guanosine triphosphate, *sGC* soluble guanylate cyclase, *cGMP* cyclic guanosine monophosphate, *ATP* adenosine triphosphate, *AC* adenylyl cyclase, *cAMP* cyclic adenosine monophosphate, *PDE5* phosphodiesterase 5 which hydrolises and inactivates cGMP, *PDE3* phosphodiesterase 3 which hydrolises and inactivates cAMP

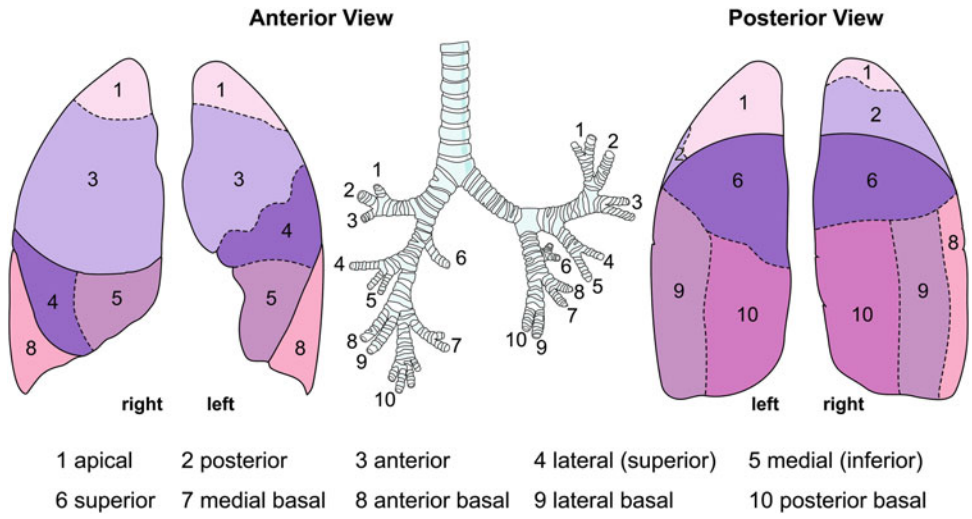


Fig. 4 Bronchial tree and bronchopulmonary segments

Respiratory Physiology of the Neonatal Period

The primary postnatal function of the respiratory system is to provide sufficient oxygenation and to eliminate CO_2. Oxygenation and CO_2 elimination are influenced by a variety of factors such as lung anatomy, pulmonary circulation, lung volume, compliance, and resistance of the respiratory system. Abnormalities in any of these factors may lead to respiratory failure. Typical symptoms of such failure during the neonatal period are tachypnea; dyspnea with signs of increased work of breathing including nasal flaring; jugular, inter-, and subcostal recessions, and cyanosis.

Anatomy

The trachea branches into right and left main bronchus. The right main bronchus divides into upper, middle, and lower, the left one into upper and lower lobar bronchi. The lobar bronchi split further into segmental bronchi. The region aerated by a segmental bronchus constitutes the functional anatomic unit of the lung. Each lung contains ten segments: numbers 1–3 form the two upper lobes; numbers 4 and 5 the middle lobe in the right lung and the lingula in the left lung, respectively; and numbers 6–10 the two lower lobes (see Fig. 4).

The segmental bronchi further subdivide into bronchioles and terminal bronchioles, which constitute the furthest parts of the air conducting system. Bronchi and bronchioles differ not only in size but also in extension of cartilage, type of epithelium, and blood supply. The amount of cartilage corresponds to the size of the respective bronchial tube, leaving no cartilage at the level of the bronchioles (Koeppen and Stanton 2008). Attached to the terminal bronchioles is a large number of small respiratory bronchioles, resulting in a substantial rise of total surface area. The respiratory bronchioles already contain alveoli, therefore presenting the beginning of the gas exchange region. They extend into the ductus alveolares and finally into the sacculi alveolares, which are saclike airspaces composed of closely adjacent alveoli.

Even though the airway anatomy in newborns is the same as in older infants and adults, it differs in some crucial aspects such as airway diameter, chest wall compliance, and strength of respiratory muscles (Kliegmann et al. 2007).

As airway resistance is inversely proportional to the fourth power of the radius of the airways (Hagen-Poiseuille's law, $V = \pi \times r^4 : 8 \times n \times l$,

× ΔP), halving of the airway lumen will increase the resistance 16-fold. Due to their inherently lower airway diameter, neonates are therefore eminently vulnerable to further reduction of airway lumen, e.g., caused by inflammation or secretion. A reduction in airway diameter leads to turbulent flow, which additionally enhances airway resistance. Furthermore, as neonates and young infants are predominantly nose breathers, even a minimal amount of nasal obstruction is already harmful.

The chest wall of a neonate is highly compliant, allowing a smooth passage through the birth canal on one hand and further lung growth on the other hand. By way of contrast, the high chest wall compliance promotes collapse of the lungs, which is particularly disadvantageous in case of an already restricted lung function, for example, in children with respiratory distress syndrome (RDS).

Another factor contributing to the sensitivity of the respiratory situation in the neonatal period is the inferior strength of the respiratory muscles leading to a limited ability to maintain adequate ventilation, a fortiori during the course of a lung disease (Abu-Shaweesh 2004).

Pulmonary Circulation

Two separate blood systems, namely, the pulmonary and the bronchial circulation, run through the lungs. The pulmonary circulation is a low-pressure, low-resistance system. It takes deoxygenated blood to the gas exchanging units for oxygenation and removal of CO_2.

The pulmonary arteries are the only arteries of the body carrying deoxygenated blood. Pulmonary vessels with a diameter larger than 50 μm contain smooth muscle and can actively regulate their diameter, thereby altering the resistance of the blood flow (Koeppen and Stanton 2008). Pulmonary vasculature constricts in response to hypoxemia, hypercapnia, and acidosis. In contrast, it dilates as a result of hyperoxemia, hypocapnia, and alkalosis. The bronchial arteries branch from the aorta, follow the bronchial tree including their divisions, and supply oxygenated blood to the lung parenchyma. Approximately one third of the blood returns to the right atrium through the bronchial veins, whereas the residual blood drains into the left atrium through pulmonary veins.

Pulmonary Gas Exchange

Pulmonary gas exchange takes place in the alveoli through a tight alveolar-capillary network. Therefore, O_2 and CO_2 exchange is limited by perfusion. The alveoli are coated with an epithelium consisting of type I and type II cells, the former being the primary site for gas exchange as their thin cytoplasm, and their proximity to the capillary endothelium is ideal for optimal gas diffusion. O_2 and CO_2 passively diffuse across this barrier into plasma and red blood cells. The extent of diffusion is influenced by differences in solubility, with CO_2 being far more soluble than O_2, and also by differences in partial pressures of the two gases. Gas exchange is best at the initial capillaries since the differences in partial pressures of O_2 and CO_2, respectively, between the capillaries and the alveoli are highest in this area. When the alveolar-capillary membrane is thickened, diffusion may become impaired.

Due to anatomic dead space, not the entire gas volume gets exchanged. Furthermore there are alveoli which are ventilated but unperfused (ventilation-perfusion mismatch). Under healthy conditions this ventilation-perfusion mismatch is minimal but it may increase considerably in special diseases such as atelectasis.

Lung Volumes

The total volume of air that can be contained in the lungs is the so-called total lung capacity (TLC). All other lung volumes (LV) are parts of the TLC (see Fig. 5):

- Tidal volume (V_T) is the volume which is moved during breathing at rest.
- FRC is the volume of air remaining in the lungs at the end of expiration during breathing.

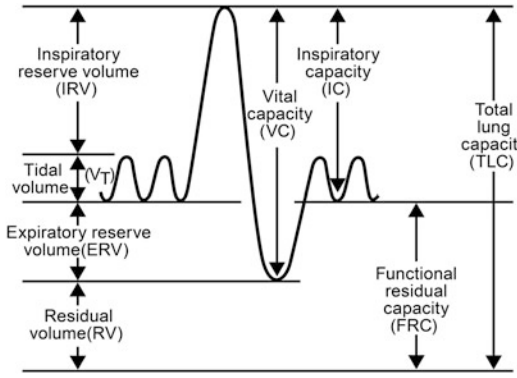


Fig. 5 Lung volumes and capacities

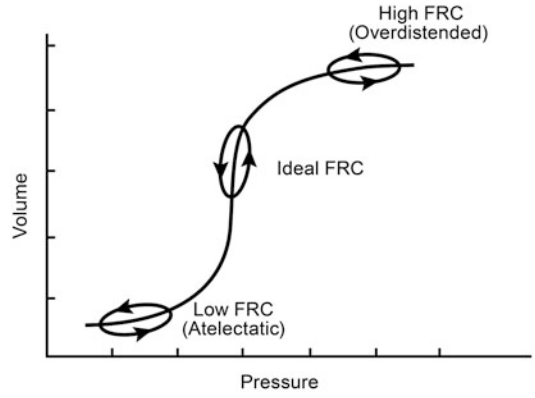


Fig. 6 Pressure-volume-curve with high, low, and ideal functional residual capacities (FRCs)

- Inspiratory capacity (IC) is the volume which can be inspired with a forced inspiration following a normal expiration.
- Inspiratory (IRV) and expiratory reserve volume (ERV) are the volumes which can additionally be in- or expired after a normal breath.
- Vital capacity (VC) is the total volume of exhaled air from a maximal inspiration to a maximal expiration.
- Residual volume (RV) is the air remaining in the lungs after a complete expiration. All except FRC and RV can be measured directly by spirometry.

The product of V_T and respiratory rate is the minute ventilation, which is defined as the total volume of air inspired each minute.

Airway Resistance

Resistance is the major factor influencing airway flow rates. According to Hagen-Poiseuille's law stated above, one might expect that the dominating site of airway resistance consists of the smallest airways. However, resistance is predominantly affected by the large bronchi. The smallest airways contribute only little to the overall total resistance for two reasons: firstly, as the total cross-sectional area increases due to further branching, airflow velocity decreases substantially because the flow becomes laminar. Secondly and even more importantly, the generations of smaller airways are built parallel rather than in series. Since the resistance of airways arranged in parallel is reciprocal to the sum of the individual resistances, the overall resistance of the small airways is negligible. Thus, as the airway diameter decreases, the resistance of each individual airway increases, but the enlargement in the number of parallel pathways reduces the resistance at each generation of branches. This is in marked contrast to the pulmonary blood vessels, in which most of the resistance is attributable to small vessels.

Lung Compliance

Lung compliance (C_L) is a measure of the elastic properties of the lung and an index on how easily the lung can be distended. It is defined as the quotient of a change of LV and required pressure ($C_L = \Delta V : \Delta p$). The ideal situation is given when small changes in pressure induce large changes in volume. At the extremes, high or low volume, even large changes in pressure result in only minimal changes in volume, which is undesirable (see Fig. 6). C_L is affected by several respiratory disorders such as RDS.

The product of compliance and resistance is the time constant, which is a value that describes how quickly expiration can be done. One time constant is defined as the time necessary to

complete 63% of V_T exhalation. After four time constants, 99% of V_T is expired. With increasing compliance or resistance, the time constant is prolonged. This has to be considered in mechanical ventilation.

Respiratory Distress Syndrome

Pathophysiology

RDS is characterized by surfactant deficiency and a structurally immature lung. The major variable is the level of both structural and biochemical lung maturation at birth.

The crucial biochemical event is the synthesis and storage of sufficient surfactant (Jobe 2012). Surfactant stabilizes the inflation of alveoli by lowering surface tension. It is of importance to remember that the effect of surfactant is markedly increased in smaller alveoli compared to larger ones. The result is an equalization of the pressure in the smaller and larger alveoli leading to a stabilization of the alveoli itself. In the absence of surfactant, small alveoli would drain into large alveoli due to their high pressure enhancing the imbalance even more. The absence of pulmonary surfactant leads to failure to attain adequate FRC and subsequently to atelectasis.

Synthesis of surfactant does not solely depend on gestational age but is additionally influenced by factors such as pH, temperature, and perfusion. Asphyxia, hypoxemia, and pulmonary ischemia especially in combination with hypovolemia, hypotension, and cold stress may suppress surfactant synthesis. Furthermore, lung injury caused by high oxygen concentrations and mechanical ventilation may result in further surfactant reduction.

Surfactant deficiency leads to a physiologically high pulmonary opening and ventilation pressure, causing epithelial lesion at the terminal airways and alveoli. This injury allows plasma transfer from vascular compartment into regions of gas exchange, leading to the typical histological picture of hyaline membrane syndrome (Hallman 2013).

Fetal growth restriction and fetal exposure to inflammation may cause early lung maturation by structural stimulation and surfactant maturation as shown in an animal model (Jobe 2012). State of lung maturation at birth is a major outcome variable. Due to persistent structural immaturity of the lung, bronchopulmonary dysplasia (BPD) develops in many of the smallest infants.

Incidence

The incidence of RDS is inversely related to gestational age and birth weight. The more premature the infant is born, the higher is the risk for RDS. Therefore, incidence of RDS is 90% in infants born <28, 15–30% in infants born between 32% and 36%, and 5% in infants born with >37 weeks of gestation (Stoll et al. 2010). Even infants born at term can rarely suffer from RDS. In those cases genetic conditions such as surfactant protein-B or ABCA3 (ATP-binding cassette subfamily A member 3) deficiency have to be considered as a differential diagnosis.

The risk for RDS increases in case of cesarean section delivery, multiple birth, male gender, white infants, and maternal diabetes. Therefore, elective cesarean section in low-risk pregnancies should not be performed before 39 weeks of gestation. A reduced risk for RDS is found in pregnancies with chronic or pregnancy-related hypertension, maternal infection, intrauterine stress, and especially antenatal corticosteroid prophylaxis (Sweet et al. 2013).

Clinical Symptoms

The typical clinical presentation of RDS is respiratory distress characterized by cyanosis, tachypnea, and increased work of breathing including nasal flaring, jugular, inter-, and subcostal recessions. Apart from these typical clinical signs, diagnosis of RDS is verified on the basis of characteristic chest x-ray findings such as ground glass appearance and air bronchograms.

X-Ray Findings in RDS

A fine reticular granularity of the parenchyma and positive air bronchograms are the typical findings in x-ray. These signs are often more prominent in the left lower lobe due to superimposition of the cardiac shadow. Depending on the extent of radiological signs, RDS is classified as grade I–IV. X-ray findings are influenced by various factors such as phase of respiration, use of continuous positive airway pressure (CPAP) or mechanical ventilation, lung expansion, and administration of surfactant, the latter possibly normalizing the image instantaneously. Therefore, in some patients x-ray findings and clinical course are poorly correlated. As x-ray findings are not pathognomonic, differential diagnoses such as early-onset sepsis must be taken into account.

Prevention/Therapy

Interventions to prevent RDS should start before birth and involve both obstetricians and pediatricians as a team. Crucial goals of this cooperation should be an in utero transfer to a perinatal center in case of high risk for preterm birth, prolongation of pregnancy, and application of antenatal corticosteroids.

Antenatal Corticosteroids

Studies carried out in preterm infants have confirmed strong evidence for the role of antenatal steroids in reducing the incidence of RDS and, additionally, the risk of neonatal death, intraventricular hemorrhage, and necrotizing enterocolitis. Therefore, antenatal corticosteroid therapy – preferably by betamethasone – is recommended for all women at risk of preterm delivery before 34 completed weeks of gestation. The optimal point of time for corticosteroid therapy is more than 24 h and less than 7 days before delivery. Beyond 14 days after antenatal corticosteroid treatment, the benefits begin to decrease (Roberts and Dalzell 2006). Studies have yet to confirm whether the benefits on the outcome outweigh the risks of side effects in short and long term if repeated courses of corticosteroids are being used.

CPAP

In preterm infants the use of mechanical ventilation should be minimized where possible. Application of CPAP with a positive end-expiratory pressure (PEEP) is beneficial for stabilization of the chest wall, assistance of respiratory muscles, and restoration of FRC.

Early use of CPAP has shown a decrease in the need for mechanical ventilation (SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network 2010a). Recent large clinical trials have demonstrated that infants of 26–29 weeks of gestation managed with early CPAP can get along without intubation or surfactant in about 50% of cases (Dunn et al. 2011). Additionally, caffeine therapy should be applied at least in very low birth weight infants to minimize need for and duration of mechanical ventilation (Schmidt et al. 2012).

Surfactant

The clinical surfactant treatment era started with the report by Fujiwara et al. in 1980 and has revolutionized neonatal respiratory care (Fujiwara et al. 1980). Since that time many strategies and therapies for surfactant application have been investigated. Studies focused on optimal surfactant preparation, dose, time, and method of administration.

Current recommendations are to apply natural surfactant preparations, to utilize a policy of early rescue surfactant therapy, and to consider the INSURE technique (INtubation, SURfactant, Extubation to CPAP). Extremely preterm infants who require intubation for stabilization in the delivery room should be given surfactant even before RDS is confirmed radiologically (Sweet et al. 2013).

A second and sometimes third intratracheal surfactant dose 6–8 h after the previous one should be given in case of ongoing oxygen requirement and need for mechanical ventilation. Immediately after surfactant application, a hyperoxic peak should be avoided by reducing oxygen supply. Although it has been shown that surfactant treatment significantly decreases mortality and air leak, one has to keep in mind that surfactant application itself bares a risk for air leak for a

brief period by reducing surface tension and improving compliance. Therefore, not only oxygen but also inspiratory pressure should be reduced after surfactant application when possible. Saturation target should be aimed between 90% and 95%, as lower oxygen saturations of 85–89% were shown to result in an increase of mortality in extremely preterm infants (SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network 2010b). Surfactant or surfactant lavages can also be applied in other situations such as severe meconium aspiration syndrome (MAS), as meconium inhibits surfactant function and surfactant treatment may decrease the need for extracorporeal membrane oxygenation (ECMO).

Perspective

Consistent use of antenatal corticosteroids, decreased exposure to mechanical ventilation, improvement of ventilation techniques, and new techniques of surfactant application have resulted in lower rates of RDS in neonates in the last years (Hallman 2013). However, many preterm infants still develop BPD despite the benefits of surfactant.

Recent techniques delivering surfactant intratracheally by using a fine catheter during spontaneous breathing on CPAP may be promising although data on long-term outcomes have yet to be evaluated.

An old idea of surfactant application without necessity of ventilation, which is currently reevaluated, is surfactant nebulization. If technically feasible, this form of surfactant treatment would be the most sophisticated and less invasive technique (Kribs 2011). Pilot trials on this issue are encouraging and randomized trials are presently ongoing.

Persistent Pulmonary Hypertension of the Newborn

Persistent pulmonary hypertension (PPHN) emerges from a failure to achieve the normal postnatal decline in PVR. In case of maximal manifestation, the right-to-left atrial and ductal shunting continue, leading to a circulatory pattern called “persistent fetal circulation” (PFC) with its typical pre-postductal difference of oxygen saturation, i.e., a much lower saturation postductal compared to the one preductal. PPHN appears as either idiopathic or as a contributing factor in various diseases like RDS, asphyxia, MAS, congenital heart defects, and lung hypoplasia especially in the cause of CDH (Lakshminrusimha and Steinhorn 1999). In spite of recent advances in therapy, PPHN still is a devastating disorder with a mortality exceeding 10% of all cases (Konduri and Kim 2009).

Etiology of PPHN

Hypoxia, an abnormal pulmonary vasculature and an elevated vascular reactivity, constitutes the characteristic features of PPHN. Vascular remodeling includes proliferation of the smooth muscles into the intra-acinar arteries (normally not muscular), an increased medial-wall thickness, where the smallest – normally muscle-free – arteries are most severely affected, and a substantial narrowing of the arterial lumen leading to a reduction of the total cross-sectional area of the pulmonary vascular bed. Besides, the adventitial connective tissue is markedly proliferated, which seems to be equally important in the development of PPHN (Murphy et al. 1981). Based on animal studies, one assumes that these structural changes are accompanied by defects in the NO and prostaglandin synthesis. In case of an inflammatory process, e.g., pneumonia, RDS, MAS, high levels of leukotrienes, thromboxane, and platelet-activating factor contribute to the missing reduction in PVR. Moreover, circulating levels of ET-1 are increased in case of PPHN (Gao and Raj 2010).

Diagnosing PPHN

Cyanosis is the striking clinical symptom of PPHN commonly in combination with respiratory distress. The suspected diagnosis is usually

confirmed by echocardiography, which allows for describing the hemodynamic profile of the infants, including estimation of pulmonary artery pressure by Doppler velocity measurement of tricuspid regurgitation jet, assessment of right ventricular function, and depiction of right-to-left atrial and ductal shunting. During treatment of PPHN, echocardiography is the determining diagnostic tool to decide about the choice of therapeutic interventions and evaluate the effects of therapy (Dhillon 2012). Right and/or left ventricular dysfunction with low output, leading to decreased oxygen transport to the periphery and acidosis, appears to be the major risk factor for poor outcome in infants with PPHN.

General Management of PPHN

General management mainly consists of mechanical ventilation, support of cardiac function, correction of systemic arterial hypotension, and maintenance of regular acid-base and electrolyte balance.

The goal of mechanical ventilation is establishment of an adequate lung expansion to ensure proper ventilation and to avoid the adverse effects of high or low lung volumes on PVR. In cases where appropriate lung recruitment is not achieved with conventional ventilation, the use of high-frequency oscillatory ventilation (HFO) is recommended. Hypoxia (enhancing pulmonary vasoconstriction) as well as hyperoxia (causing oxidative stress) should be avoided, and oxygen tension should be kept at a low normal range, i.e., 60–80 torr, to ensure adequate pulmonary blood flow (Konduri and Kim 2009). Gentle ventilation with moderate hypercapnia is worth considering to prevent further lung damage. Analgesia and sedation by use of morphine, fentanyl, or midazolam should be consistently applied to avoid stress reaction, which contributes to elevated PVR.

Acidosis must be eliminated as it can act as a pulmonary vasoconstrictor, whereas the use of alkalosis is still under controversy because long-term benefits have not yet been proven and its constricting effect on cerebral vessels, leading to reduced cerebral perfusion, is associated with worse neurodevelopmental outcome in survivors of PPHN (Konduri and Kim 2009). To stabilize right and left ventricular function and systemic hemodynamics, the application of volume, preferably balanced electrolyte solution, and inotropic and vasopressor agents often are necessary. Commonly, dobutamine, epinephrine, and noradrenaline are utilized.

ECMO is the treatment of ultima ratio being generally indicated if the oxygenation index ((mean airway pressure $\times$ FiO_2 $\times$ 100)/PaO_2) is above 40. While ECMO can be lifesaving in severe cases, its use is associated with potential side effects like intracranial hemorrhage and damage of the carotid artery.

Specific Medical Treatment

Pulmonary vasodilation can be achieved either by supporting the endogenous vasodilator capacity, i.e., increasing the levels of NO and PGI_2 or by antagonizing the effects of vasoconstricting agents, i.e., application of phosphodiesterase inhibitors like sildenafil and milrinone or the ET-1 receptor antagonist bosentan (see Table 1). Due to the complexity of the signaling pathways

Table 1 Mediators of pulmonary hypertension and medical approach

Support of endogenous vasodilator capacity		Antagonism of the effect of vasoconstricting agents	
Substance	Mode of action	Substance	Mode of action
NO	Increase of smooth muscle cGMP level	Sildenafil ($C_{22}H_{30}N_6O_4S$)	inhibition of PDE 5 with subsequent increase of intracellular cGMP
Prostacyclin ($C_{20}H_{32}O_5$)	Increase of smooth muscle cAMP level	Milrinone ($C_{12}H_9N_3O$)	Inhibition of PDE 3 with subsequent increase of intracellular cAMP
		Bosentan ($C_{27}H_{29}N_5O_6S$)	ET-1 receptor antagonism with attenuation of the vasoconstricting effect of ET-1

in PPHN, using combinations of therapies seems to be particularly promising.

Inhaled NO (iNO) is the mainstay of PPHN medication, since it causes immediate selective pulmonary vasodilation by increasing the intracellular cGMP levels in the smooth muscle. iNO improves the oxygenation within a few minutes after starting its application. Several randomized controlled trials revealed that iNO significantly reduces mortality and the need of ECMO in newborns with PPHN (Konduri and Kim 2009). iNO should be initiated with a dose of 20 ppm, although once established, lower doses of 6–10 ppm may suffice. During treatment, a close monitoring of methemoglobin, a toxic by-product of NO, is badly needed.

In cases of poor response to iNO, pulmonary dilation can be achieved by inhalative administration of PGI_2 (iloprost), which causes vasodilation by enhancing the cAMP levels in the smooth muscle cells therefore acting complementary to iNO.

As phosphodiesterases (PDE) are responsible for hydrolyzing cGMP to GMP (PDE 5) and cAMP to AMP (PDE 3), therefore inactivating these substrates and limiting the vasodilating effect of NO and PGI_2, the application of PDE inhibitors offers an additional benefit in the treatment of PPHN. Sildenafil is a selective inhibitor of PDE 5 and operates synergistically with NO by preserving the increased cGMP produced by NO. Sildenafil has to be administered orally with a starting dose of 0.25–0.5 mg/kg up to a maximum of 2 mg/kg/dose. Due to its short half-life, sildenafil should be delivered every 4 h (Porta and Steinhorn 2012).

Recent data indicate that milrinone, a selective PDE 3 inhibitor and therefore increasing the bioavailability of cAMP, has a special benefit in the treatment of PPHN, as it improves oxygenation even in the case of diminished response to iNO by both enhancing pulmonary blood flow as well as left and right ventricular output (McNamara et al. 2013). The usual dose by intravenous infusion ranges between 0.3 and 0.5 μg/kg/min.

The ET-1 receptor antagonist bosentan inhibits the vasoconstricting effect of ET-1. Bosentan has to be administered orally with a dose of 1 mg/kg twice a day. Data regarding the application in newborns are limited, and its benefit in improvement of oxygenation in case of PPHN is controversial (Mohamed and Ismail 2012; Steinhorn et al. 2016; More et al. 2016).

Conclusion and Future Directions

During fetal life a high level of lung distension, which is attained by both FBMs and the presence of lung fluid, is crucial for regular lung growth and structural maturation. Premature birth or a lack of FBMs and/or lung fluid causes infants to have structurally immature or abnormal lungs resulting in respiratory distress in combination with more or less pronounced pulmonary hypertension. Despite considerable advances in neonatal care, i.e., antenatal corticosteroids, surfactant application, and improvement of ventilation techniques, there is quite some evidence that those lungs will be persistently impaired during postnatal life. In many cases neonatal care comes too late to achieve further regular lung development. Therefore, major attempts should be made to prevent preterm birth on the one hand and to develop and improve intrauterine treatment strategies on the other.

Cross-References

- ▶ Congenital Diaphragmatic Hernia
- ▶ Extracorporeal Membrane Oxygenation for Neonatal Respiratory Failure
- ▶ Perinatal Physiology
- ▶ Pediatric Respiratory Physiology
- ▶ Specific Risks for the Preterm Infant

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