Physiology of Transition from Intrauterine to Extrauterine Life

Noah H. Hillman, MD, Suhas G. Kallapur, MD, Alan H. Jobe, MD, PhD *

KEYWORDS

• Corticosteroids • Catecholamines • Lung function • Cardiovascular
• Cesarean section

KEY POINTS

• The transition from fetal to extrauterine life is the summation of multiple rapid organ adaptations that often have redundant mediators.
• The primary mediators that both prepare the fetus for birth and support the multiorgan transitions are cortisol and catecholamines.
• Lung adaptation requires the coordinated clearance of fetal lung fluid, surfactant secretion, and the onset of consistent breathing.
• Cardiovascular transition requires striking changes in blood flow, pressures, and pulmonary vasodilation.
• Abnormalities in adaptation are frequent following preterm birth or delivery by cesarean section at term.

OVERVIEW

The transition from a fetus to a newborn is the most complex physiologic adaptation that occurs in human experience. Before medicalization of delivery, the transition had to occur quickly for survival of the newborn. All organ systems are involved at some level, but the major immediate adaptations are the establishment of air breathing concurrently with changes in pressures and flows within the cardiovascular system. Other essential adaptations are striking changes in endocrine function, substrate metabolism, and thermogenesis (Box 1). Hospital-based deliveries increase the difficulties for transition for many fetuses because of the frequent use of cesarean sections, deliveries before the onset of labor, rapid clamping of the cord, and the anesthetics and analgesics associated with these hospital deliveries. The net result is the...

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frequent need to assist the newborn with the birth transition. Preterm deliveries cause particular difficulties for transition and expose the preterm infant to lung injury from mechanical ventilation. These components of the fetal to neonatal transition are reviewed for preterm and term deliveries.

ENDOCRINE ADAPTATIONS TO BIRTH

Cortisol

Cortisol is the major regulatory hormone for terminal maturation of the fetus and for neonatal adaption at birth. The “cortisol surge” is initiated with the switch from maternal-transplacental–derived corticosteroids to the ability of the fetal adrenal to synthesize and release cortisol under fetal hypothalamic control. Fetal cortisol levels in the human are low (5–10 μg/mL) relative to normal cortisol levels until about 30 weeks’ gestation. Cortisol levels progressively increase to about 20 μg/mL by about 36 weeks’ gestation and increase further to about 45 μg/mL before labor at term. Cortisol increases further during labor to peak at high levels of about 200 μg/mL several hours after term delivery. The increase in fetal cortisol throughout late gestation supports multiple physiologic changes that facilitate normal neonatal adaption. For example, over the final weeks of gestation, the conversion of T₄ to T₃ increases, catecholamine release by the adrenal and other chromaffin tissues increases, glucose metabolic pathways in the liver mature, gut digestive capacity increases (enzyme induction), β-adrenergic receptor density increases in many tissues, including the heart and the lungs, and the surfactant system in the lungs is induced to mature. Cortisol, in association with increasing thyroid hormones, activates the sodium pump that clears fetal lung fluid at birth. These cortisol-modulated changes are normally a progressive process of preparation for birth as the cortisol levels rise before birth then peak soon after delivery. This normal increase in cortisol supports an integrated transition following birth (Box 2). Cesarean section without labor at term blunts

<p>| Box 1 |</p>
<table>
<thead>
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<th>Essential components for a normal neonatal transition</th>
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<tr>
<td>• Clearance of fetal lung fluid</td>
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<td>• Surfactant secretion and breathing</td>
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<td>• Transition of fetal to neonatal circulation</td>
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<td>• Decrease in pulmonary vascular resistance and increased pulmonary blood flow</td>
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<td>• Endocrine support of the transition</td>
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<p>| Box 2 |</p>
<table>
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<th>Some effects of cortisol on factors contributing to a normal fetal-to-newborn transition</th>
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<tr>
<td>• Lung maturation: anatomy and surfactant</td>
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<tr>
<td>• Clearance of fetal lung fluid</td>
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<tr>
<td>• Increased β receptor density</td>
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<tr>
<td>• Gut functional maturation</td>
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<tr>
<td>• Maturation of thyroid axis</td>
</tr>
<tr>
<td>• Regulate catecholamine release</td>
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<td>• Control energy substrate metabolism</td>
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the postnatal rise in cortisol, and the cortisol responses to preterm birth also are attenuated because of unresponsiveness and immaturity of the adrenal gland. A particularly stressful delivery can uncover a "functional" adrenal insufficiency if the adrenal gland cannot respond to the increased stress. The very preterm infant may have low cortisol levels around birth with symptoms, such as low blood pressure, that are responsive to cortisol treatment. In contrast, antenatal exposure to chorioamnionitis may increase fetal cortisol levels before delivery.

### Catecholamines

Despite the enthusiasm of clinicians to use catecholamine infusions to increase the blood pressure of very preterm infants following birth, the normal physiology of endogenous catecholamines during and after birth are not reviewed in recent neonatology textbooks. The term human fetus can release catecholamines (norepinephrine, epinephrine, and dopamine) from adrenal medullary and other sympathetic tissues in response to fetal stresses of various sorts, as evaluated by catecholamine values in cord blood. The preterm fetus has higher cord catecholamine levels than the term fetus, and cesarean delivery is associated with lower cord catecholamine levels. The details of the catecholamine responses to term and preterm labor and delivery were characterized elegantly by Padbury and colleagues in a series of reports beginning in the 1980s. Using catheterized fetal sheep that were transitioned through delivery, they demonstrated that norepinephrine and epinephrine increase to high levels within minutes of term delivery and cord clamping. In contrast, the catecholamines increased more slowly following preterm delivery but to levels that were about threefold higher for norepinephrine and fivefold higher for epinephrine than after term delivery (Fig. 1). The lower increases in catecholamines in the term newborn were associated with larger increases in plasma glucose and free fatty acids than in the preterm. Careful measurement of thresholds for responses of fetal sheep to epinephrine and norepinephrine infusion demonstrated that the term fetus had lower thresholds and greater responses for blood pressure, glucose, and free fatty acid increases than did the preterm fetuses. The catecholamine increases at delivery resulted primarily from adrenal release as adrenalectomy ablated the increase in epinephrine and norepinephrine and blunted blood pressure, glucose, and fatty acid increases and pulmonary adaption. The fetus is in part protected from the cardiovascular and metabolic effects of stress-mediated catecholamine release because the placenta increases catecholamine clearance.

These studies demonstrate the importance of a large catecholamine release as a normal response to the birth process for fetal adaption. The catecholamine surge is primarily responsible for the increase in blood pressure following birth, adaption of energy metabolism with support of the primary substrates for metabolism after birth (glucose and fatty acids), and for initiating thermogenesis from brown fat. The preterm secretes more catecholamines because the organ systems are less responsive: higher concentration thresholds for response and lower responses. Cesarean section of the unlabored fetus depresses catecholamine release. Catecholamine release at birth can be viewed as the "gas" that drives the adaptive responses. However, fetal exposure to cortisol is the "carburetor" that is the potent regulator of the responses of the newborn to catecholamines. Antenatal corticosteroid treatments decrease catecholamine levels in preterm infants compared with unexposed infants. Cortisol treatments of fetal sheep also greatly decrease the postnatal increase in both norepinephrine and epinephrine (Fig. 2). Nevertheless, the animals had better cardiovascular and metabolic adaptation to preterm birth. These studies demonstrate the importance of both cortisol and catecholamines to adaptations to birth.
Fig. 1. Catecholamine response to delivery of term lambs, preterm lambs, and term lambs following adrenalectomy. Fetal term (145 ± 2 day gestation) and preterm (130 ± 1 day gestation) lambs were delivered at 0 time following fetal catheter placement. The adrenalectomy lambs had adrenal glands removed at 138 ± 1 days and received continuous cortisol supplemental until delivery at 142 days' gestation. Epinephrine and norepinephrine values are expressed relative to the values measured 10 minutes before delivery. (A) Epinephrine increased about 12-fold over the –10-minute value for the term lambs, and this increase was ablated by adrenalectomy. The increase in epinephrine was much larger for the preterm lambs. (B) There was a similar pattern for the norepinephrine responses. (C) Blood pressure increased in term and preterm animals but not in term adrenalectomized animals. (D, E) Glucose and free fatty acids in blood increased more for term than preterm lambs with minimal increases following adrenalectomy. (Data from Padbury JF, Polk DH, Newnham JP, et al. Neonatal adaptation: greater sympathoadrenal response in preterm than full-term fetal sheep at birth. Am J Physiol 1985;248:E443–9; and Padbury J, Agata Y, Ludlow J, et al. Effect of fetal adrenalectomy on catecholamine release and physiologic adaptation at birth in sheep. J Clin Invest 1987;80:1096–103.)
Other vasoactive substances, such as angiotensin II and rennin, also increase greatly at birth in association with increases in blood pressure. The net effect is the normal exposure of the newborn to very high levels of multiple vasoactive substances to support adaption. The basic physiology of these agents was described more than 20 years ago in animal models, with confirmation in term and moderately preterm infants. Much of this work could be profitably repeated for extremely low birth weight infants to better understand how their catecholamine responses to preterm birth may be dysregulated and to better target therapies. For example, Ezaki and colleagues recently reported that very low birth weight infants with severe hypotension had a decreased conversion of dopamine to norepinephrine.

**Thyroid Hormones**

The thyroid axis matures in late gestation in parallel to the increase in cortisol with increased thyroid simulating hormone (TSH), T₃ and T₄ levels, and decreased rT3 levels as term approaches. Following term birth, TSH quickly peaks and decreases, and T₃ and T₄ increase in response primarily to the increased cortisol, to cord clamping, and to the cold stimulus of birth. Acute ablation of thyroid function at birth did not greatly alter thermogenesis or cardiovascular adaptation in experimental animals. However, inhibition of thyroid function more chronically before birth did interfere with postnatal cardiovascular adaptation and thermogenesis in newborn lambs.**

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**Fig. 2.** Antenatal cortisol alters postnatal catecholamine secretion and blood pressure responses to delivery in preterm lambs. Fetal sheep had vascular catheters placed at 122–125 days’ gestation, and the fetuses were randomized to a 60-hour cortisol or vehicle infusion at 128 days’ gestation. The fetuses were delivered and supported on mechanical ventilation. During transition, epinephrine (A) and norepinephrine (B) increased more in control lambs than in cortisol-exposed lambs. Nevertheless, blood pressure (C) was higher in the cortisol-exposed newborns than the control animals. (*Data from* Stein HM, Martinez A, Oyama K, et al. Effect of corticosteroids on free and sulfoconjugated catecholamines at birth in premature newborn sheep. Am J Physiol 1995;268:E28–32.)

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These results demonstrate a supportive and preparative role for thyroid hormones for birth rather than as acute modulators of endocrine adaptation to birth. For example, fetal infusions of T₃ and cortisol can activate the Na⁺, K⁺, ATPase that helps clear fetal lung fluid after birth. Term infants with congenital hypothyroidism generally do not have abnormalities of early neonatal adaptation that are evident in the controlled environment of hospital deliveries. Very preterm infants have a blunted thyroid functional transition from fetal to newborn life with very low levels of plasma T₃ and T₄ relative to term infants. The effects of the depressed thyroid function on the early postnatal transition in the preterm are unclear but probably contribute to the depressed adaptive behavior of the preterm.

**METABOLIC ADAPTATIONS**

**Energy Metabolism**

Fetal energy needs are supported primarily by the transplacental transfer of glucose to the fetus. Although the fetal liver is capable of gluconeogenesis from early gestation, gluconeogenesis is minimal during normal fetal homeostasis. Rather, as term approaches, glucose and other substrates are being stored as glycogen and fat in anticipation of birth in the high insulin and low glycogen fetal environment. With delivery and cord clamping, the maternal glucose supply is removed, and plasma glucose levels normally fall over the early hours after birth. The glucose and free fatty acid levels are accompanied by a fall in insulin, and increase in glycogen, the normal glucose homeostatic hormones. However, the large catecholamine release and increase in cortisol are probably the major acute regulators of plasma glucose and free fatty acid levels in the immediate newborn period. For example, adrenalectomy of the fetal sheep who received cortisol replacement blunts and delays the postdelivery increase in plasma free fatty acids and results in persistent hypoglycemia (see Fig. 1). Fetal treatments with cortisol decrease the catecholamine surge at birth, but increase both plasma glucose, and free fatty acids relative to control animals (see Fig. 2). Therefore, the metabolic adaptations to birth are regulated by acute changes in insulin and glucogen, but also by catecholamines and cortisol in term infants.

Cortisol and catecholamine responses to preterm birth are dysregulated with less cortisol and more catecholamine release. The preterm also has minimal glycogen and fat stores. Therefore, the availability of energy substrates during the birth transition will be severely challenging for the preterm. This aspect of adaptation in the immediate newborn period is treated routinely with glucose infusion to prevent hypoglycemia; however, the integrated effects of the endocrine abnormalities and responses to glucose infusions have not been well described in extremely low birth weight infants.

**Thermoregulation**

Fetal body temperature is about 0.5°C above the maternal temperature. Although the fetus produces heat from metabolism, that heat is effectively dissipated across the placenta and fetal membranes. At birth, the sympathetic release resulting from the redundant stimuli of increased oxygenation, ventilation, cord occlusion, and a cold stimulus to the skin activates thermogenesis by brown adipose tissue. This thermogenic response potential has developed during late gestation by an increase in brown adipose tissue around the kidney and in the intrascapular areas of the back to become about 1% of fetal weight at term. Brown adipose tissue generates heat by uncoupling oxidative metabolism from ATP synthesis in the mitochondria, with the release of heat. This uncoupling is mediated by the mitochondrial membrane protein uncoupling protein 1 (UCP1), which is activated by norepinephrine released by the
sympathetic innervation of brown adipose tissue. UCP1 levels increase in the brown adipose tissue during late gestation in response to a local conversion of T4 to T3 and to induction of UCP1 synthesis in response to the increasing cortisol levels in the fetal plasma as term approaches. Thus, the same hormones that modulate the fetal preparation for birth and the transition period are central to thermogenesis by brown adipose tissue. The term infant also can generate some heat by shivering thermogenesis, which is an increase in nonpurposeful skeletal muscle activity signaled by cutaneous nerve endings via central motor neurons. Shivering thermogenesis seems to be of secondary importance to the newborn human. The preterm human is at a major disadvantage for thermoregulation following birth, as brown adipose tissue has not developed in quantity or response potential for a cold stress.

CARDIOVASCULAR ADAPTATIONS

Profound changes in the cardiovascular system occur after delivery in response to removal of the low resistance placenta as the source of fetal gas exchange and nutrition. Much of our knowledge regarding cardiovascular adaptation after birth is based on studies in animals, particularly sheep. The major changes are an increase in the cardiac output and transition of fetal circulation to an adult-type of circulation. Increased cardiac output is required to provide for increases in basal metabolism, work of breathing, and thermogenesis. In the close-to-term fetus, the combined ventricular output is about 450 mL/kg/min, with the right ventricular output accounting for two-thirds of the cardiac output and the left ventricle ejecting one-third of the cardiac output.20 Soon after birth, the circulation changes from “parallel” to “series,” where the right ventricular output equals the left ventricular output. The cardiac output nearly doubles after birth to about 400 mL/kg/min (for the right and the left ventricle). This marked increase in cardiac output parallels closely the rise in oxygen consumption. The organs experiencing increased blood flow after birth are the lungs, heart, and kidney, and the gastrointestinal tract.21 Although the precise mechanisms mediating increased cardiac output after birth are not known, the increase in cortisol and vasoactive hormones, which include catecholamines, the rennin-angiotensin system, vasopressin, and thyroid hormone, contribute to support of blood pressure and cardiovascular function.20

In the fetus, the relatively well-oxygenated blood from the placenta is delivered via the umbilical cord and ductus venous. This ductus venous blood enters the right atrium from the inferior vena cava and is directed preferentially to the left atrium by the foramen ovale and subsequently delivered preferentially to the brain and the coronary circulation by the fetal left ventricle. The right ventricle is the predominant ventricle in the fetus, and most of the right ventricular output goes to the descending aorta via the ductus arteriosus because very little blood enters the pulmonary circulation. With birth and removal of the low resistance placenta, blood flow increases to the pulmonary circulation. Shortly after birth, functional closure of the ductus arteriosus begins. The mechanisms contributing to the high pulmonary vascular resistance in the fetal lung are primarily the low oxygen tension and low pulmonary blood flow, which suppresses the synthesis and release of nitric oxide (NO) and prostaglandin I2 from the pulmonary endothelium.22 Fetal exposure to hypoxia will increase the already high pulmonary vascular resistance and hyperoxia will decrease pulmonary vascular resistance and increase fetal pulmonary blood flow.23 Experimentally, ventilation of the fetal lung without changing oxygenation will decrease pulmonary vascular resistance and increase pulmonary blood flow by 400%. With delivery, ventilation, and oxygenation, NO and PGI2 increase with a rapid fall in pulmonary vascular resistance.
The use of supplemental oxygen for the initiation of ventilation will cause pulmonary vascular resistance to decrease more rapidly with the resultant more rapid increase in pulmonary blood flow. There is no benefit in systemic oxygenation, however, and the pulmonary vessels subsequently become more refractory to dilation by NO or acetylcholine.

The cardiovascular transition at birth also is modulated by corticosteroids. Exposure of fetal sheep to betamethasone increased fetal pulmonary blood flow but did not alter postnatal pulmonary vasodilation in preterm sheep. Heart function after preterm birth is improved by antenatal exposure to corticosteroids. The fetal and newborn blood pressures increase, as does cardiac output and left ventricular contractibility. These effects are partially explained by an increase in beta-receptor signaling to an increase in cyclic AMP. Similarly, adrenalectomy ablates the increase in blood pressure that normally occurs at birth (see Fig. 2). Thus, although there are specific mediators such as NO and PGI2 that facilitate cardiovascular transition, the consistent theme is that the same mediators, corticosteroids and catecholamines, also facilitate this transition.

The normal oxygen saturation of fetal blood in the left atrium is about 65%. During labor, the human fetus tolerates oxygen saturations as low as 30% without developing acidosis. After birth, the preductal saturation in healthy term infants gradually increases to about 90% at 5 minutes of age. This knowledge is important to avoid unnecessary administration of supplemental oxygen during resuscitation.

**LUNG ADAPTATIONS**

**Fetal Lung Fluid**

The most essential adaptation to birth is the initiation of breathing, but the airspaces of the fetal lung are filled with fetal lung fluid. What is fetal lung fluid and how is it cleared from the airspaces? Fetal lung fluid is secreted by the airway epithelium as a filtrate of the interstitial fluid of the lung by the active transport of chloride. Consequently, the chloride content of fetal lung fluid is high and protein content is very low. The production rate is high, although direct measurements are not available for the human fetus. The volume of lung fluid of the fetal sheep increases from mid gestation and the secretion rate increases to about 4 mL/kg per hour by late gestation. Production and maintenance of the normal volume of fetal lung fluid is essential for normal lung growth. The electrochemical gradient for the production of fetal lung fluid is essential for normal lung growth. The electrochemical gradient for the production of fetal lung fluid is substantial and can overdistend the airspaces. This behavior of the production of fetal lung fluid is useful to advantage to obstruct the trachea, which will distend the hypoplastic lungs of fetuses with diaphragmatic hernia.

In experiments with fetal rabbits and sheep, Bland and colleagues demonstrated that fetal lung fluid production decreased before the onset of labor, and the volume of lung fluid in the airspaces decreased from about 25 mL/kg to 18 mL/kg. The fetal lung fluid volume decreased further with labor such that the airways contained about 10 mL/kg at delivery. Harding and Hooper measured an airspace fluid volume of about 50 mL/kg in fetal sheep at term and without labor, which is about twice the functional residual capacity of the newborn term lamb after adaptation to air breathing.

The endocrine adaptations that begin before delivery are critical to fluid clearance. Cortisol, thyroid hormones, and catecholamines all increase and shut down the active chloride-mediated secretion of fetal lung fluid and activate the basal Na\(^{+}, K^{+}\), ATPase of type II cells on the airway epithelium. Sodium in fetal lung fluid enters the apical surfaces of type II cells and is pumped into the interstitium with water and other electrolytes following passively, thus removing fluid from the airways. In preterm fetal
sheep, infusion of cortisol and T₃ will activate the sodium pump, which normally occurs at term.¹⁶ The components of fetal lung fluid then are cleared directly into the vasculature or via lymphatics from the lung interstitium over many hours.

This clearance of a large volume of airspace fluid is remarkably efficient normally. The essential contribution of activation of Na⁺ transport was demonstrated by respiratory distress in animals from amiloride inhibition of the Na⁺, K⁺, and ATPase. Mice with defective Na⁺ transporters will die following delivery because of failure to clear fetal lung fluid.³² The frequent clinical scenario in which retained lung fluid contributes to poor respiratory adaptation is the operative delivery of infants who were not in labor. These infants do not increase their oxygen saturations as quickly as vaginally delivered term infants,²⁸ and there is an increased incidence of transient tachypnea of the newborn and other respiratory morbidities (Table 1)²⁹ In experimental studies in sheep, the increased volume of fetal lung fluid interferes with respiratory adaptation, and vaginal delivery facilitates adaptation relative to operative delivery at equivalent volumes of fetal lung fluid.³³

Transient tachypnea of the newborn is most frequent in late preterm infants. This syndrome is thought to directly result from ineffective clearance of fetal lung fluid because of inadequate Na⁺ transport, either because of decreased numbers of transporters or lack of activation.³⁴ Preterm infants also have decreased Na⁺ transport, and late preterm infants with transient tachypnea of the newborn have low amounts of surfactant.³⁵ Thus, the infant with transient tachypnea of the newborn has immaturity of Na⁺ transport and a tendency for surfactant deficiency, whereas the infant with respiratory distress syndrome (RDS) has more severe surfactant deficiency that also includes immature Na⁺ transport. These 2 diseases probably are, in fact, a continuum of these 2 abnormalities from mild to severe.

A hypothetical calculation may help the clinician to understand why lung fluid can compromise neonatal adaptation. If the 3-kg term infant has about 30 mL/kg of fetal lung fluid in the airspaces at cesarean delivery without labor and that infant is intubated, then no fluid can passively drain from the lungs. Assuming that the blood volume of this infant is 80 mL/kg and the hematocrit is 50%, then the plasma volume is 40 mL/kg. The fetal lung fluid will move from the airspace to the lung interstitium, initially interfering with lung mechanics and gas exchange. This fluid then will be transferred to the plasma, which if this occurred acutely would expand plasma volume from 40 mL/kg to 70 mL/kg. This transfer occurs over hours in reality. Nevertheless, the fetal lung fluid volume that must be accommodated during neonatal adaptation is added stress for the newborn.

| Table 1 |
| Respiratory morbidities are increased by Cesarean section deliveries without labor relative to vaginal births after a previous Cesarean section |

<table>
<thead>
<tr>
<th></th>
<th>Cesarean Section</th>
<th>Vaginal Birth</th>
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<tbody>
<tr>
<td>Number</td>
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<td>8336</td>
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<tr>
<td>Respiratory distress syndrome</td>
<td>2.1%</td>
<td>1.4%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Transient tachypnea</td>
<td>4.1%</td>
<td>1.9%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Oxygen therapy</td>
<td>4.4%</td>
<td>2.5%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>1.3%</td>
<td>0.8%&lt;sup&gt;a&lt;/sup&gt;</td>
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<sup>a</sup> P<.001 versus cesarean section.

Data from Jain L, Eaton DC. Physiology of fetal lung fluid clearance and the effect of labor. Semin Perinatol 2006;30:34–43.
Breathing at Birth

The essential component to neonatal adaptation to birth is the maintenance of adequate respiratory effort. The stimuli changing the fetal breathing pattern virtually instantaneously to continuous breathing remain incompletely defined and probably are redundant, as are the stimuli for other adaptations to birth. Most of the information about fetal breathing and its transition after birth is from quite old studies using fetal sheep models, with some verification in the human fetus. The fetal state in utero can be classified into rapid eye movement (REM) sleep and quiet sleep with no clear periods of wakefulness. During REM sleep, the fetus has irregular breathing activity characterized by long inspiratory and expiratory times with movement of variable volumes of fetal lung fluid (mixed with amniotic fluid) into and out of the lung. Fetal breathing, swallowing, and licking activities are confined to REM sleep, with minimal movements during quiet sleep. Fetal hypoxia abolishes fetal breathing, whereas high fetal PO₂ values stimulate fetal breathing. With birth, the fetal sheep will not breathe consistently until the cord is clamped. This observation has generated the hypothesis that breathing is suppressed by a placentally derived substance except in the REM state. Fetal sheep given prostaglandin E2 infusions stop breathing, and treatment with prostaglandin synthetase inhibitors, such as indomethacin, cause continuous fetal breathing. The net effect is that the normal fetal-to-neonatal transition results in the rapid onset of vigorous breathing because of the combined stimuli of cord clamping (and the probable removal of rapidly catabolized prostaglandins that suppress breathing), diffuse tactile and cold stimuli that act centrally, and changes in PCO₂ and PO₂ levels in the blood. The newborn will not initiate breathing if hypoxia is severe. Remarkably, in the absence of hypoxia, virtually all term infants will effectively initiate breathing. Most very preterm infants also will successfully initiate breathing if given the opportunity.

Surfactant and Lung Adaptation

The adequate development of the fetal lung to support gas exchange is the essential adaptation in preparation for birth. During the last third of gestation, the fetal lung septates into about 4 million distal saccules (respiratory bronchioles and alveolar ducts) derived from the 17 generations of airways by about 32 weeks and then further separates to form alveoli. In parallel, the lung parenchymal tissue mass decreases relative to body weight such that the potential gas volume of the airways and alveoli increase greatly. Concurrently, from about 22 weeks’ gestational age, surfactant lipid and the lipophilic proteins SP-B and SP-C begin to be synthesized and aggregated into lamellar bodies in the maturing type II cells. The lamellar bodies are the storage and secretory packets for the essential biophysically active components of surfactant. As the lung matures, more and more of the lamellar bodies are released into fetal lung fluid and subsequently mix with amniotic fluid or are swallowed. By term, type II cells in the fetal lung contain much more surfactant than does the adult lung, and this large pool of surfactant is poised for release before and at delivery.

As delivery approaches, fetal lung fluid secretion ceases (see earlier in this article) and fetal lung fluid volume may decrease. Simultaneously, surfactant is secreted into the fetal lung fluid with labor, which will increase the surfactant concentration in the fetal lung fluid. The presumed mediators of this secretion are the increases in catecholamines that stimulate Beta-receptors. Purinergic agonists, such as ATP, may also promote this predelivery secretion. Subsequently, the initiation of ventilation following birth causes alveolar stretch and therefore deformations of type II cells, another secretion signal. The large increase in catecholamines following delivery
probably further stimulates surfactant secretion. In term animals shortly after birth, the alveolar pool size of surfactant is about 100 mg/kg. This value is 5-fold to 20-fold higher than the amount of surfactant in the alveoli of healthy adult animals or humans. Although no measurements are available for the term human, a similar value is likely based on the amount of surfactant present in amniotic fluid at term. Thus, the term fetus is ensured of having adequate surfactant for the transition to air breathing. The high surfactant pool size decreases to adult levels over the first week of life in animal models. Following operative delivery of preterm lambs, a stable surfactant pool of alveolar surfactant is achieved in about 3 hours despite no labor. Although there has been no surfactant secretion before delivery, the endocrine and lung stretch effects allow the unlabored fetal lung to quickly adapt to air breathing. The secretory events concurrent with birth do not appreciably deplete surfactant stores in type II cells because surfactant synthesis and packaging into lamellar bodies continues and the surfactant that has been secreted also is recycled back into type II cells for secretion as needed.

The preterm lung has several disadvantages for transition to air breathing. The structurally immature lung has less potential lung gas volume relative to body weight and metabolic needs, and secretion of fetal lung fluid may not cease before and after delivery, which will delay clearance of fetal lung fluid. Further, the amount of surfactant stored in type II cells is low, and, thus, less surfactant can be secreted in response to birth. The result is a lower concentration of surfactant to form a surface film and stabilize the lung. Surprisingly, many preterm lungs can adapt, perhaps with a bit of help from continuous positive airway pressure. The small alveolar surfactant pool size need not be more than about 5 mg/kg for the preterm lamb supported by continuous positive airway pressure. This result illustrates that the term infant has large excesses of surfactant to ensure a successful transition to air breathing.

Injury of the Preterm Lung

The transition from a fetus to a newborn requires the initiation of breathing, clearance of fluid from airways, and ventilation of the distal airspaces. Healthy newborns inflate their lungs at birth by generating large negative pressure breaths, which pull the lung fluid from the airways into the distal airspaces. The infant continues to clear lung fluid with subsequent inflations. Spontaneously breathing newborn rabbits quickly move fluid from their airways to the alveoli and subsequently into the interstitium at birth, with 50% of lung aeration occurring with the first 3 breaths. They use an increased inspiratory volume-to-expiratory volume ratio to achieve functional residual capacity (FRC). Most of the clearance of fetal lung fluid occurs during inspiration, with a return of lung fluid into airways during expiration when positive end-expiratory pressure (PEEP) is not used. In newborn preterm rabbits, the use of PEEP during initiation of ventilation facilitates the development of FRC and surfactant treatment creates more uniformed distribution of FRC.

Many preterm or asphyxiated term infants do not have adequate spontaneous respirations at birth and require positive pressure ventilation. Premature infants have immature lungs that are more difficult to ventilate because of inadequate surfactant to decrease surface tension and maintain FRC. The airways in the preterm lung stretch with positive pressure ventilation and the decreased surfactant pools contribute to nonuniform expansion of the lung with areas of focal overdistension and atelectasis. The initial ventilation of the preterm lung will occur before much of the endogenous surfactant is secreted and surfactant therapy cannot practically be given before the initiation of ventilation. The movement of fluid at the air interface across epithelial cells generates high surface forces that distort the cells and injure...
the epithelium of the small airways, a feature prominent in the lungs of infants who have died of RDS. Continuous positive airway pressure or PEEP should minimize the movement of fluid in the airways, and surfactant will lower the pressure required to move fluid into the small airways and decrease the injury from fluid movement. As few as 6 large tidal volume breaths at birth can eliminate the surfactant treatment responses of preterm sheep because of acute lung injury. In preterm sheep models, we demonstrated that airway stretch occurs during initiation of ventilation and initial injury is localized primarily to the bronchi and bronchioles. Acute phase response genes involved in inflammation, angiogenesis, vascular remodeling, and apoptosis were activated within the lung, and immunologically active proteins (HSP70, HSP60) were released by the airway epithelium into the airspace fluid.

As with preterm sheep, ventilated very low birth weight infants have increased proinflammatory cytokines (interleukin [IL]-8, IL-1β, IL-6, and monocyte chemotactic protein 1) in tracheal aspirates soon after birth, which correlate with an increased risk of bronchopulmonary dysplasia. Ventilation of preterm infants with respiratory distress increased plasma levels of IL-1β, IL-8, and tumor necrosis factor α, and decreased levels of the anti-inflammatory cytokine IL-10. We previously demonstrated that regardless of the tidal volume or PEEP used, initiation of ventilation in fluid-filled, surfactant-deficient preterm lambs is injurious. Small increases in the endogenous surfactant pool size can increase the uniformity of lung expansion and thus decrease focal injury. The preterm lung is likely at risk for small and large airway injury from initiation of ventilation during resuscitation.

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The Pulmonary Circulation in Neonatal Respiratory Failure

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KEYWORDS
- Pulmonary circulation
- Respiratory failure
- Lungs
- Neonates

KEY POINTS
- Pulmonary vascular resistance increases during late gestation and decreases at birth.
- Pulmonary vascular transition at birth can be influenced by mode of delivery, asphyxia, body temperature, and oxygen concentration of the resuscitation gas.
- Neonatal hypoxemic respiratory failure (HRF) is often secondary to parenchymal lung disease, ventilation-perfusion mismatch, or extrapulmonary right-to-left shunt.
- Hypoxia causes pulmonary vasoconstriction, normoxia results in pulmonary vasodilation, but hyperoxia does not lead to additional vasodilation.
- Inhaled nitric oxide (iNO) is a specific pulmonary vasodilator and is effective in 60% to 70% of late preterm and term neonates with HRF.
- Inadequate or ill-sustained response to iNO may be secondary to poor alveolar recruitment, remodeled pulmonary vasculature, abnormalities of target enzymes, presence of reactive oxygen species, left ventricular dysfunction, or increased vasoconstrictive mediators.
- Pulmonary hypertension associated with bronchopulmonary dysplasia and congenital diaphragmatic hernia is associated with high morbidity and mortality and its management is challenging.

INTRODUCTION
The pulmonary circulation is a unique system that differs from the systemic circulation in structure, function, and regulation. For example, hypoxia causes pulmonary vasoconstriction but dilates the systemic circulation. In neonates with hypoxemic respiratory failure (HRF), circulatory changes in the lung can be primary, as in idiopathic persistent pulmonary hypertension of the newborn (PPHN), or secondary to lung disease. This article provides a brief overview of normal pulmonary circulation, changes

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in neonatal pulmonary circulation in common causes of neonatal HRF, and its response to therapeutic interventions in the neonatal intensive care unit (NICU).

FETAL CIRCULATION

Gas exchange is the primary function of the postnatal lung. The low-resistance, high-volume pulmonary circulation, which receives half of the combined ventricular output, is a crucial factor in achieving efficient gas exchange by the aerated lung during postnatal life. During fetal life, the placenta serves as the organ of gas exchange; placental vascular resistance is low and receives nearly half of fetal combined ventricular output. During this period, fetal pulmonary vascular resistance (PVR) is high (physiologic pulmonary hypertension), and blood flow is diverted from the pulmonary artery to the aorta and umbilical arteries toward the placenta.\(^1\) Fetal pulmonary circulation must prepare the lungs for adequate structural growth and functional maturation in anticipation for the switch to air breathing in the postnatal period. During the normal transition at birth, PVR decreases and is associated with an increase in pulmonary blood flow. Abnormal pulmonary transition leads to sustained increase of PVR, similar to the fetal state, resulting in PPHN. Parenchymal lung diseases such as meconium aspiration syndrome can result in ventilation-perfusion (V/Q) mismatch, hypoxemia, and structural and functional changes in pulmonary circulation resulting in HRF.

Most of the knowledge of fetal pulmonary hemodynamics is derived from studies in fetal lambs. Data from fetal lambs suggest that PVR is high, with only 8% to 10% of combined ventricular output entering the lungs during fetal life.\(^2,3\) More recently, Doppler flow studies in human fetuses have shown significantly higher flow into the left and right pulmonary arteries with 13% of combined ventricular output at 20 weeks' gestation (canalicular stage), increasing to 25% at 30 weeks (saccular stage) and 21% at 38 weeks (alveolar stage).\(^4\) The fetal PVR is high during the canalicular stage secondary to paucity of pulmonary vascular network and reduced cross-sectional area of an immature pulmonary vascular bed (Fig. 1). Rasanen and colleagues\(^5\) showed that, between 20 and 26 weeks of gestation, maternal hyperoxygenation using 60% humidified oxygen by face mask does not result in pulmonary vasodilation in human fetuses, suggesting a lack of sensitivity to oxygen in early gestation. During the early saccular stage, rapid proliferation of pulmonary vessels decreases fetal PVR. During late preterm and early term gestation (34–36 and 37–38 weeks gestational age [GA], respectively), there is a marked increase in cross-sectional area of the pulmonary vascular bed. However, pulmonary vessels become more sensitive to vasoconstrictive mediators, such as endothelin (ET) and relative hypoxemia, resulting in active pulmonary vasoconstriction and an increase in PVR.\(^6,7\) During this period, maternal hyperoxygenation increases pulmonary blood flow in human fetuses\(^5\) and fetal lambs.\(^8\)

In fetal lambs, pulmonary vasodilation in response to endothelium-independent mediators, such as nitric oxide (NO), precedes responses to endothelium-dependent mediators, such as acetylcholine and oxygen. Response to NO depends on activity of its target enzyme, soluble guanylate cyclase (sGC), in the smooth muscle cell. In the ovine fetus, sGC messenger RNA levels are low during early preterm (126 days) gestation and increase during late preterm and early term gestation (137 days).\(^9\) In rats, abundant sGC activity is present in the lung at late gestation and early newborn periods and gradually decreases in adulthood.\(^10\) Low levels of pulmonary arterial sGC activity during late canalicular and early saccular stages of lung development are probably responsible for the poor response to iNO observed in preterm infants delivered at less than 29 weeks GA.\(^11\)
Modulation of Fetal PVR

Conditions such as congenital diaphragmatic hernia (CDH), antenatal closure of the ductus arteriosus, and idiopathic PPHN are often associated with vascular remodeling and increased PVR during fetal life. Studies in animal models suggest that maternal therapy can alter fetal PVR. Loong and colleagues reported that antenatal administration of sildenafil improved lung structure (decreased mean linear intercept) and reduced pulmonary hypertension (decreased right ventricle/left ventricle + septum ratio) in nitrofen-induced CDH rat pups. Maternal betamethasone similarly reduces oxidative stress and improves relaxation response to adenosine triphosphate (ATP) and NO donors in fetal lambs with PPHN induced by ductal ligation. Antenatal tracheal occlusion in animal models of CDH reduces pulmonary circulatory impedance and pulmonary arterial remodeling. Further translational and clinical research into reducing fetal PVR and improving lung structure and function by antenatal medical and surgical intervention is critical to reduce mortality and morbidity.

Fig. 1. Changes in PVR and systemic vascular resistance (SVR) during the last half of gestation and the postnatal period. During the canalicular phase of lung development, high PVR is caused by low density of the vasculature. In the saccular stage, broad intersaccular septae contain the double capillary network and, with increasing vascular density, PVR decreases. In the alveolar phase, despite the rapid increase in the number of small pulmonary arteries, high PVR is maintained by active vasoconstriction. Fetal pulmonary vasodilator response to endothelium-independent (direct smooth muscle relaxant) vasodilators such as NO precedes the maturation of the vasodilator response to oxygen and acetylcholine (Ach), endothelium-dependent vasodilators. After birth, lung liquid is absorbed and an air-liquid interphase is established with juxtaposition of capillaries and alveolar epithelium to promote effective gas exchange. The dashed line represents the delay in decrease of PVR observed following elective cesarean section. SVR markedly increases after occlusion of the umbilical cord and removal of the low-resistance placental circuit from the systemic circulation. (Copyright © Satyan Lakshminrusimha.)
Maternal medications can also increase fetal PVR and increase the risk of PPHN. Two classes of medications, antidepressants and antiinflammatory agents, have been well studied.

**Selective serotonin uptake inhibitors**
Maternal intake of selective serotonin uptake inhibitors (SSRIs) during the last half of pregnancy has been associated with an increased risk of PPHN. Exposure of pregnant rats to fluoxetine resulted in pulmonary hypertension in rat pups (more profound in female pups) and was associated with hypoxia and increased mortality. The mechanism by which fluoxetine induces pulmonary hypertension in newborns is unknown. It is speculated that higher drug-induced serotonin levels result in pulmonary vasoconstriction. A more recent retrospective analysis has questioned this association. Obstetricians must weigh the maternal psychological benefits of antidepressant therapy during pregnancy against the risk of adverse neonatal effects.

**Nonsteroidal antiinflammatory medications**
Ingestion of nonsteroidal antiinflammatory drugs (NSAIDs), such as aspirin, during late gestation may be associated with utero closure of the fetal ductus arteriosus. Experimental ligation of the ductus arteriosus in lambs during fetal life is associated with pulmonary vascular remodeling and PPHN. Prostaglandins maintain ductal patency in utero and are important mediators of pulmonary vasodilation in response to ventilation at birth. Pharmacologic blockade of prostaglandin production by NSAIDs can result in PPHN. Analysis of meconium from newborn infants with PPHN revealed the presence of NSAID in approximately half of the samples, linking antenatal NSAID exposure to PPHN.

**TRANSITION AT BIRTH**
The entry of air into the alveoli with crying and breathing improves oxygenation of the pulmonary vascular bed, decreasing PVR and increasing pulmonary blood flow. The increase in pulmonary blood flow raises left atrial pressures more than right atrial pressures, closing the foramen ovale. Removal of the low-resistance placental bed from the systemic circulation at birth increases systemic vascular resistance (SVR). As PVR decreases to less than SVR, flow reverses across the ductus. Oxygen-induced vasodilation and lung expansion decrease PVR to approximately half of SVR within a few minutes after birth. Over the first few hours after birth, the ductus arteriosus closes, largely in response to the increase in oxygen tension, and with this the normal postnatal circulatory pattern is established. The recognition of the role of NO in mediating pulmonary vascular transition at birth has led to the development of inhaled NO (iNO) as a therapeutic strategy in the life-threatening clinical disorder of PPHN. A detailed review of NO and other mediators of pulmonary vascular transition at birth is presented in a previous issue.

**Factors Altering Pulmonary Vascular Transition at Birth**

**Mode of delivery**
Vaginal delivery is associated with reduction in fetal PVR at birth. Delivery by elective cesarean section delays the decrease in pulmonary arterial pressure (see Fig. 1), as shown by prolonged right-sided systolic time intervals, and increases the risk for PPHN. Compared with matched controls, infants with PPHN are more likely to have been delivered by cesarean section.
**Timing of delivery**

Timing of delivery influences the risk and outcome of HRF in neonates. Delivery during late preterm or early term gestation is associated with a higher risk of admission to the NICU with respiratory distress. Among patients with severe HRF requiring extracorporeal membrane oxygenation (ECMO), mortality is higher among late preterm and early term infants compared with term infants. However, infants with CDH without other anomalies have been observed to have reduced need for ECMO and marginally better survival when delivered early term compared with late term. More recent population-based studies have not confirmed these findings.

**Antenatal glucocorticoids**

Administration of glucocorticoids, such as betamethasone, before elective cesarean section has been shown to reduce the incidence of respiratory distress and admission to the NICU. This regimen is being adapted in some centers in Europe. Preliminary data from our laboratory suggest that antenatal betamethasone decreases PVR and increases fetal pulmonary blood flow. Recent identification of genetic variations involving corticotropin-releasing hormone in patients with PPHN, as well as the effectiveness of hydrocortisone in improving oxygenation in lambs with PPHN, suggest that glucocorticoids may have a role in prevention and management of PPHN and HRF.

**Early versus delayed cord clamping**

The current neonatal resuscitation guidelines recommend delayed umbilical cord clamping for at least 1 minute for newborn infants who do not require resuscitation at birth. Delayed cord clamping results in more stable blood pressures and improved iron status. Arcilla and colleagues evaluated the effect of late cord clamping on pulmonary hemodynamics in newborn infants by catheterizing the pulmonary artery. The mean ratio of pulmonary artery to systemic arterial pressure decreased to 0.7 by 2 hours and to 0.5 by 4 hours following early cord clamping. Following late cord clamping, pulmonary arterial pressures were almost 90% of systemic pressures by 9 hours. The investigators speculated that increased blood volume following late cord clamping results in distension of the pulmonary capillary and venous bed, resulting in increased pulmonary arterial pressure. Polycythemia with increased viscosity may contribute to high PVR. There are no reports of an increased incidence of PPHN associated with delayed cord clamping.

**Temperature**

Induction of severe hypothermia in lambs between 1 and 3 days old (decreasing temperature from 40°C to 30°C) increases mean pulmonary arterial pressure from 29 to 40 mm Hg. Perinatal asphyxia is a well-known predisposing factor for PPHN. There was considerable concern that therapeutic hypothermia in asphyxiated infants would increase the risk of PPHN. Pooled analysis of randomized trials has not shown an increased incidence of PPHN with hypothermia in this population. The type of cooling (selective head cooling vs whole body cooling) does not alter the incidence of PPHN.

**Asphyxia**

Perinatal asphyxia interferes with the mechanisms of pulmonary transition at birth and modifies this complex adaptation impeding the decrease in PVR, and increasing the risk for PPHN. Multiple mechanisms cause respiratory failure and affect pulmonary circulation in asphyxia: fetal hypoxemia, ischemia, meconium aspiration, ventricular dysfunction, and acidosis can all increase PVR. Acute asphyxia is associated with reversible pulmonary vasoconstriction but chronic in utero asphyxia with or
without meconium aspiration may be associated with vasoconstriction and vascular remodeling.46

**Oxygen during neonatal resuscitation**

Oxygen is a potent and specific pulmonary vasodilator. The use of 100% oxygen during initial ventilation of normal lambs at birth results in a small but significant decrease in PVR during the first few minutes of life compared with 21% or 50% oxygen.47 However, ventilation with 100% oxygen at birth impairs subsequent relaxation to iNO and acetylcholine, probably because of the formation of reactive oxygen species (ROS). Similar results were observed in lambs with pulmonary hypertension and a remodeled pulmonary vasculature.48 In lambs with asphyxia induced by umbilical cord occlusion, PVR was lower with 100% oxygen resuscitation compared with 21% oxygen at 1 minute of age but, by 2 minutes, PVR was similar in both groups. These findings suggest that optimal ventilation (and not hyperoxygenation) is the key to reducing PVR.49 Thirty minutes of resuscitation with 100% oxygen increased pulmonary arterial contractility and superoxide anion formation in pulmonary arteries. Using 100% oxygen therefore has transient advantages in rapidly reducing PVR but increases ROS formation, increases pulmonary arterial contractility, and impairs vasodilation to endothelium-dependent (acetylcholine) and endothelium-independent (iNO) agents. These findings support the neonatal resuscitation guidelines’ recommendations to use room air for initial resuscitation of term asphyxiated newborn infants.39

**PULMONARY CIRCULATORY CHANGES IN HRF**

**Fig. 2** shows the 4 different patterns of pulmonary vascular changes in neonatal HRF. PPHN is characterized by increased ratio of pulmonary vascular resistance (PVR) to SVR resulting from (1) vasoconstriction; (2) structural remodeling of the pulmonary vasculature (**Fig. 3**); (3) intravascular obstruction from increased viscosity of blood, and (4) intravascular obstruction caused by increased viscosity as seen in polycythemia in the presence of normal pulmonary vasculature can cause PPHN. Asphyxia or parenchymal lung disease can lead to alveolar hypoxia and acute pulmonary vasoconstriction. Chronic pulmonary vascular remodeling can result from chronic intrauterine hypoxia, antenatal ductal closure, or CDH. Lung hypoplasia with paucity of pulmonary vasculature accompanies CDH; intrathoracic space occupying lesions, such as adenomatoid malformations; or chronic oligohydramnios syndromes, which could be secondary to chronic leakage of amniotic fluid or fetal oliguria from renal dysfunction. (Copyright © Satyan Lakshminrusimha.)

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**Fig. 2.** Pathologic changes in pulmonary circulation in neonatal HRF follows 4 patterns. Intravascular obstruction caused by increased viscosity as seen in polycythemia in the presence of normal pulmonary vasculature can cause PPHN. Asphyxia or parenchymal lung disease can lead to alveolar hypoxia and acute pulmonary vasoconstriction. Chronic pulmonary vascular remodeling can result from chronic intrauterine hypoxia, antenatal ductal closure, or CDH. Lung hypoplasia with paucity of pulmonary vasculature accompanies CDH; intrathoracic space occupying lesions, such as adenomatoid malformations; or chronic oligohydramnios syndromes, which could be secondary to chronic leakage of amniotic fluid or fetal oliguria from renal dysfunction. (Copyright © Satyan Lakshminrusimha.)
as in polycythemia; or (4) lung hypoplasia. This condition leads to right-to-left shunting of blood across the foramen ovale and ductus arteriosus, resulting in hypoxemia. Numerous disease states with diverse causes can result in a similar final pathophysiology. About 10% of cases with PPHN are idiopathic, with no associated pulmonary airspace disorder. However, PPHN is usually associated with other acute respiratory conditions, such as meconium aspiration syndrome (MAS), respiratory distress syndrome (RDS), pneumonia, or CDH. Hypoxemia in these conditions can be caused by parenchymal lung disease, surfactant deficiency (RDS) or inactivation (MAS, pneumonia), ventilation/perfusion (V/Q) mismatch, and intrapulmonary as well as extrapulmonary right-to-left shunting of blood (Fig. 4).

In some newborns with HRF, a single mechanism predominates (eg, extrapulmonary right-to-left shunting in idiopathic PPHN). However, more commonly, several of these mechanisms contribute to hypoxemia. In MAS, obstruction of the airways by meconium results in decreasing V/Q ratios and increasing intrapulmonary right-to-left shunt. Other segments of the lungs may be overventilated relative to perfusion, causing increased physiologic dead space. The same patient may also have severe PPHN with extrapulmonary right-to-left shunting at the level of the ductus arteriosus and foramen ovale.

Pneumonia or meconium aspiration may release inflammatory mediators that induce vasoconstriction. Vasoconstrictors such as leukotrienes, platelet-activating factor, thromboxanes, and ET-1 have been found to be increased in PPHN. Chronic intrauterine ET\(_A\) receptor blockade following antenatal ductal ligation decreases pulmonary arterial pressure in utero, decreases right ventricular hypertrophy and distal muscularization of small pulmonary arteries, and further decreases the PVR at delivery in newborn lambs with PPHN. Thus ET-1 acting through ET\(_A\) receptor stimulation might contribute to the pathogenesis and pathophysiology of PPHN. Derangements in the NO pathway of vasodilation can also result in the physiologic characteristics of PPHN. Pulmonary endothelial nitric oxide synthase (eNOS) gene and protein expression and enzyme activity are decreased in fetal lambs with PPHN induced by antenatal ductal ligation. In addition, the response to stimulators of eNOS is lost. In these lambs with PPHN, the vascular response to NO is also diminished, whereas the response to cyclic guanosine monophosphate-phosphodiesterase (cGMP) is normal. Thus, the decreased responsiveness seems to result from decreased vascular smooth

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**Fig. 3.** Pulmonary arterial remodeling in HRF. (A) Preterm infant with respiratory distress syndrome and PPHN; (B) Term infant with asphyxia and PPHN; note the smooth muscle cell layer thickening around pulmonary arteries.
muscle sensitivity to NO at the level of sGC. Because NO relaxes smooth muscle and inhibits vascular smooth muscle growth, diminished eNOS expression may contribute to both abnormal vasoreactivity and excessive muscularization of pulmonary vessels in PPHN.

Pulmonary hypertension sometimes occurs because of an abnormal pulmonary vascular bed despite the absence of alveolar hypoxia and hypercapnia and of lung inflammation. These infants can be grouped according to the degree of muscularization and the number of pulmonary arteries. In infants with hypoplastic lungs, as in CDH and oligohydramnios sequence (sometimes secondary to fetal renal dysfunction), PPHN may arise primarily as a consequence of a decreased number of vessels, causing decreased cross-sectional area of the pulmonary vascular bed, and leading to flow restriction. Patients with alveolar capillary dysplasia may have a similar vascular hypoplasia. These cases may be complicated by increased muscularization of the vessels.

Many infants who have HRF do not have right-to-left extracardiac shunting, and may have hypoxia because of intrapulmonary shunting or cardiac dysfunction (see Fig. 4). Determination of the hemodynamic profile of these babies using functional echocardiography is important to make the diagnosis, initiate therapy, and follow the changes with therapy. The gold standard in defining PPHN rests on the echocardiographic findings of right-to-left shunting of blood at the foramen ovale and/or the

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**Fig. 4.** Hemodynamic changes in PPHN/HRF. Surfactant deficiency (RDS) or inactivation (MAS or pneumonia) results in parenchymal lung disease and ventilation-perfusion (V/Q) mismatch. Increased PVR results in reduced pulmonary blood flow and right-to-left shunt through the PDA and/or PFO. Pulmonary hypertension, often associated with systemic hypotension, results in septal deviation to the left. Cardiac dysfunction secondary to asphyxia, sepsis, or CDH may contribute to pulmonary venous hypertension and complicate HRF. LA, left atrium; LV, left ventricle; PA, pulmonary artery; PDA, patent ductus arteriosus; PFO, patent foramen ovale; RA, right atrium; RV, right ventricle; TR, tricuspid regurgitation. (Copyright © Satyan Lakshminrusimha.)
ductus arteriosus, as well as estimates of pulmonary arterial pressure using tricuspid regurgitation jet velocity. Using the modified Bernoulli equation, systolic right ventricular pressure (mm Hg) is estimated by $4v^2 + \text{right atrial pressure}$, where $v$ is the maximal velocity of tricuspid regurgitation jet in meters per second on continuous-wave Doppler echocardiogram. The velocity of tricuspid regurgitation jet may also be influenced by right ventricular dysfunction, leading to underestimation of pulmonary arterial pressure. Right ventricular dysfunction caused by excessive afterload seems to be a major risk factor for poor outcome in HRF.

Doppler measurements of atrial and ductal level shunts provide essential information to optimize management of a newborn with HRF. For example, left-to-right shunting at the foramen ovale and ductus arteriosus with marked hypoxemia suggests predominant intrapulmonary shunting, and interventions should be directed at optimizing lung inflation and recruitment. Increasing mean airway pressure and administering surfactant are likely to be more effective than iNO in improving oxygenation in babies with parenchymal lung disease and left-to-right shunt at patent ductus arteriosus (PDA) and patent foramen ovale (PFO). Presence of right-to-left shunting at the ductal level and left-to-right shunting at the atrial level similarly suggests PPHN with left ventricular dysfunction with some pulmonary venous hypertension (Table 1). This finding may be associated with the CDH and left ventricular dysfunction seen in sepsis and asphyxia. If right-to-left shunting is present at ductal and atrial levels and is associated with labile hypoxemia and tricuspid regurgitation, PPHN is the most likely diagnosis. However, patients with fixed hypoxemia with right-to-left shunting at ductal and atrial levels associated with a small left atrium without tricuspid regurgitation may have anomalous pulmonary venous return (see Table 1).

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Ductal Shunt</th>
<th>Atrial Shunt</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenchymal lung disease and V/Q mismatch and intrapulmonary shunt</td>
<td>L → R</td>
<td>L → R</td>
<td>Lung recruitment, specific therapy (antibiotics for pneumonia) NO may be beneficial</td>
</tr>
<tr>
<td>PPHN</td>
<td>R → L</td>
<td>R → L</td>
<td>Oxygenation, correction of acidosis and inhaled NO</td>
</tr>
<tr>
<td>Left ventricular dysfunction (common in diaphragmatic hernia, asphyxia, and sepsis)</td>
<td>R → L</td>
<td>L → R</td>
<td>Inotropes and vasodilators (Milrinone)</td>
</tr>
<tr>
<td>Tricuspid atresia/stenosis or pulmonic atresia/stenosis</td>
<td>L → R</td>
<td>R → L</td>
<td>Prostaglandin E1 + surgery</td>
</tr>
<tr>
<td>Total anomalous pulmonary venous return</td>
<td>R → L (large PA)</td>
<td>R → L (small LA and no tricuspid regurgitation)</td>
<td>Surgery</td>
</tr>
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**Pulmonary Circulatory Changes in Some Specific Conditions Resulting in Neonatal Respiratory Failure**

### Idiopathic PPHN
Idiopathic PPHN (also known as black-lung PPHN) is characterized by increase of PVR without a primary parenchymal lung disease. Autopsy studies of fatal idiopathic PPHN show severe hypertensive structural remodeling with vessel wall thickening and smooth muscle hyperplasia. The vascular smooth muscle extends to the level of intra-acinar arteries, resulting in increased PVR and failure to respond to birth-related stimuli, such as ventilation and oxygenation. A well-known cause of black-lung PPHN is exposure to indomethacin during the third trimester, resulting in closure of the ductus arteriosus in utero. A fetal lamb model of idiopathic PPHN is created by antenatal ductal ligation. This model shows the clinical and histopathologic features of PPHN. Abnormalities of the nitric oxide pathway (decreased eNOS, decreased sGC, and increased phosphodiesterase type 5 [PDE5]), superoxide anion pathway (increased superoxide and hydrogen peroxide), and prostacyclin pathway (decreased prostacyclin synthase and prostacyclin IP receptor) have been described in this model. Similar abnormalities in enzyme pathways may occur in human neonates with idiopathic PPHN.

### CDH
CDH occurs in approximately 1 in 3000 births and is the most common cause of pulmonary hypoplasia in the neonate. Diaphragmatic hernia is associated with ipsilateral and contralateral lung hypoplasia, vascular paucity, and vascular remodeling. Most cases are diagnosed in the antenatal period. Initial delivery room management focuses on stabilization, gastrointestinal decompression, and immediate intubation. Bag-mask ventilation and introduction of more gas into the gastrointestinal tract should be avoided. Early corrective surgery is often associated with deterioration of respiratory function in the immediate postoperative period. There has been a paradigm shift focusing on cardiorespiratory stabilization and management of PPHN followed by surgery. There are 2 animal models of CDH: the rat model created by maternal ingestion of nitrofen, a herbicide, resulting in lung hypoplasia and a diaphragmatic defect; and a second model that is created by fetal surgery in lambs. Abnormalities in the nitric oxide synthase, sGC, and PDE5 function have been observed in these models. These abnormalities, associated with left ventricular hypoplasia, may contribute to poor response to iNO in CDH.

### MAS
A combination of preexisting in utero hypoxia and meconium aspiration into the lungs with pulmonary hypertension often carries high morbidity. In the 1980s and 1990s, MAS was the most common cause of severe HRF and PPHN in neonates, but the incidence has decreased in recent years in the United States. A review of annual neonatal ECMO data from the Extracorporeal Life Support Organization (ELSO) registry (accessed in February 2012) shows that CDH accounts for more ECMO runs than MAS in recent years. This reduction is partly caused by reduction in postterm births in the United States in recent years, because MAS is more common in this population. Meconium aspiration with perinatal asphyxia leads to an immediate release of circulating vasoactive substances, which favor contraction and proliferation of smooth muscle fibers in the pulmonary circulation. Most cases of fatal MAS show evidence of smooth muscle hypertrophy in small pulmonary arteries. In addition, a decrease in the expression of eNOS was reported in umbilical venous endothelial cells isolated from human infants with MAS. In piglets, meconium instillation into the lungs...
increases PVR and asphyxia decreases SVR, and a combination of MAS and asphyxia worsen the ratio between PVR and SVR.  

**Transient tachypnea of the newborn with HRF and PPHN (malignant transient tachypnea of the newborn)**

Ramachandrappa and Jain reviewed the pathogenesis of respiratory morbidity following elective cesarean section. Many infants with hypoxemia following elective cesarean section are considered to have transient tachypnea of the newborn and wet lung syndrome and are placed on oxygen by hood or nasal cannula without positive pressure. Absorption atelectasis results in increasing oxygen requirements and progressive respiratory failure. It is possible that formation of ROS from high alveolar PaO2 may lead to increased pulmonary vascular reactivity and contribute to PPHN. Severe respiratory failure following elective cesarean section may occasionally require therapy with ECMO.  

**Premature infant with bronchopulmonary dysplasia and pulmonary hypertension**

Bronchopulmonary dysplasia (BPD) continues to be a major cause of morbidity and late mortality in extremely preterm infants. Pulmonary hypertension is observed in approximately 1 in 6 extremely low birth weight (ELBW) infants. BPD is associated with reduced cross-sectional perfusion area with decreased arterial density and abnormal muscularization of peripheral pulmonary arteries. Risk factors for developing pulmonary hypertension include low birth weight (small for GA), oligohydramnios, and prolonged mechanical ventilation. A recent prospective analysis showed that the onset of pulmonary hypertension in BPD is variable and can be as late as 3 to 4 months of age. A delay in diagnosis is associated with progressive pulmonary vascular disease, cor pulmonale, and high mortality. It is prudent to screen babies that are ventilated or require greater than 30% oxygen or have radiological evidence of BPD with an echocardiogram at 1 month of age and every 4 weeks until discharge to diagnose pulmonary hypertension early, leading to appropriate therapy. The optimal intervention strategies for reversing early pulmonary hypertension or treating established pulmonary hypertension are not clear. Multiple therapies, such as maintaining higher oxygen saturations, iNO, and sildenafil, are reported anecdotally to have been tried with mixed results.  

**Air-leak syndromes**

Air-leak syndromes such as pulmonary interstitial emphysema (PIE), pneumothorax, and pneumomediastinum are common complications of mechanical ventilation in preterm infants and are associated with respiratory failure. Among late preterm and term newborn infants, spontaneous pneumothorax is common and results in respiratory failure. Most of these infants improve spontaneously or require thoracocentesis or chest tube drainage with resolution of HRF. Smith and colleagues recently reported that almost half of late preterm/term infants with spontaneous, symptomatic pneumothorax that required needle or chest tube drainage developed PPHN. Acute increases in PVR with shunting secondary to hypoxemia or acidosis or caused by the primary lung disease must be considered in the differential diagnosis of persistent HRF in infants with pneumothorax.

**PULMONARY HEMODYNAMIC CHANGES CAUSED BY THERAPY**

A detailed review of inhaled NO, sildenafil, milrinone, and other pulmonary vasodilator agents is provided in the March 2012 issue of *Clinics*. This article focuses on the impact of various therapies in the NICU on the pulmonary circulation.
Mechanical Ventilation

Optimal lung recruitment during mechanical ventilation with appropriate use of positive end expiration pressure (PEEP) and/or mean airway pressure is a critical step during the management of HRF. When lungs are inflated at functional residual capacity (FRC), PVR is low. PVR is a combination of resistance offered by alveolar vessels and extra-alveolar vessels. When the lungs are underinflated or collapsed, the alveolar vessels are wide open but the extra-alveolar vessels are narrowed, resulting in increased PVR. When the alveoli are overinflated, the alveolar vessels are compressed, resulting in high PVR. Moreover, high PEEP or mean airway pressure may impair venous return and reduce cardiac output. An optimal balance is achieved when the lung expansion is at FRC. It is important to check frequent radiographs during the acute phase of PPHN to assess optimal lung expansion.

Many clinicians use high-frequency ventilation (HFV) to manage infants with PPHN. Considering the important role of parenchymal lung disease in specific disorders resulting in PPHN, adequate lung inflation and optimal ventilation are as essential as pharmacologic vasodilator therapy. In the case of inhaled vasodilators, optimal inflation and ventilation may be necessary for drug delivery. Infants with PPHN with a variety of causes have been successfully treated with HFV. High-frequency oscillatory ventilation (HFOV) decreases PaCO₂ and increases oxygenation in infants with PPHN. HFOV may improve oxygenation through safer use of higher mean airway pressures to maintain lung volume and prevent atelectasis. Two studies have evaluated the effectiveness of HFV compared with conventional ventilation in rescuing infants with respiratory failure and PPHN from potential ECMO therapy. Neither mode of ventilation was more effective in preventing ECMO in these infants. In clinical pilot studies using iNO, a combination of HFOV and iNO resulted in the greatest improvement in oxygenation in some newborns who had severe PPHN complicated by diffuse parenchymal lung disease and underinflation. A randomized controlled trial showed that treatment with HFOV and iNO was often successful in patients who failed to respond to HFOV or iNO alone in severe PPHN, and the differences in responses were related to the specific disease associated with PPHN. Infants with RDS and MAS benefit most from a combination of HFOV and iNO therapy.

Oxygen

Oxygen is a specific and potent pulmonary vasodilator and increased oxygen tension is an important mediator of reduction in PVR at birth. Alveolar hypoxia and hypoxemia increase PVR and contribute to the pathophysiology of PPHN. Avoiding hypoxemia by mechanical ventilation with high concentrations of oxygen used to be the mainstay of PPHN management. However, exposure to hyperoxia may result in formation of oxygen free radicals and lead to lung injury. As mentioned previously, brief exposure to 100% oxygen in newborn lambs increases contractility of the pulmonary arteries and formation of superoxide anions and reduces response to inhaled NO. Administration of intratracheal recombinant human superoxide dismutase (SOD; an antioxidant that breaks down superoxide anions) results in improved oxygenation in lambs with PPHN. Based on these studies, it seems that avoiding hyperoxia is as important as avoiding hypoxia in the management of PPHN.

The optimal PaO₂ in the management of PPHN is not clear. Wung and colleagues suggested that gentle ventilation with avoidance of hyperoxia and hyperventilation results in good outcomes in neonates with respiratory failure. Decreasing PaO₂ to less than 45 to 50 mm Hg results in increased PVR in newborn calves and lambs. In contrast, maintaining PaO₂ at greater than 70 to 80 mm Hg does not result in
additional decrease in PVR in both control lambs and lambs with PPHN. Maintaining preductal oxygen saturations in the 90% to 97% range seems to be associated with low PVR in the ductal ligation model of PPHN (Fig. 5). In animal studies, hypoxemia results in pulmonary vasoconstriction; normoxemia reduces PVR but hyperoxemia does not result in additional pulmonary vasodilation. To date, randomized studies comparing different PaO₂ targets have not been conducted in infants with PPHN.

**Acidosis/Alkalosis**

Acidosis (both metabolic and respiratory) constricts the pulmonary vasculature and increases PVR, whereas alkalosis selectively decreases PVR. Acidosis (pH<7.30) was associated with an exaggerated constrictor response to hypoxia. In 1978, Peckham and Fox published a study of 10 infants with significant PPHN who were treated with hyperventilation and showed significant improvement. Despite the small number of infants in this report, hyperventilation soon became a common therapy in the treatment of this disease and was effectively used as a strategy to improve PaO₂. In 1985, Wung and colleagues challenged this practice. They managed 15 infants with severe PPHN using gentle ventilation maintaining PaO₂ between 50 and 70 mm Hg and allowing PaCO₂ to increase as high as 60 mm Hg. All infants survived, with only 1 developing chronic lung disease, thus questioning the strategy of hyperventilation. Moreover, studies in asphyxiated lambs showed that respiratory alkalosis reduced cerebral blood flow. Alkalosis achieved via ventilator-induced hypocarbia was subsequently shown to be associated with poor neurodevelopmental outcome and hearing loss. In a retrospective review of PPHN management at National Institute of Child Health and Human Development (NICHD) centers, Walsh-Sukys and colleagues reported that continuous alkali infusion was associated with increased use of ECMO and increased use of oxygen at 28 days of age. With the availability of selective pulmonary vasodilators, therapeutic alkalosis is no longer recommended in the management of PPHN. Based on animal data, avoiding acidosis (pH<7.30) may offer some protection.

**Fig. 5.** The effect of oxygen saturation on PVR in lambs with PPHN induced by antenatal ductal ligation: Median (solid line) and 25th and 75th percentile lines (dashed lines) are shown in the figure. Saturation range of 90% to 97% is associated with low PVR. (From Lakshminrusimha S, Swartz DD, Gugino SF, et al. Oxygen concentration and pulmonary hemodynamics in newborn lambs with pulmonary hypertension. Pediatr Res 2009;66(5):542; with permission.)
against pulmonary vasoconstrictor response to hypoxia. However, this effect has not been systematically evaluated in human infants with PPHN.

**Surfactant**

Administration of intratracheal surfactant is a common practice in the presence of RDS, pneumonia, or MAS. In surfactant-depleted piglet models, instillation of surfactant is associated with a significant reduction in systemic and pulmonary arterial pressures. However, in human preterm infants, administration of surfactant is associated with selective reduction in pulmonary arterial pressure without any change in systemic pressure. Surfactant therapy has been shown to reduce the need for ECMO in term neonates with MAS. The effect of surfactant is probably a combination of its direct effect on compliance and recruitment and, when used in conjunction with iNO, an indirect effect through enhancing iNO delivery and V/Q matching.

**iNO**

The introduction of iNO, following its approval by the US Food and Drug Administration (FDA) in 1999 revolutionized the management of PPHN and HRF in the NICU. Large multicenter trials, the Neonatal Inhaled Nitric Oxide Study Group (NINOS) trial, the Clinical Inhaled Nitric Oxide Research Group (CINRGI) trial, and Roberts and colleagues trial, showed that iNO reduced the need for ECMO. Treatment with iNO results in improved oxygenation and reduction in oxygenation index (OI; mean airway pressure in cm H$_2$O × forced inspiratory oxygen [Fio$_2$] × 100/PaO$_2$ in mm Hg) in 50% to 60% of patients over a wide range of severity of HRF. Approximately two-thirds of neonates with parenchymal lung disease, such as MAS and RDS, and HRF respond well to iNO with improved oxygenation. The percentage of responders can be further enhanced with the use of HFOV, emphasizing the importance of lung recruitment during iNO therapy. A similar oxygenation response is observed in infants with idiopathic PPHN, but implementation of HFOV does not enhance this response. In contrast, HRF resulting from CDH responds poorly to both iNO and HFOV. Possible causal factors resulting in inadequate or ill-sustained response to iNO are discussed later (Fig. 6):

**Poor alveolar recruitment**

Inhaled NO has to reach its target organ, the resistance pulmonary arteriole, to induce pulmonary vasodilation. If there is parenchymal lung disease and/or atelectasis, iNO cannot reach alveoli and pulmonary vasculature. Appropriate alveolar recruitment with increased PEEP, mean airway pressure, and use of surfactant before initiation of iNO is likely to increase pulmonary vasodilation in response to iNO. Once iNO enters the pulmonary vasculature and interacts with hemoglobin in the red blood cells, methemoglobin (MHb) is formed. The increase in MHb following iNO therapy can be considered to reflect that iNO has reached the pulmonary vasculature. We have observed that MHb levels (corrected for NO dose) are significantly higher in neonates with a positive oxygenation response to iNO compared with neonates that do not respond to iNO. Better alveolar recruitment with HFV and surfactant is at least partly responsible for lower ECMO/death rates following iNO therapy in recent studies (19.5%) compared with the NINOS study (39%).

**Remodeled pulmonary vasculature**

Chronic intrauterine pulmonary hypertension, such as is seen in CDH, and antenatal closure of the ductus arteriosus can result in thickening of the smooth muscle layer and adventitia with distal extension of musculature to normally nonmuscular arterioles. Remodeled vasculature tends to be associated with a fixed component of
vasoconstriction and does not respond well to exogenous vasodilators. Endothelial dysfunction results in poor response to endothelium-dependent vasodilators, such as oxygen and acetylcholine. These abnormal vasodilator responses secondary to impaired sGC activity are well described in animal models of neonatal pulmonary hypertension and diaphragmatic hernia.

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**Fig. 6.** Common causes of failure to respond to iNO in neonatal HRF. (1) Failure to recruit alveoli before iNO administration prevents delivery of NO to its target organ, the resistance level pulmonary artery. (2) Remodeled pulmonary artery may have a fixed component of pulmonary vasoconstriction and not respond to vasodilators. (3) Enzyme abnormalities such as decreased sGC activity or increased PDE5 activity can decrease cGMP formation. (4) Increased formation of ROS such as superoxide anions can inactivate NO and stimulate PDE5. (5) Left ventricular failure results in pulmonary venous hypertension, and use of NO in this situation may worsen pulmonary edema and oxygenation. (6) High concentrations of vasoconstrictors, such as ET, may counteract the vasodilation induced by iNO. (7) Rare abnormalities such as alveolar capillary dysplasia with misaligned pulmonary veins (ACD/MPV) and surfactant protein-B deficiency or ATP binding cassette A3 (ABCA3) deficiency. AC, adenylate cyclase; BNP, B-type natriuretic peptide; COX, cyclooxygenase; NO, nitric oxide; NOS, nitric oxide synthase; PDE, phosphodiesterase; pGC, particulate guanylate cyclase; PGi, prostacyclin; ROS, reactive oxygen species; sGC, soluble guanylate cyclase. (Copyright © Satyan Lakshminrusimha.)
Abnormalities of target enzymes
Nitric oxide stimulates sGC in the pulmonary arterial smooth muscle cell (PASMC) to produce cGMP. sGC is a heme-containing enzyme and can be inactivated by a variety of conditions. Animal models of PPHN have decreased sGC activity reducing cGMP production and relaxation to NO donors. An increase in PDE5 activity results in catabolism of cGMP and limitation of NO-induced vasodilation. Ventilation with high concentrations of inspired oxygen and exposure to ROS stimulates PDE5 activity and decreases cGMP levels. Inhibition of PDE5 with the use of sildenafil has been an effective strategy in the treatment of PPHN. Sildenafil, the first PDE5 inhibitor to be approved by the FDA for treatment of pulmonary hypertension in adults, is currently available for both oral and intravenous administration. Therapy with sildenafil has been studied in the acute phase of PPHN and in patients with chronic pulmonary hypertension. Sildenafil is currently not approved for use in neonates but has been used off label in the following circumstances: (1) management of PPHN in the acute phase in situations in which iNO and ECMO are not available, as in developing countries. In a recent pharmacokinetic study, intravenous sildenafil was shown to be effective in improving oxygenation as a primary agent (without the use of iNO). (2) To augment the effect of iNO in patients with partial or ill-sustained response to iNO. It may be particularly effective in patients following prolonged hyperoxic ventilation because ventilation with high oxygen concentrations and superoxide anions stimulates PDE5 activity. (3) To reduce the severity of, or to prevent rebound, pulmonary hypertension observed after weaning iNO. (4) Chronic oral therapy in infants with prolonged pulmonary hypertension, as in that associated with BPD or CDH. (5) Antenatal use of sildenafil was recently shown to decrease pulmonary hypertension in nitrofen-induced CDH in rat pups; there are no human studies to show the effect of antenatal sildenafil on fetal PVR. The primary concern with the use of intravenous or oral vasodilators, such as sildenafil, is the potential for a decrease in SVR with worsening of right-to-left shunt. The dose of sildenafil should be carefully adjusted to achieve pulmonary vasodilation without significant systemic vasodilation. The optimal dose of sildenafil in term neonates has been evaluated in a recent pharmacokinetic study. A slow load of 0.4 mg/kg over 3 hours results in early buildup of therapeutic plasma levels without significant reduction in systemic blood pressure. The dose of continuous infusion is 1.6 mg/kg/d. This intravenous dose (approximately 2 mg/kg/d) corresponds with the recommended oral dose of 4 to 8 mg/kg/d, assuming that oral bioavailability of sildenafil in neonates is similar to that in adults (40%). Hepatic immaturity or dysfunction and severe renal impairment can prolong the half-life of sildenafil and potentially increase in the risk of systemic hypotension.

ROS
The primary determinant of the biologic half-life of endogenous NO is the local concentration of superoxide anions. The reaction between NO and superoxide anion yields toxic peroxynitrite with a second-order rate constant near the diffusion-controlled limit (K constant = 6.7 ± 0.9 × 109 M⁻¹ s⁻¹). This reaction constitutes an important sink for superoxide anions because it is about twice as fast as the maximum velocity of superoxide dismutase. In addition to direct inactivation of NO, ROS can decrease eNOS activity and sGC activity, and increase PDE5 activity, resulting in decreased cGMP levels. Increased ROS can be secondary to (1) ventilation or exposure to high oxygen; (2) poor antioxidant defense mechanisms such as superoxide dismutase, catalase, and glutathione peroxidase levels; and (3) increased production of...
superoxide anions from increased activity of enzymes such as nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase (Nox). The effect of prior oxygen exposure (in the form of OI) on response to iNO has been evaluated. Konduri and colleagues randomized near-term and term infants with HRF into early initiation of iNO (when OI is ≥15 but <25) or standard initiation (OI ≥25). There was no difference in the incidence of death (early iNO, 6.7% vs standard, 9.4%), ECMO (10.7% vs 12.1%), or death and ECMO combined (16.7% vs 19.5%). However, control infants receiving standard iNO deteriorated to OI greater than 40 more often than the early iNO group (14% vs 7%, \(P = .056\)). Based on this study, starting iNO at an OI less than 25 does not reduce the need for ECMO but may prevent progression of HRF and decrease exposure to high levels of oxygen in some neonates with HRF. Data from multiple trials of iNO in HRF are shown in Fig. 7. Based on these results, it seems that OI at initiation of iNO roughly corresponds with the frequency of ECMO/death in that cohort. The case series of gentle ventilation and iNO use from Columbia-Presbyterian hospital with lower target PaO2 and permissive hypercapnia was associated with a lower frequency of ECMO/death (28%) despite a high mean OI at initiation of iNO (46.8 ± 24.5). This association suggests that targeting lower PaO2 and limiting FiO2 (and possibly ROS generation) and barotrauma improves outcomes in PPHN.

**Left ventricular dysfunction**

Patients with HRF and PPHN typically have a right-to-left shunt at the level of ductus arteriosus and foramen ovale. In the presence of left ventricular dysfunction and/or hypoplasia, left atrial pressures are increased, resulting in a left-to-right shunt at the foramen ovale (see Table 1). Increased left atrial pressure results in pulmonary venous hypertension. Administration of iNO to a patient with pulmonary venous hypertension can result in potential flooding of the pulmonary capillary bed and worsening of pulmonary edema, resulting in clinical deterioration. Left ventricular hypoplasia associated

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**Fig. 7.** The effect of OI at initiation of iNO on the incidence of ECMO and death in various trials: the size of the bubble is based on the number of infants enrolled in the iNO arm in that trial. The OI at initiation corresponds approximately with the incidence of ECMO or death. A case series from Columbia-Presbyterian Hospital using gentle ventilation is associated with lower incidence of ECMO/death despite high OI at initiation of iNO, suggesting that prior exposure to oxygen is a more important factor than precise OI at initiation of iNO.
with CDH may contribute to pulmonary venous hypertension and could be a potential explanation for impaired response to iNO in these patients. It has been suggested that an inodilator such as milrinone may be more effective than iNO in improving left ventricular function and reducing pulmonary venous hypertension.

Two case series report the effectiveness of milrinone in improving oxygenation in iNO-resistant PPHN. Unlike iNO, which acts through cGMP, milrinone inhibits phosphodiesterase 3A (PDE3A) enzyme in PASMCs and increases the level of a different second messenger, cAMP, resulting in pulmonary vasodilation. Pulmonary vasodilation in response to milrinone is proportional to PDE3A activity in PASMCs. Exposure to NO donors increases PDE3A expression in rat PASMCs. Ventilation of newborn lambs with oxygen and iNO increases PDE3A activity in resistance level pulmonary arteries compared with ventilation with oxygen alone. Pulmonary arterial rings isolated from lambs ventilated with iNO relax significantly better to milrinone compared with lambs ventilated with oxygen only. These studies suggest that exposure to iNO increases PDE3A activity and that milrinone may be uniquely effective in promoting pulmonary vasodilation and improving oxygenation in iNO-resistant PPHN, in addition to its cardiac inotropic effect.

Increased vasoconstrictor mediators

ET-1 is produced by the endothelium and exerts its powerful vasoconstrictor effect by acting on ET-A receptors on vascular smooth muscle cells. Increased levels of plasma immunoreactive ET-1 levels have been reported in neonates with PPHN, and these levels correlate with the severity of disease. Bosentan, an ET receptor antagonist, has been used in PPHN. Mohamed and colleagues recently reported a prospective randomized trial of bosentan versus placebo in PPHN. Oral bosentan (1 mg/kg twice a day) resulted in a significant improvement in OI compared with placebo. Close monitoring of liver function is important during bosentan therapy.

Rare causes of PPHN/HRF in term neonates

In some patients with PPHN/HRF resistant to all treatments including ECMO, lung biopsy may be required to confirm the diagnosis. Patients with alveolar capillary dysplasia and misalignment of pulmonary veins (ACD/MPV) typically present with HRF and PPHN shortly after birth. Lung histology shows simplification of alveolar architecture, widened and poorly developed septa, with a paucity of capillaries. Small pulmonary arteries are muscularized, accompanied by pulmonary veins within the same connective tissue sheath (see Fig. 6). Patients with surfactant protein-B (SP-B) deficiency and ATP binding cassette A3 (ABCA3) transporter deficiencies present with intractable HRF. Infants with prolonged, severe HRF/PPHN out of proportion to their lung disease may require a lung biopsy or targeted genetic evaluation for definitive diagnosis.

Inotropes

PPHN is a syndrome associated with an increased PVR/SVR ratio. Systemic hypotension is a common feature of patients with PPHN and can be multifactorial. Common causes include (1) direct effect of the primary underlying disease such as sepsis or pneumonia, (2) myocardial dysfunction secondary to asphyxia or sepsis, (3) septal deviation to the left impinging on left ventricular end-diastolic volume and outflow tract, (4) ventilator therapies such as increased mean airway pressure reducing venous return, and (5) decreased pulmonary venous return caused by increased PVR reduces left ventricular preload.

It is a common practice in the NICU to obtain an echocardiogram to estimate systolic pulmonary arterial pressure and to increase systemic systolic pressure with an infusion
of inotropes such as dopamine. Dopamine is a nonselective vasoconstrictor and can increase systemic arterial pressure as well as pulmonary arterial pressure in newborn goats\textsuperscript{140} and preterm human infants with PDA. Initiation of norepinephrine infusion (0.5–1 \textmu g/kg/min) increased mean systemic arterial pressure from 39 ± 4 to 49 ± 4 mm Hg and increased mean pulmonary arterial pressure from 33 ± 4 to 42 ± 5 mm Hg, decreased pulmonary/systemic pressure ratio, and improved oxygenation in late preterm and term infants with PPHN.\textsuperscript{141} The investigators report echocardiographic findings that suggest increased pulmonary blood flow and speculate that norepinephrine may mediate an \(\alpha\)2 receptor–mediated pulmonary vasodilation.

We recently evaluated the effect of dopamine on systemic arterial pressure and pulmonary arterial pressure in newborn lambs with PPHN induced by antenatal ductal ligation\textsuperscript{64} and their control twins. Control lambs without PPHN have significantly higher systemic blood pressure compared with pulmonary arterial pressure (Fig. 8). Administration of dopamine selectively increases systemic arterial pressure at a lower dose without significantly increasing pulmonary arterial pressure, and increases pulmonary blood flow in control lambs with normal pulmonary vasculature. In PPHN lambs with remodeled pulmonary arteries, pulmonary arterial pressure is at systemic levels and is more sensitive to vasoconstrictor effects of dopamine. Dopamine did not increase pulmonary blood flow in lambs with PPHN. These findings emphasize the need for frequent echocardiograms to evaluate pulmonary arterial pressure in patients with PPHN on high doses of dopamine and norepinephrine.

**Partial Liquid Ventilation**

Partial liquid ventilation (PLV) with perfluorocarbons has been studied in HRF in animal models\textsuperscript{142,143} and human infants.\textsuperscript{144} PLV has been shown to improve gas exchange and improve spatial distribution of pulmonary blood flow in models of lung injury.\textsuperscript{145} However, PLV does not prevent hypoxic pulmonary vasoconstriction in the absence of parenchymal lung injury.\textsuperscript{146} A combination of iNO and PLV improved oxygenation in a lamb model of CDH\textsuperscript{147} but did not decrease PVR in a piglet model of MAS\textsuperscript{142} with conventional ventilation. The use of high-frequency PLV results in a significant

![Fig. 8. Effect of dopamine infusion on mean systemic arterial and mean pulmonary arterial pressure in normal newborn lambs and lambs with PPHN induced by antenatal ductal ligation. In newborn lambs with normal pulmonary vasculature, systemic blood pressure is significantly higher than pulmonary arterial pressure and increases relatively selectively in response to low doses of dopamine. In PPHN, systemic and pulmonary blood pressures are similar and increase in parallel in response to dopamine.](image-url)
decrease in PVR and an improvement in pulmonary blood flow in a preterm lamb model of RDS.\textsuperscript{148} It is likely that PLV improves alveolar recruitment, compliance, and gas exchange, and its effect on pulmonary hemodynamics is secondary to these changes.

**ECMO**

ECMO refers to a life support technique designed to enhance gas exchange and provide pulmonary and/or cardiac support in severe HRF. ECMO requires diversion of blood from a major systemic vessel through a gas exchange device (membrane oxygenator) and back to a major vessel. The venoarterial approach (VA) has served as the primary mode of cannulation for both cardiac and respiratory failure in neonates and uses a central vein (usually jugular) for drainage and an artery (usually carotid) for return. As blood is diverted from the pulmonary circuit, immediate decompression of the right ventricle occurs in VA-ECMO. Venovenous (VV) cannulation is appropriate for patients with severe respiratory failure who do not require cardiac support and uses a major vein for blood drainage and a vein for return of oxygenated blood to the right heart.\textsuperscript{149,150} Pulmonary and right ventricular hemodynamics are not altered, although the blood entering the pulmonary artery has substantially higher $P_O_2$. The impact of such increased oxygen tension in the pulmonary circulation on PVR is not known. The presence of pulsatile flow in VV ECMO is associated with better cerebral hemodynamics but this could be a reflection of patient selection bias.\textsuperscript{151} Overall, no major differences have been reported in respiratory outcome between VA and VV ECMO.\textsuperscript{152,153}

**SUMMARY**

Increased understanding of the pathophysiologic changes in the pulmonary circulation in neonatal HRF and PPHN in the last 2 decades has led to a substantial decrease in the number of neonatal respiratory patients requiring ECMO. Further clinical research into pulmonary vasodilator therapy has become more challenging because of a decreased number of patients and widespread availability of iNO, resulting in difficult study recruitment. Two unmet challenges remain in pulmonary circulatory disorders: CDH and premature infants with BPD and pulmonary hypertension.\textsuperscript{154} Multicenter trials to evaluate and develop appropriate strategies to ameliorate pulmonary vascular disease in these conditions are warranted.

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