Persistent Pulmonary Hypertension of the Newborn: Pathophysiology and Treatment

Steven H. Abman, MD
Professor of Pediatric Pulmonary and Critical Care Medicine
Director, Pediatric Heart Lung Center
Department of Pediatrics
University of Colorado School of Medicine and The Children's Hospital
Denver, Colorado

Survival at birth requires an immediate and sustained fall in pulmonary vascular resistance from its elevated level in utero to a low resistance, high flow circulation after delivery. This rapid drop allows for the eightfold increase in pulmonary blood flow that enables the lung to serve its postnatal function for gas exchange. Physiologic mechanisms that contribute to the normal fall in pulmonary vascular resistance at birth include increased oxygen tension, ventilation, and shear stress, leading to altered production of several vasoactive products, especially the enhanced release of nitric oxide and prostacyclin (PgI_2).[1-8] Some infants do not achieve or sustain the normal decrease in pulmonary vascular resistance at birth, leading to severe respiratory distress and profound hypoxemia, which is referred to as persistent pulmonary hypertension of the newborn (PPHN). PPHN is a major clinical syndrome, contributing significantly to high morbidity and mortality in both full-term and premature neonates.[9,10] Newborns with PPHN are at risk for severe asphyxia and its complications, including death, chronic lung disease, abnormal neurocognitive outcomes, and related problems. Over the past two decades, insights into basic mechanisms underlying the normal physiology of the fetal and transitional lung circulations have led to better understanding of the pathophysiology of PPHN, and have contributed to the development of a physiologic approach to the treatment of newborns with severe PPHN.

Physiology of the Normal Perinatal Pulmonary Circulation

Pulmonary vascular resistance is high throughout fetal life, especially in comparison with the very low resistance of the systemic circulation partly due to the placenta. As a result, the fetal lung receives less than 8% of combined ventricular output, with most of the right ventricular output crossing the ductus arteriosus to the aorta. Mechanisms that contribute to high pulmonary vascular resistance in the fetus include low oxygen tension, relatively low basal production of vasodilator products (such as PgI_2 and nitric oxide), increased production of vasoconstrictors (including endothelin-1 or leukotrienes), and altered smooth muscle cell reactivity (such as enhanced myogenic tone). During development, the fetal pulmonary circulation becomes progressively responsive to vasoactive stimuli, especially during late gestation. Oxygen administration to pregnant women to increase fetal PO_2 does not increase pulmonary blood flow between 20 to 26 weeks' gestation, but can cause pulmonary vasodilation in the 31-to-36-week fetus.[11] These findings suggest that in addition to lung vascular growth, progressive maturation of vascular function during development is also critical in preparation for the normal transition at birth.[12,13]

Several mechanisms regulate pulmonary vasoreactivity during development, including maturational changes in endothelial cell function, especially with regard to nitric oxide production.[14,15] Lung endothelial nitric oxide synthase (eNOS) mRNA and protein is present in the early fetus and increases with advancing gestation in utero and during the early postnatal period in rats and sheep.[16-18] Expression and activity of eNOS are regulated by several factors, including oxygen tension, hemodynamic forces, hormonal stimuli (eg, estradiol), paracrine factors (including vascular endothelial growth factor, VEGF), substrate and cofactor availability, superoxide production (which inactivates nitric oxide), and others.[19-22] Nitric oxide causes vasodilation by stimulating soluble guanylate cyclase in vascular smooth muscle, which increases sooth muscle cGMP content. Cyclic GMP-specific phosphodiesterase (PDE5) activity, which limits smooth muscle cGMP content, is high in the normal fetus, thereby playing a critical role in maintaining high pulmonary vascular resistance in utero.[23] Other vasodilators, including prostacyclin (PgI_2), are released on stimulation of the fetal lung (eg, increased shear stress), however, basal prostaglandin production appears to play a less important role on basal pulmonary vascular resistance in the fetal lung than nitric oxide. Physiologic roles of other dilators, including adrenomedullin, adenosine, and endothelium-derived hyperpolarizing factor (EDHF), are uncertain in the fetus. EDHF is a short-lived product of cytochrome P450 activity that is produced by vascular endothelium and has been found to cause vasodilation through activation of calcium-activated K+ channels in vascular smooth muscle in vitro. K+-channel activation appears to modulate basal pulmonary vascular resistance and vasodilator responses to shear stress and increased oxygen tension in the fetal lung, and may be particularly important in relaxation responses in resistance vessels.[5]

Vasoconstrictors, including lipid mediators (thromboxane A_2, leukotrienes C_4 and D_4, and platelet-activating factor) and endothelin-1, may also contribute to high pulmonary vascular resistance in utero. Endothelin-1, a potent vasoconstrictor and smooth muscle cell mitogen that is produced by vascular endothelium, plays a key role in fetal pulmonary vasoregulation.[24] PreproET-1 mRNA (the precursor to endothelin-1) was identified in fetal rat lung early in gestation, and high circulating endothelin-1 levels are present in umbilical cord blood. Endothelin-1 causes an intense vasoconstrictor response through activation of its ET-A and -B receptors on vascular smooth muscle. Inhibition of ET-A receptors causes fetal pulmonary vasodilation, suggesting an important role in maintaining high basal pulmonary vascular resistance.

Within minutes after delivery, pulmonary artery pressure falls and blood flow increases in response to birth-related stimuli. Mechanisms contributing to the fall in pulmonary vascular resistance at birth include establishment of an air-liquid interface, rhythmic lung distension, increased oxygen tension, and altered production of vasoactive substances. Physical stimuli, such as increased shear stress, ventilation and increased oxygen, cause pulmonary vasodilation in part by increasing production of vaosodilators, nitric oxide, and PgI_2. Inhibition of NOS activity attenuates the decline in pulmonary vascular resistance after delivery of fetal lambs, and suggest that about 50% of the rise in pulmonary blood flow at birth may be directly related to the acute release of nitric oxide.[2] Other vasodilator products, including PgI_2 and adenosine also modulate changes in pulmonary vascular tone at birth.

Experimental Models of PPHN

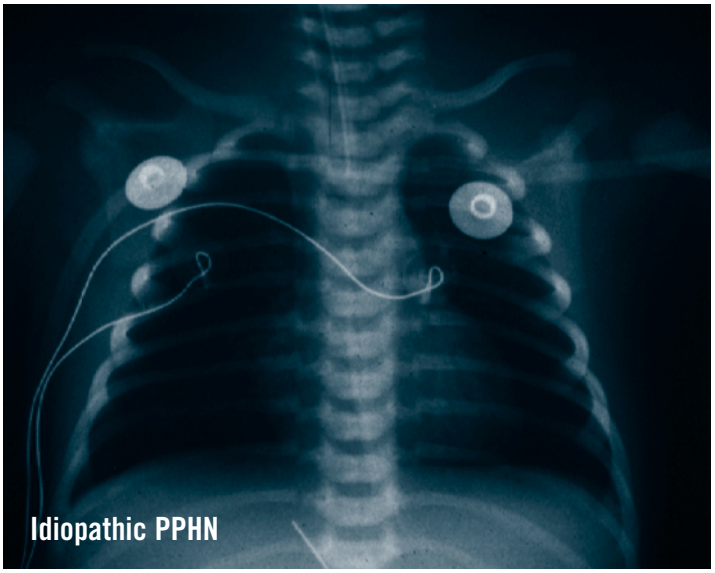
Mechanisms that lead to the failure of pulmonary vascular resistance to fall at birth have been pursued in various animal models in order to better understand the pathogenesis and pathophysiology of PPHN.[25,26] Such models have included exposure to acute or chronic hypoxia after birth, chronic hypoxia in utero, placement of meconium into the airways of neonatal animals, sepsis and others. Although each model demonstrates interesting physiologic changes that may be especially relevant to particular clinical settings, most studies examine only brief changes in the pulmonary circulation, and mechanisms underlying altered lung vascular structure and function of PPHN remain poorly understood. Clinical observations that neonates with severe PPHN who die during the first days after birth already have pathologic signs of chronic pulmonary vascular disease suggest that intrauterine events may play an important role in this syndrome. Adverse intrauterine stimuli during late gestation, such as abnormal hemodynamics, changes in substrate or hormone delivery to the lung, hypoxia, inflammation or others, may potentially alter lung vascular function and structure, contributing to abnormalities of postnatal adaptation. Several investigators have examined the effects of chronic intrauterine stresses, such as hypoxia or hypertension, in animal models in order to attempt to mimic the clinical problem of PPHN. Whether chronic hypoxia alone can cause PPHN is controversial.[27]

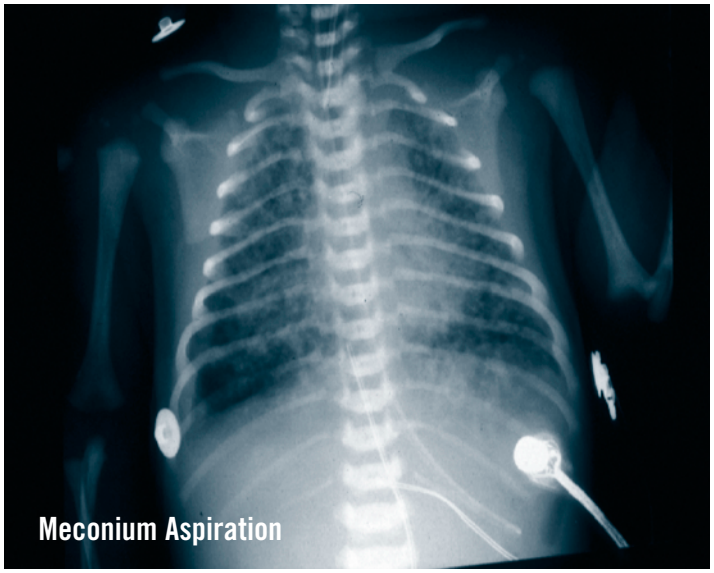
Pulmonary hypertension induced by early closure of the ductus arteriosus in fetal lambs alters lung vascular reactivity and structure, causing the failure of postnatal adaptation at delivery, and providing an experimental model of PPHN.[27-29] After delivery, these lambs have persistent elevation of pulmonary vascular resistance despite mechanical ventilation with high oxygen concentrations. This model is further characterized by endothelial cell dysfunction and altered smooth muscle cell reactivity and growth, including findings of impaired nitric oxide production and activity due to downregulation of lung eNOS mRNA and protein expression.[30-31] Fetal pulmonary hypertension also impaired soluble guanylate cyclase and upregulated cGMP-specific phosphodiesterase (type 5; PDE5) activities, suggesting further impairments in the nitric oxide-cGMP cascade.[32,33] Thus, alterations in the nitric oxide-cGMP cascade appear to play an essential role in the pathogenesis and pathophysiology of experimental PPHN. Abnormalities of nitric oxide production and responsiveness contribute to altered structure and function of the developing lung circulation, leading to failure of postnatal cardiorespiratory adaptation. Recent evidence indicates that excessive production of reactive oxygen species such as superoxide in the pulmonary vasculature may further contribute to the disruption in nitric oxide-cGMP signaling in this model.[34]

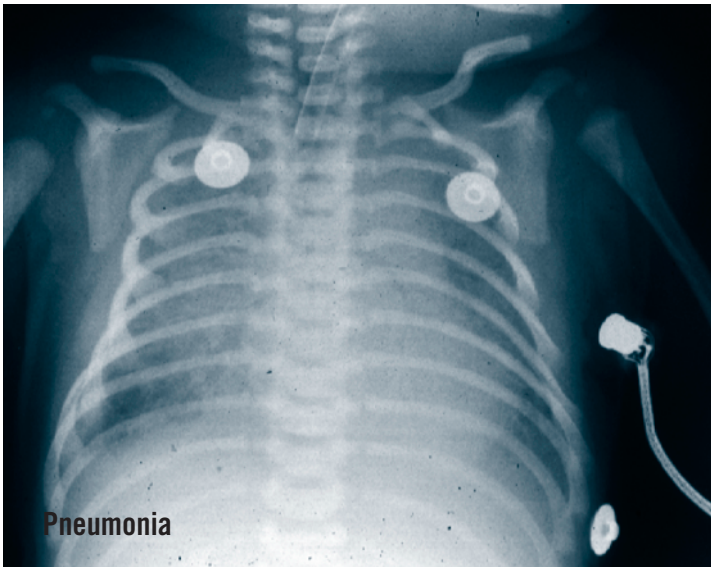
Circulating levels of endothelin-1, a potent vasoconstrictor and co-mitogen for vascular smooth muscle cell hyperplasia, are increased in human newborns with severe PPHN.[35] In the experimental model of PPHN due to compression of the ductus arteriosus in fetal sheep, lung endothelin-1 mRNA and protein content is markedly increased, and the balance of endothelin receptors are altered, favoring vasoconstriction.[36,37] Chronic inhibition of the ET-A receptor attenuates the severity of pulmonary hypertension, decreases pulmonary artery wall thickening, and improves the fall in pulmonary vascular resistance at birth in this model. Thus, experimental studies have shown the important role of the nitric oxide-cGMP cascade and the endothelin-1 system in the regulation of vascular tone and reactivity of the fetal and transitional pulmonary circulation. Finally, in addition to vasoactive mediators, such as nitric oxide and endothelin-1, it has become clear that alterations of growth factors, such as VEGF and platelet-derived growth factor (PDGF), are likely to play key roles in the modulation of vascular maturation, growth and structure. For example, inhibition of PDGF-B attenuates smooth muscle hyperplasia in experimental pulmonary hypertension in fetal lambs, suggesting a potential role in the pathogenesis of PPHN.[38]

PPHN: Clinical Physiology and Epidemiology

The first reports of PPHN described term newborns with profound hypoxemia who lacked radiographic evidence of parenchymal lung disease and echocardiographic evidence of structural cardiac disease. In these patients, hypoxemia was caused by marked elevations of pulmonary vascular resistance leading to right–to-left extrapulmonary shunting of blood across the patent ductus arteriosus or foramen ovale during the early postnatal period. Because of the persistence of high pulmonary vascular resistance and blood







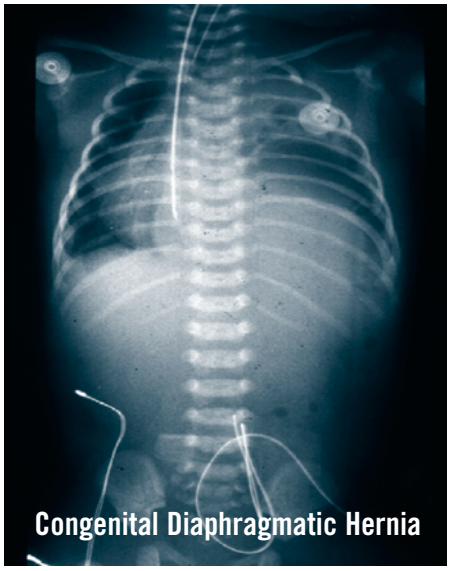


Figure. Chest x-ray findings illustrating disorders associated with persistent pulmonary hypertension of the newborn.

flow through these "fetal shunts," the term "persistent fetal circulation" was originally used to describe this group of patients. Consequently, it was recognized that this physiologic pattern can complicate the clinical course of neonates with diverse causes of hypoxemic respiratory failure. As a result, the term "PPHN" has been considered as a syndrome, and is currently applied more broadly to include neonates that have a similar physiology in association with different cardiopulmonary disorders, such as meconium aspiration, sepsis, pneumonia, asphyxia, congenital diaphragmatic hernia, respiratory distress syndrome, and others. (**Figure**) Striking differences exist between these conditions, and mechanisms that contribute to high pulmonary vascular resistance can vary between these diseases. However, these disorders are included in the syndrome of PPHN because of common pathophysiologic features, including sustained elevation of pulmonary vascular resistance leading to hypoxemia due to right-to-left extrapulmonary shunting of blood flow across the ductus arteriosus or foramen ovale.

Diseases associated with PPHN are often classified within one of three categories: (1) maladaptation, in which vessels are presumably of normal structure but have abnormal vasoreactivity; (2) excessive muscularization, increased smooth muscle cell thickness and increased distal extension of muscle to vessels that are usually nonmuscular; and (3) underdevelopment, lung hypoplasia associated with decreased pulmonary artery number. These designations are imprecise, however, and high pulmonary vascular resistance in most patients likely involves overlapping changes among these categories. For example, neonates with congenital diaphragmatic hernia are primarily classified as having vascular "underdevelopment" due to lung hypoplasia, yet lung histology of fatal cases typically shows marked muscularization of pulmonary arteries, and clinically, these patients can respond to vasodilator therapy. Similarly, neonates with meconium aspiration often have clinical evidence of altered vasoreactivity, but often have muscularization at autopsy.

Recent estimates suggest an incidence for PPHN of 1.9/1000 live births, or an estimated 7400 cases per year.[39] Epidemiologic studies have demonstrated strong associations between PPHN and maternal smoking and ingestion of cold remedies that include aspirin or other nonsteroidal anti-inflammatory products.[40] Since these agents can induce

Table. Disorders Associated with Neonatal Pulmonary Hypertension

Pulmonary
Meconium aspiration syndrome
Respiratory distress syndrome (* term and preterm newborns)
Lung hypoplasia, primary
Congenital diaphragmatic hernia
Pneumonia/sepsis
Idiopathic transient tachypnea of the newborn
Alveolar-capillary dysplasia
Associated abnormalities in lung development:
- Genetic abnormalities in surfactant proteins and metabolism
- Congenital lobar emphysema (rare association)
- Cystic adenomatoid malformation (rare association)
- Idiopathic, with impaired distal alveolarization
- Others

Cardiovascular
Myocardial dysfunction (asphyxia, infection, stress)
Structural cardiac diseases
- Mitral stenosis, cor triatriatum
- Endocardial fibroelastosis
- Pompe disease
- Aortic atresia, coarctation of the aorta, interrupted aortic arch
- Transposition of the great vessels
- Ebstein anomaly, tricuspid atresia

Hepatic arteriovenous malformations
Cerebral arteriovenous malformations
Total anomalous pulmonary venous return
Pulmonary vein stenosis (isolated)
Pulmonary atresia

Associations with Other Diseases
Neuromuscular disease
Metabolic disease
Polycythemia
Thrombocytopenia
Maternal drug use (antidepressants, cold medications) or smoking

partial constriction of the ductus arteriosus, it is possible that pulmonary hypertension due to narrowing of the ductus arteriosus contributes to PPHN. Recently, maternal ingestion of antidepressants, particularly serotonin-reuptake inhibitors, during late gestation was strongly associated with an increased risk of PPHN.[41] Other perinatal stresses, including placenta previa and abruption, and asymmetric growth restriction, are associated with PPHN; however, most neonates who are exposed to these prenatal stresses do not develop PPHN. Circulating levels of L-arginine, the substrate for nitric oxide, are decreased in some newborns with PPHN, suggesting that impaired nitric oxide production may contribute to the pathophysiology of PPHN, as suggested by experimental studies. It is possible that genetic factors increase susceptibility for neonatal pulmonary hypertension. A recent study reported strong links between PPHN and polymorphisms of the carbamoyl phosphate synthase gene, which is associated with decreased circulating arginine and nitric oxide metabolite levels.[42] Studies of adults with idiopathic primary pulmonary hypertension have identified abnormalities of bone morphogenetic protein receptor genes; whether polymorphisms of genes for the BMP or TGF-beta receptors, other critical growth factors, vasoactive substances, or other products increase the risk for some newborns to develop PPHN is unknown.

Clinical Presentation and Evaluation

Clinically, PPHN is most often recognized in term or near term neonates, but clearly can occur in premature neonates as well (**Table**). PPHN is often associated with perinatal distress, such as asphyxia, low APGAR scores, meconium staining, and other factors; however, idiopathic PPHN can lack signs of acute perinatal distress. PPHN often presents as respiratory distress and cyanosis within 6 to 12 hours of birth. Laboratory findings can include low glucose, hypocalcemia, hypothermia, polycythemia, or thrombocytopenia. Radiographic findings are variable, depending on the primary disease associated with PPHN. Classically, the chest x-ray in idiopathic PPHN is oligemic, may appear slightly hyperinflated, and lacks parenchymal infiltrates. In general, the degree of hypoxemia is often disproportionate to the severity of radiographic evidence of lung disease.

Not all term newborns with hypoxemic respiratory failure have PPHN-type physiology.[43] Hypoxemia in the newborn can be due to several mechanisms, including: extrapulmonary shunt, in which high pulmonary artery pressure at systemic levels leads to right-to-left shunting of blood flow across the patent ductus arteriosus or patent foramen ovale; and intrapulmonary shunt or ventilation-perfusion mismatch, in which hypoxemia results from the lack of mixing of blood with aerated lung regions due to parenchymal lung disease, without the shunting of blood flow across the patent ductus arteriosus or patent foramen ovale. In the latter setting, hypoxemia is related to the amount of pulmonary arterial blood that perfuses nonaerated lung regions. Although pulmonary vascular resistance is often elevated in hypoxemic newborns without PPHN, high pulmonary vascular resistance does not contribute significantly to hypoxemia in some cases.

Several factors can contribute to high pulmonary artery pressure in neonates with PPHN-type physiology. Pulmonary hypertension can be due to vasoconstriction or structural lesions that directly increase pulmonary vascular resistance. Changes in lung volume in neonates with parenchymal lung disease can also be an important determinant of pulmonary vascular resistance. Pulmonary vascular resistance increases at low lung volumes due to dense parenchymal infiltrate and poor lung recruitment, or with high lung volumes due to hyperinflation associated with overdistension or gas trapping. Cardiac disease is also associated with PPHN. High pulmonary venous pressure due to left ventricular dysfunction can also elevate pulmonary arterial pressure (eg, asphyxia, sepsis), causing right-to-left

shunting, with little vasoconstriction. In this setting, enhancing cardiac performance and systemic hemodynamics may lower pulmonary arterial pressure more effectively than achieving pulmonary vasodilation. Thus, understanding the cardiopulmonary interactions is key to improving outcome in PPHN.

PPHN is characterized by hypoxemia that is poorly responsive to supplemental oxygen. In the presence of right-to-left shunting across the patent ductus arteriosus, "differential cyanosis" is often present, which is difficult to detect by physical examination, and is defined by a difference in PaO_2 between right radial artery versus descending aorta values of 10 torr or greater, or an O_2 saturation gradient greater than 5%. However, the echocardiogram plays an essential diagnostic role and is an essential tool for managing newborns with PPHN. The initial echocardiographic evaluation is important to rule-out structural heart disease causing hypoxemia (eg, coarctation of the aorta and total anomalous pulmonary venous return). As stated above, not all term newborns with hypoxemia have PPHN physiology. Although high pulmonary artery pressure may be common, the diagnosis of PPHN is uncertain without evidence of bidirectional or predominantly right-to-left shunting across the patent ductus arteriosus or patent foramen ovale. Echocardiographic signs suggestive of pulmonary hypertension (eg, increased right ventricular systolic time intervals and septal flattening) are less helpful. In addition to demonstrating the presence of PPHN physiology, the echocardiogram is critical for the evaluation of left ventricular function and diagnosis of anatomic heart disease, including such "PPHN mimics" as coarctation of the aorta; total anomalous pulmonary venous return; hypoplastic left heart syndrome; and others. Studies should carefully assess the predominant direction of shunting at the patent foramen ovale as well as the patent ductus arteriosus. Although right-to-left shunting at the patent ductus arteriosus or patent foramen ovale is typical for PPHN, predominant right-to-left shunting at the patent ductus arteriosus but left-to-right shunt at the patent foramen ovale may help to identify the important role of left ventricular dysfunction to the underlying pathophysiology. In the presence of severe left ventricular dysfunction with pulmonary hypertension, pulmonary vasodilation alone may be ineffective in improving oxygenation. In this setting, efforts to reduce pulmonary vascular resistance should be accompanied by targeted therapies to increase cardiac performance and decrease left ventricular afterload. Thus, careful echocardiographic assessment provides invaluable information about the underlying pathophysiology and will help guide the course of treatment.

Treatment

In general, management of the newborn with PPHN includes the treatment and avoidance of hypothermia, hypoglycemia, hypocalcemia, anemia and hypovolemia; correction of metabolic acidosis; diagnostic studies for sepsis; serial monitoring of arterial blood pressure, pulse oximetry (pre- and post-ductal); and transcutaneous PCO_2, especially with the initiation of high frequency oscillatory ventilation (HFOV). Therapy includes aggressive management of systemic hemodynamics with volume and cardiotonic therapy (dobutamine, dopamine, and milrinone), in order to enhance cardiac output and systemic O_2 transport. In addition, increasing systemic arterial pressure can improve oxygenation in some cases by reducing right-to-left extrapulmonary shunting. Failure to respond to medical management, as evidenced by failure to sustain improvement in oxygenation with good hemodynamic function, often leads to treatment with extracorporeal membrane oxygenation (ECMO).[44] Although ECMO can be a life-saving therapy, it is costly, labor intensive, and can have severe side effects, such as intracranial hemorrhage. Since arteriovenous ECMO usually involves ligation of the carotid artery, acute and long-term central nervous system injury remains a major concern.

The goal of mechanical ventilation is to improve oxygenation and to achieve "optimal" lung volume to minimize the adverse effects of high or low lung volumes on pulmonary vascular resistance, while minimizing the risk for lung injury ("volutrauma"). Failure to achieve adequate lung volumes (functional residual capacity) contributes to hypoxemia and high pulmonary vascular resistance in newborns with PPHN. Some newborns with parenchymal lung disease with PPHN physiology improve oxygenation and decrease right-to-left extrapulmonary shunting with aggressive lung recruitment during high frequency oscillatory ventilation or with an "open lung approach" of higher positive end-expiratory pressure with low tidal volumes, as more commonly utilized in older patients with ARDS. Acute hyperventilation can improve PaO_2 in neonates with PPHN, providing a diagnostic test and therapeutic strategy. However, depending upon the ventilator strategy and underlying lung disease, hyperventilation is likely to increase ventilator-associated lung injury, and the ability to sustain decreased pulmonary vascular resistance during prolonged hyperventilation is unproven. Experimental studies suggest that the response to alkalosis is transient, and that alkalosis may paradoxically worsen pulmonary vascular tone, reactivity and permeability edema. In addition, prolonged hyperventilation reduces cerebral blood flow and oxygen delivery to the brain, potentially worsening neurodevelopmental outcome.

Additional therapies, including infusions of sodium bicarbonate, surfactant therapy and the use of intravenous vasodilator therapy, are also highly variable between centers. Surfactant may improve oxygenation in some lung diseases, such as meconium aspiration and respiratory distress syndrome, a multicenter trial failed to show a reduction in ECMO utilization in newborns with PPHN. The use of intravenous vasodilator drug therapy, with such agents as tolazoline, magnesium sulfate, prostacyclin and sodium nitroprusside, is also controversial due to the non-selective effects of these agents on the systemic circulation. Systemic hypotension worsens right-to-left shunting, may impair oxygen delivery and worsen gas exchange in patients with parenchymal lung disease.

Inhaled nitric oxide (iNO) therapy at low doses (5 to 20 ppm) improves oxygenation and decreases the need for ECMO therapy in patients with diverse causes of PPHN.[44-48] Multicenter clinical trials support the use of iNO in near-term (more than 34 weeks' gestation) and term newborns, and the use of iNO in infants less than 34 weeks' gestation remains investigational. Studies support the use of iNO in infants who have hypoxemic respiratory failure with evidence

of PPHN, who require mechanical ventilation and high inspired oxygen concentrations. The most common criterion employed has been the oxygenation index (OI; mean airway pressure times FiO_2 times 100 divided by PaO_2). Although clinical trials commonly allowed for enrollment with OI levels above 25, the mean OI at study entry in multicenter trials approximated 40. It is unclear whether infants with less severe hypoxemia would benefit from iNO therapy. Available evidence, therefore, supports the use of doses of iNO beginning at 20 ppm in term newborns with PPHN, since this strategy decreased ECMO utilization without an increased incidence of adverse effects.[46] Although brief exposures to higher doses (40 to 80 ppm) appear to be safe, sustained treatment with 80 ppm nitric oxide increases the risk of methemoglobinemia. In our practice, we discontinue iNO if the FiO_2 is below 0.60 and the PaO_2 is above 60 without evidence of "rebound" pulmonary hypertension or an increase in FiO2 greater than 15% after iNO withdrawal. Prolonged need for iNO therapy without resolution of disease should lead to a more extensive evaluation to determine whether previously unsuspected anatomic lung or cardiovascular disease is present (for example, pulmonary venous stenosis, alveolar capillary dysplasia, severe lung hypoplasia, or others).[49]

In newborns with severe lung disease, HFOV is frequently used to optimize lung inflation and minimize lung injury. In clinical pilot studies using iNO, the combination of HFOV and iNO caused the greatest improvement in oxygenation in some newborns who had severe PPHN complicated by diffuse parenchymal lung disease and underinflation (eg, respiratory distress syndrome, pneumonia). A randomized, multicenter trial demonstrated that treatment with HFOV plus iNO was often successful in patients who failed to respond to HFOV or iNO alone in severe PPHN, and differences in responses were related to the specific disease associated with the complex disorders of PPHN.[48]

Although clinical improvement during iNO therapy occurs with many disorders associated with PPHN, not all neonates with acute hypoxemic respiratory failure and pulmonary hypertension respond to iNO. Several mechanisms may explain the clinical variability in responsiveness to iNO therapy. An inability to deliver nitric oxide to the pulmonary circulation because of poor lung inflation is the major cause of poor responsiveness. In some settings, administration of nitric oxide with HFOV has improved oxygenation more effectively than during conventional ventilation in the same patient. In addition, poor nitric oxide responsiveness may be related to myocardial dysfunction or systemic hypotension, severe pulmonary vascular structural disease, and unsuspected or missed anatomic cardiovascular lesions (such as total anomalous pulmonary venous return, coarctation of the aorta, alveolar capillary dysplasia, and others).[49]

Another mechanism of poor responsiveness to iNO may be altered smooth muscle cell responsiveness, and there are emerging therapies that take advantage of our increased understanding of the cellular effects of iNO. Inhibition of cGMP-metabolizing phosphodiesterase (PDE5) activity may increase efficacy of iNO by increasing cGMP concentrations. Recently approved by the FDA for the treatment of pulmonary hypertension in older patients, the potent and specific PDE5 inhibitor, sildenafil, has recently been shown to be effective in a small study of newborns with severe PPHN.[50]

New studies indicate that scavengers of reactive oxygen species (eg, superoxide anion) with superoxide dismutase causes marked pulmonary vasodilation and can augment responsiveness to iNO in experimental PPHN.[51] In addition, Moya et al have recently suggested that treatment with a unique gas, O-nitrosoethanol (ethyl nitrite, ENO), may increase the endogenous pool of S-nitrosothiols in the airway and circulation, thereby providing a new treatment strategy for PPHN.[52] In a brief report, ENO briefly improved postductal arterial saturation for 4 hours in 7 neonates. However, only a few patients improved in terms of oxygenation and the response was small, was associated with a rapid rise in methemoglobinemia, and may have had systemic effects. Another potential approach to augment pulmonary vasodilation may be to combine treatment with PgI_2. Whereas intravenous PgI_2 can decrease systemic arterial pressure, inhaled PgI_2 improved oxygenation in four infants with PPHN who did not respond or sustain their response to iNO without worsening systemic hemodynamics.[53] Whether these strategies will be more effective or will improve responsiveness in neonates who fail to respond to iNO therapy is unknown.

Summary

PPHN is a clinical syndrome that is associated with diverse cardiopulmonary diseases, with pathophysiologic mechanisms including pulmonary vascular, cardiac and lung disease. Experimental work on basic mechanisms of vascular regulation of the developing lung circulation and models of perinatal pulmonary hypertension has improved our therapeutic approaches to neonates with PPHN. Inhaled nitric oxide has been shown to be an effective pulmonary vasodilator for infants with PPHN, but successful clinical strategies require meticulous care of associated lung and cardiac disease. More work is needed to expand our therapeutic repertoire in order to further improve the outcome of the sick newborn with severe hypoxemia, especially in patients with lung hypoplasia and advanced structural vascular disease. ■

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