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Neonatal pulmonary physiology

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ABSTRACT

Managing pulmonary issues faced by both term and preterm infants remains a challenge to the practicing pediatric surgeon. An understanding of normal fetal and neonatal pulmonary development and physiology is the cornerstone for understanding the pathophysiology and treatment of many congenital and acquired problems in the neonate. Progression through the phases of lung development and the transition to postnatal life requires a symphony of complex and overlapping events to work in concert for smooth and successful transition to occur. Pulmonary physiology and oxygen transport in the neonate are similar to older children; however, there are critical differences that are important to take into consideration when treating the youngest of patients. Our understanding of fetal and neonatal pulmonary physiology continues to evolve as the molecular and cellular events governing these processes are better understood. This deeper understanding has helped to facilitate groundbreaking research, leading to improved technology and treatment of term and preterm infants. As therapeutics and research continue to advance, a review of neonatal pulmonary physiology is essential to assist the clinician with his/her management of the wide variety of challenging congenital and acquired pulmonary disease.

Managing pulmonary issues faced by both term and premature infants remains a challenge to the practicing pediatric surgeon. An understanding of normal fetal and neonatal pulmonary development and physiology is the cornerstone for understanding the pathophysiology and treatment of many congenital and acquired problems in the neonate. Pulmonary complications remain a major source of morbidity and mortality for neonates and represent an evolving area of pioneering research.

Normal lung development

The respiratory system consists of elements of air conduction and exchange. The uptake of oxygen from the environment and removal of carbon dioxide serve to maintain cellular aerobic metabolism and acid–base balance. In order to effectively perform these processes, normal structural and cellular development is essential. The respiratory system normally develops through five phases: embryonic, pseudoglandular, canalicular, saccular, and alveolar. The boundaries between these phases blend into each other with overlap at any given time point between areas of the lung and vary temporally among individuals.[1]

Embryonic phase (3–7 weeks)

Lung growth begins in the third week of gestation with the outgrowth of a small diverticulum from the ventral wall of the foregut called the primitive respiratory diverticulum or lung bud. This extends in the ventral caudal direction into the surrounding mesoderm, growing anterior and parallel to the primitive esophagus. Within a few days, the grove between the diverticulum and the foregut closes with the only luminal attachment remaining at the site of the future hypopharynx and larynx.[2] By gestational day 28, the respiratory diverticulum bifurcates into the right and left primary bronchial buds (main stem).[3] This is followed by a second round of branching occurring around the fifth week, yielding the secondary bronchial buds. Finally, the third branching takes place during the sixth week postconception, producing 10 tertiary bronchi on the right and eight on the left. The vascular components of the respiratory system also begin to develop with the pulmonary arteries forming as branches off the sixth aortic arch while the pulmonary veins emerge from the developing heart.[3] The primitive lung bud is lined by epithelium derived from endoderm, which will become the epithelium lining the airways and alveoli. The lung buds grow into the surrounding mesodermal cells that will differentiate into the blood vessels, smooth muscle, cartilage, and other connective tissue. Ectoderm will eventually give rise to the innervation of the lung.[1]

Pseudoglandular phase (5–17 weeks)

In the pseudoglandular phase, the lung is composed of multiple epithelial tubules surrounded by extensive regions of mesenchyme,

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giving a glandular appearance. Cellular proliferation rate increases during this stage and by postconception week 16, all bronchial divisions are completed with further growth occurring only by elongation and widening of existing airways. The intrapulmonary arterial system develops branching in parallel with the bronchial and bronchiolar tubules. The respiratory epithelium begins to differentiate with cilia appearing in the proximal airways and cartilage begins to develop to support the airways.[1] Concurrently, closure of the pleuroperitoneal folds is completed.

Canalicular stage (16–26 weeks)

During the canalicular stage, the capillary beds rapidly expand with condensation and thinning of the mesenchyme, starting the first critical step in the formation of the gas exchange regions of the lung. The ingrowth of capillaries results in thinning in one population of overlying epithelial cells, narrowing the air–blood interface, and differentiating into type I pneumocytes that make up the alveolar wall. In other overlying epithelial cells, lamellar bodies associated with surfactant synthesis appear, identifying type II pneumocytes. The airways continue to develop with completion of the airways through the level of the terminal bronchioles with their associated acinus.

Saccular stage (24–38 weeks)

The terminal clusters of acinar tubules and buds dilate and expand into transitory alveolar saccules and ducts with a marked reduction of the surrounding mesenchymal tissue. By 24 weeks, there is a sufficiently thin alveolocapillary membrane distance (0.6 μm) to participate in gas exchange with the efficacy of exchange being determined beyond this point by the total surface area available for exchange.[3] By the end of this stage, three additional generations of alveolar ducts have formed and the conducting airways have developed mucous and ciliated cells. Overall, cell proliferation slows and ultrastructural cytodifferenitation occurs. The saccules consist of smooth-walled airspaces and a thick interstitial space. Type II epithelial cells continue to mature and there is an increase in surfactant synthesis, but overall synthesis levels remain low.

Alveolar stage (36 weeks–8 years)

This is the final stage of lung development and is characterized by the formation of secondary alveolar septa that divide the terminal ducts and saccules into true alveolar ducts and alveoli. There is maturation of the alveolar–capillary membrane, which increases the surface area for gas exchange. As the terminal saccule restructures during this stage the double capillary networks fuse, becoming a single capillary network with each capillary being simultaneously exposed to at least two alveoli. The barrier to gas exchange thins to a few nanometers. Type I and type II cells increase in number, but only type II cells are proliferating actively suggesting that type I cells are derived from type II cells.[3] When alveolization is complete by 8 years of age, further lung growth occurs by increasing alveolar size.

Glucocorticoids

A major advance in the treatment of prematurity has been the maternal administration of glucocorticoids in pregnant women with preterm labor after 24 weeks in order to promote surfactant production and maturation of the fetal lung.[4,5] The exact mechanism remains unknown; however, studies have shown that anatomic maturation, in particular thinning of the alveolar wall, and synthesis of mRNAs encoding surfactant proteins increase after steroid administration.[6–8]

Physiologic control of lung growth before and after birth

While the fetus and neonate proceed through the phases of lung growth and development, physiologic and physical factors play an important role in directing this growth. While not all factors affecting this process are well understood, the role of fetal lung fluid and mechanical distension appear to play critical roles. During fetal life, the lung produces a unique fluid, fetal lung fluid (FLF), that is a result of net transpithelial chloride and sodium flux and is produced within the lungs and leaves via the trachea.[9] As the fluid moves from the lung toward the oropharynx, it is either swallowed or contributes to amniotic fluid. Throughout gestation the volume of FLF increases[10] and keeps the airway distended in order to stimulate growth.

The volume of FLF is primarily regulated by the resistance to lung liquid efflux through the upper airways and by fetal breathing movements (FBM), which include the associated diaphragmatic activity, and is largely independent of production. When there is no FBM (apnea), the transpulmonary pressure is usually 1–2 mmHg above the amniotic sac pressure due to the elastic recoil of the chest wall. Lung fluid efflux is prevented by high resistance of the upper airways which prevents FLF loss and maintains an approximately 2 mmHg distending pressure and fetal lung expansion.[11] During periods of FBM, the larynx actively dilates to decrease the resistance to FLF efflux, allowing fluid to leave at an increased rate. To compensate during periods of FBM, rhythmic contraction of the diaphragm slows the loss of lung fluid and helps to maintain lung expansion during periods of low upper airway resistance, demonstrating that FBM serve to maintain lung expansion and promote lung growth. Sustained reduction of fetal lung expansion can slow the structural development of both the vascular bed and alveolar epithelial cell phenotypes. On the other hand, prolonged overexpansion of the fetal lungs via tracheal occlusion is a potent stimulator for fetal lung growth and tissue remodeling.[12] Additionally, it has been observed that fetal airways undergo peristaltic contractions similar to the gut, which move intraluminal contents distally and cause expansion of end buds, which also likely play a role in fetal lung growth and expansion.[13]

Gas exchange and oxygen transport and delivery

The most important function of the respiratory system is to uptake oxygen from the environment in order to allow for aerobic metabolism to meet the changing energy demands of the fetus and neonate. In neonates, the ability to receive adequate oxygen delivery depends on the partial pressure of oxygen in inspired air, ventilation and perfusion matching, hemoglobin concentration and affinity, cardiac output, and blood volume.[14] While the fetal oxygen transport system is set up to provide optimal oxygen delivery and has the capacity to adjust delivery to match demand in the setting of the intra-uterine environment, this system can be stressed as it adjusts to life outside the womb. The delivery of oxygen to tissues depends on the pressure gradient between the blood and the mitochondria and varies with regional oxygen delivery, tissue oxygen consumption, and hemoglobin–oxygen affinity.

Oxygen is transported through the blood stream either dissolved in aqueous solution or bound to hemoglobin. Arterial oxygen content can be calculated using the following formula: arterial oxygen content = (Hgb × 1.36 × SaO_2) + (0.0031 × PaO_2), where Hgb is hemoglobin concentration in grams, SaO_2 is