9 Transition to Extrauterine Life

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Introduction

The transition from intrauterine to extrauterine life is a complex process involving virtually every organ system in the body. The most dramatic changes are seen in the lung and the cardiovascular system, resulting in the transition from placental to pulmonary gas exchange. Failure to adequately make this transition can be life-threatening and these infants often require supportive care. In order to select the optimal intervention, it is essential to understand the normal physiology of respiratory and cardiovascular transition. It is important to realize that most data on neonatal transition are obtained from animal studies, because of the limitations in studying human fetuses and newborn infants at this critical time.

Respiratory Transition

The Fetal Lung

During intrauterine development the fetal lungs are filled with fluid, receive little blood flow, and take no part in gas exchange. Experimental studies in fetal sheep have shown that lung fluid is produced by the pulmonary epithelium as the net result of active chloride secretion via Cl^- channels and relatively low reabsorption activity of Na^+ channels. There is some efflux of liquid from the lung via the trachea, but this process is restricted by the fetal upper airway (mainly the glottis), thereby promoting the retention of fluid and causing a continuous distending pressure within the fetal lungs, which is critical to normal lung growth and development. Besides lung fluid, fetal breathing movements, which start as early as 10 weeks' gestation, also play an important role in maintaining fetal lung distension. During fetal breathing movements rhythmic contractions of the diaphragm seem to oppose the pulmonary recoil pressure, thereby preventing lung deflation. Although never directly measured in humans, animal studies indicate that the fetal lung volume is probably at or above functional residual capacity (FRC), i.e., the volume that remains inside the lung after a normal expiration. Fetal lung distension and the associated lung tissue stretch is an essential stimulus for normal lung growth and structural development. Studies in fetal lambs have shown that a reduction (lung liquid drainage, absent fetal breathing) or an increase (tracheal occlusion) in lung expansion causes, respectively, a decrease or an increase in lung growth.

As the fetal lung slowly matures to an organ capable of extrauterine gas exchange, it undergoes enormous structural and biochemical changes. Structurally, the lung passes through four developmental stages: the pseudoglandular (5–17 weeks), the canalicular (16–26 weeks), the saccular (24–38 weeks), and finally the alveolar stage (36 weeks 2 years). The most important hallmark of the biochemical maturation is the formation of pulmonary surfactant. Lamellar bodies – containing pulmonary surfactant – in the type II pneumocytes appear between 20 and 24 weeks' gestation, but actual secretion is delayed until 30 weeks' gestation. Besides playing a role in host defense, the most important function of pulmonary surfactant is stabilization of the alveoli after birth when air has entered the lung and the alveolar surface tension has greatly increased by the creation of an air–liquid interface.

As the fetal lung grows and matures, intrauterine gas exchange is governed by the placenta. It is important to realize that, compared to extrauterine life, the fetus lives in a relatively hypoxemic environment with arterial oxygen saturation of approximately 60%.

Clearance of Lung Fluid at Birth

In order to make the transition from placental to pulmonary gas exchange successful, fluid need to be cleared rapidly from the newborn lung. Although the precise mechanisms are still unclear, animal and a few human studies have provided some of the answers.

With the onset of labor, there is a dramatic change in the transepithelial ion and fluid movement in the fetal lung. The pulmonary epithelial cells stop secreting and start reabsorbing lung liquid by activating the so far dormant epithelial sodium channels. This shift from fluid

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excretion to absorption seems to be mediated by epinephrine, which is secreted in large amounts by the fetus at the onset of labor. Maternal thyroid hormone and glucocorticoids also play an important role by augmenting the absorptive response to epinephrine.

During labor, intrauterine pressures can increase up to 75 cmH_2O and these pressures are transmitted to the fetus causing changes in fetal posture and chest wall configuration. As a result, the intra-abdominal and intrathoracic pressures increase leading to an efflux of lung fluid. As the infant passes through the distal part of the birth channel, the pressure on the thorax may increase to as much as 200 cmH_2O, causing further egress of lung fluid (vaginal squeeze).

Despite these prenatal mechanisms promoting lung liquid clearance, the lungs and airways are still filled with fluid prior to the first breath after birth. Studies in rabbit pups using phase contrast imaging have shown that the entry of air into the airways is an essential part for completing the process of liquid clearance. As air enters the airways, fluid is pushed distally and moves into the interstitial compartment where it is gradually cleared via the pulmonary circulation and lymphatics.

Aeration of the Lungs After Birth

The basic goal of lung aeration after birth is to replace lung liquid by air and to build up a normal FRC of about 30 ml/kg of body weight. Although many theories such as thoracic recoil, frog breathing, and pulmonary capillary erection have been postulated to explain the start of lung aeration in spontaneously breathing newborn infants, it is now believed that the most important mechanism for air entry is the generation of a negative transpulmonary pressure via an inspiratory effort of the infant. Studies in newborn infants have shown that this inspiratory effort during the first breath consists of a diaphragmatic contraction and results in mean subatmospheric intrathoracic pressure of 52 cmH_2O (range 28–105 cmH_2O) producing a mean tidal volume of 38 ml (range 6–69 ml). Immediately after the first inspiration, expiration is postponed by closure of the upper airways (glottis), which prevents the inspired air to escape. This process, also called expiratory breaking, generates a high positive intrathoracic pressure (mean 71 cmH_2O, range 18–115 cmH_2O) during expiration, which facilitates the distribution of air within the lung and promotes lung liquid clearance. Following this first breath, almost half of the inspired tidal volume is maintained in the lung. It usually takes several hours to achieve a normal FRC.

The moment air enters the lung, it creates an air–liquid interface at the alveolar level, which greatly increases the surface tension and thereby the elastic recoil force of the lung. This increased recoil force tends to collapse the lungs as it encounters little resistance from the relatively compliant newborn chest wall. Pulmonary surfactant which lines the alveolar surface helps to counteract this tendency by reducing the surface tension. Normally surfactant is already present in the lung during the transition at birth, as it is secreted in the lung liquid from 30 weeks' gestation. Alveolar stretch during tidal breathing after birth results in the secretion of large quantities of surfactant from the type II pneumoctyes in the alveolar space. The newborn infant also maintains end-expiratory lung volume by extending the process of expiratory breaking beyond the first breath after birth. Studies in term newborn infants have shown that 90% of the breaths in the first minutes after birth contain some form of expiratory breaking, such as crying and grunting.

As mentioned previously, the placental gas exchange provides a hypoxemic fetal environment compared to the postnatal conditions. Studies in healthy vigorous term newborn infants have shown that oxygen saturation measured by pulse oximetry gradually increases from a median saturation of 65–70% at 1 min to 85–92% at 5 min and do not reach 95% until 7–10 min of life. However, many normal healthy term newborns do not reach saturation of 90% until after 10 min of life. Data on carbon dioxide (PCO_2) changes after birth in term newborn infants are limited, but seem to indicate that PCO_2 remains stable at approximately 50 mmHg during the first 5 min of life, after which there is a steady decline toward 40 mmHg at 30 min after birth.

Respiratory Transition in Preterm Infants

There are several reasons why preterm infants have an increased risk for failing to achieve normal respiratory transition at birth. First, studies in fetal sheep have indicated that the epinephrine-induced reabsorption of fetal lung liquid during labor is compromised during preterm delivery. Studies in preterm infants with respiratory distress syndrome also showed a reduced sodium transport capacity in the nasal epithelial cells. This less efficient prenatal clearance of lung liquid may hinder aeration of the preterm lung at birth. The fact that many preterm newborn infants are born by cesarean delivery contributes to these problems (see below).

Second, the preterm infants' muscle strength is often insufficient to create the high inspiratory pressures

needed to aerate the lungs during the first breaths. The highly compliant chest wall deforms during diaphragmatic contraction, thereby limiting the inspired tidal volume. Due to the deficit of pulmonary surfactant and the high chest wall compliance, preterm infants are unable to effectively counteract the high recoil forces of the lung, which reduces the lung gas volumes at the end of expiration (FRC). This is probably the reason why preterm infants frequently continue to use expiratory breaking during spontaneous breathing (manifested as grunting).

Finally, the preterm lung is structurally immature with the lungs of most infants still being in the saccular stage. This will reduce lung surface area and thus compromise gas exchange.

Today, most preterm infants receive antenatal steroids, which stimulate both the structural and biochemical (surfactant) maturation of the lung and the prenatal clearance of lung liquid in response to epinephrine. This way many preterm infants are now able to successfully aerate their lungs at birth and create a stable FRC with only nasal continuous positive airway pressure.

Due to the above mentioned differences in respiratory transition between preterm and term infants, most preterm infants will take a longer time to reach a preductal oxygen saturation of 90% (preterm 6.5 min vs term 4.7 min). In contrast to term infants who often do not need supplemental oxygen during their transition, greater proportion of the preterm infants less than 30 weeks' gestation need supplemental oxygen at some point during their transition.

Most preterm infants will need some supportive care during their respiratory transition after birth. Studies in preterm rabbit pups have shown that supporting the first breath with positive pressure at the airway opening using prolonged inspiration time (sustained inflation) and a positive end-expiratory pressure (PEEP) facilitates lung aeration. Applying this strategy in preterm infants significantly reduces the need for intubation in the delivery room and within 72 h of age. It is, however, important to realize that this support needs to be accurately tailored to the needs of each individual infant because inappropriate ventilator support (high tidal volumes, insufficient PEEP) during the first minutes after birth can cause irreversible lung injury which increases the risk for bronchopulmonary dysplasia (BPD).

Several randomized controlled trials have shown that restoring the surfactant function in preterm infants by administration exogenous surfactant soon after birth (prophylactic use) improves lung function and reduces mortality.

Respiratory Transition After Cesarean Section

Several studies have documented the high incidence of respiratory distress and neonatal intensive care admission in infants born by Cesarean section (CS) before the onset of spontaneous labor (elective CS). There are strong indications that this increased risk for pulmonary morbidity is caused by an abnormal respiratory transition.

As mentioned previously, lung liquid clearance starts before birth in response to the epinephrine surge at the onset of labor. Studies in fetal rabbits have shown that absence of labor and thus epinephrine results in excessive retention of lung fluids. Studies in infants with transient tachypnea of the newborn are consistent with this finding showing an immaturity of the transepithelial sodium transport.

Lung liquid clearance is facilitated by the intrauterine contractions prior to delivery and the vaginal squeeze as the infants passes through the birth canal. During elective CS, intrauterine contractions are absent and a study in newborn infants showed that the delivery pressures are halved compared with vaginal delivery. In addition, significantly fewer infants born by CS retained air at the end of their first breath. This probably explains the slower increase in postnatal oxygen saturation in newborn infants delivered by CS.

Cardiovascular Transition

The Fetal Circulation

The fetal circulation differs considerably from the extrauterine circulation because the placenta and not the lung provides intrauterine gas exchange. Placental oxygenated blood needs to be directed to the left side of the heart as efficiently as possible and poorly oxygenated blood returning to the right side of the heart needs to be directed to the placenta without passing through the liquid-filled lungs. This is accomplished by the presence of central shunts via the foramen ovale and the ductus arteriosus. After passing through the umbilical vein and the ductus venosus, oxygenated blood returning from the placenta enters the right atrium via the medial aspect of the inferior vena cava. The latter facilitates oxygenated blood to cross the foramen ovale into the left atrium. The left ventricle delivers the majority of its output to the heart, brain, and upper body for optimal oxygen use. Poorly saturated blood returning from the upper body via the superior vena cava and the lower body via the lateral aspect of the

inferior vena cava predominantly crosses the tricuspid valve. Most of the right ventricular output passes through the patent ductus arteriosus into the distal aorta and reaches the placenta via the umbilical arteries. Studies in fetal lambs have shown that only 8–10% of the right ventricular output passes through the lung. In human fetuses, this percentage increases from 13% at 20 weeks to approximately 20–25% in the third trimester. The main reason for the right ventricular output to bypass the lungs via the ductus arteriosus is the relatively high pulmonary vascular resistance compared with the low systemic vascular resistance. It has been suggested that the high pulmonary vascular resistance is caused by compression of small pulmonary arteries by the liquid filling the alveolar space, but hypoxic pulmonary vasoconstriction mediated through several vasoactive substances is the most important mechanism. The placenta is the biggest contributor to the low systemic vascular resistance.

Transitional Changes at Birth

For a successful transition from placental to pulmonary gas exchange at the time of birth, lung liquid clearance and aeration needs to be accompanied by a rapid increase in pulmonary perfusion. This means that the intrauterine central right-to-left shunts must close or reverse, a process triggered by a fall in pulmonary vascular resistance and an increase in systemic vascular resistance.

The fall in pulmonary vascular resistance, resulting in an eight- to tenfold increase in pulmonary blood flow at birth, is caused by physical changes at lung expansion and the concomitant increase in oxygenation. Studies in fetal lambs have shown that lung expansion decreases PVR by unkinking of small pulmonary arteries and by exerting a direct dilating effect on these same vessels via the increased alveolar surface tension at the air–liquid interface. In addition, pulmonary vascular resistance is decreased by the stretch-induced release of prostaglandins (PGI_2, PGD_2).

Oxygenation causes pulmonary vasodilatation via the synthesis of nitric oxide (NO), although the exact stimuli for NO production are not yet fully defined.

The systemic vascular resistance increases as soon as the umbilical cord is clamped and the low-resistance placental circulation is cut off. This will further decrease the ratio between the pulmonary and systemic vascular resistance and increase pulmonary perfusion.

Studies in newborn infants have also shown a rapid decrease in the ratio between pulmonary and systemic arterial pressure during the first 12–24 h after birth. This was accompanied by a decrease in ductal right-to-left shunt and an increase in left-to-right shunt. In most term infants, the ductus arteriosus will close within 48 h after birth. As soon as pulmonary blood flow increases, the left atrial filling pressure becomes higher than the right atrial filling pressure, causing the foramen ovale to close functionally; anatomical closure occurs days to weeks later.

Cardiovascular transition also results in a significant increase in cardiac output. Although the precise mechanisms responsible for this increased output are not fully understood, several explanations have been suggested. First, studies in fetal lambs have shown a thyroid hormone mediated increase beta-adrenoreceptor responsiveness during the last weeks of pregnancy, which potentiates the ability of the heart to increase its output in response to the catecholamine surge that occurs at birth. Second, the decrease in right ventricular afterload after birth probably reduces the constraining effect of the right ventricle on the left ventricle, allowing the latter to contract more efficiently in response to the large increase in preload at birth. Finally, cardiac output is probably stimulated by the increased cardiorespiratory and thermoregulatory work after birth.

Animal studies and human data clearly demonstrate that the process of labor is also important for cardiovascular transition. Labor results in key changes in the hormonal milieu of the fetus and impacts on the key mechanisms responsible for postnatal fall in pulmonary vascular resistance. Slower fall in pulmonary vascular resistance and increased incidence of persistent pulmonary hypertension have been documented in infants born by elective Cesarean delivery without labor, compared to infants born vaginally.

It is clear from the above that cardiovascular transition is a complex process consisting of several physical and biochemical changes. Failure of just one of these changes can jeopardize normal cardiovascular transition and lead to severe disease states such as persistent pulmonary hypertension of the newborn (see Chap. 15, "Respiratory System").

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