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NeoReviews 2007;8:e14-e21
DOI: 10.1542/neo.8-1-e14

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Pulmonary Hypertension in the Neonate

Robin H. Steinhorn, MD,* Kathryn N. Farrow, MD, PhD*

Author Disclosure
Dr Steinhorn has served as a consultant for INO Therapeutics. Dr Farrow did not disclose any financial relationships relevant to this article.

Objectives
After completing this article, readers should be able to:

1. Delineate the characteristics of normal pulmonary vascular transition.
2. Describe the process of meconium aspiration syndrome and how it leads to pulmonary hypertension.
3. Explain the pathophysiology of idiopathic persistent pulmonary hypertension of the newborn (PPHN).
4. Explain how congenital diaphragmatic hernia contributes to pulmonary hypertension.
5. Review the treatment options for PPHN.

Abstract
Persistent pulmonary hypertension of the newborn (PPHN), a major clinical problem in the neonatal intensive care unit, can contribute significantly to morbidity and mortality in both term and preterm infants. Hypoxemic respiratory failure or PPHN can place newborns at risk for death, neurologic injury, and other morbidities. PPHN is categorized into parenchymal lung disease (meconium aspiration syndrome, respiratory distress syndrome, sepsis), idiopathic (or “black-lung”), and pulmonary hyperplasia (as seen in congenital diaphragmatic hernia). Treatment involves correction of factors that may promote vasoconstriction, mechanical ventilation to achieve optimal lung volume that may include high-frequency oscillatory ventilation, medical optimization of cardiac output and left ventricular function, and inhaled nitric oxide. A number of alternative and emerging pulmonary vasodilators are being investigated.

Introduction
Following birth, the fetus must adapt its cardiopulmonary system rapidly to the new demands of extrauterine life. If a newborn fails to achieve or sustain the normal decrease in pulmonary vascular resistance (PVR) at birth, the result is hypoxemic respiratory failure or persistent pulmonary hypertension of the newborn (PPHN). PPHN is a major clinical problem in the neonatal intensive care unit and can contribute significantly to morbidity and mortality in both term and preterm neonates. Newborns who experience hypoxemic respiratory failure or PPHN are at risk for numerous complications, including death, neurologic injury, and other morbidities. The incidence of severe PPHN is estimated at 0.2% of liveborn term infants.

The Fetal Pulmonary Vasculature
The fetal pulmonary circulation undergoes striking developmental changes in vascular growth, structure, and function. Because the placenta, not the lung, serves as the organ of gas exchange, less than 10% of the combined ventricular output is circulated through the pulmonary vascular bed, and most of the right ventricular output crosses the ductus arteriosus to the aorta. Despite increases in pulmonary vascular surface area, PVR increases with gestational age when corrected for lung or body weight, suggesting that vascular tone actually increases during late gestation and is high prior to birth. Therefore, pulmonary pressures in utero are equivalent to systemic pressures due to elevated PVR.

Multiple pathways are involved in maintaining high pulmonary vascular tone in utero, including low oxygen tension and mediators such as endothelin-1 (ET-1) and leukotri-
enes. In addition, basal production of vasodilator products such as prostacyclin (PGI₂) and nitric oxide (NO) is relatively low, despite the presence of all three nitric oxide synthase (NOS) isoforms in the fetal lung. The fetal vasculature also has the interesting ability to oppose vasodilation. A mechanically induced increase in pulmonary blood flow or exposure to vasodilators, such as a raised oxygen tension, prostaglandins, and acetylcholine, only induces short-lasting vasodilation.

Normal Pulmonary Vascular Transition

The pulmonary vascular transition at birth is characterized by a rapid increase in pulmonary blood flow, reduction in PVR, and clearance of lung liquid. Pulmonary endothelial cells play a central role in the pulmonary vascular transition via numerous mediators that act on the smooth muscle cells. The primary endothelial products currently believed to be responsible for the pulmonary vascular changes during transition include NO and arachidonic acid metabolites.

NO production increases dramatically at the time of birth. Pulmonary expression of both endothelial nitric oxide synthase (eNOS) and its downstream target, solu-

ble guanylate cyclase (sGC), increases during late gestation. Ultimately, increased NO production and sGC activity lead to increased cyclic guanosine monophosphate (cGMP) concentrations in vascular smooth muscle cells, which produce vasorelaxation via decreasing intracellular calcium concentrations (Figure). Acute or chronic inhibition of NOS in fetal lambs produces pulmonary hypertension following delivery, indicating the agent’s fundamental importance in the normal pulmonary vascular transition. New evidence suggests that NOS activity can be reduced by the action of endogenous inhibitors, primarily asymmetric dimethylarginine (ADMA), which competes with the NO substrate L-arginine. The low levels of eNOS activity in fetal life potentially could be caused by ADMA, and it is interesting to note that ADMA concentrations sufficient to inhibit NOS are found in amniotic fluid and fetal blood. These concentrations increase toward term, are present in the urine of healthy newborns, and subsequently decline to become undetectable by 5 days of age. ADMA is metabolized to citrulline by the dimethylarginine dimethylaminohydrolase enzymes DDAH I and II. Expression of these enzymes is regulated developmentally and increases rapidly after birth. It is possible that ADMA and DDAH regulate NOS production in fetal life and play a significant role during transition.

The prostacyclin pathway is another potentially important vasodilatory pathway in the normal transition to extrauterine life. Cyclooxygenase (COX) is the rate-limiting enzyme that generates prostacyclin from arachidonic acid. Both COX-1 and COX-2 are found in the lung, but COX-1 in particular is upregulated during late gestation. There is evidence that the increase in estrogen concentrations in late gestation may play a role in upregulating PGI₂ synthesis. This upregulation leads to an increase in prostacyclin production in late gestation and early postnatal life. Prostacyclin interacts with adenylate cyclase to increase intracellular cyclic adenosine monophosphate (cAMP) levels, which leads to vasorelaxation.

At the time of birth, multiple factors regulate these
The most critical signals for such transitional changes are believed to be mechanical distention of the lung, a decrease in carbon dioxide tension, and an increase in oxygen tension in the lungs. When near-term fetal lambs are ventilated without changing carbon dioxide or oxygen tensions, pulmonary blood flow increases to approximately two thirds of levels observed following birth. Similarly, near-term fetal lambs can be exposed to oxygenation without ventilation through hyperbaric oxygenation of the ewe. Under these conditions, fetal PVR decreases and pulmonary blood flow increases to levels comparable to after birth.

Oxygen stimulates the activity of both eNOS and COX-1 immediately after birth, leading to increased levels of NO and prostacyclin. Oxygen also stimulates the release of adenosine triphosphate from oxygenated red blood cells, which increases the activity of both eNOS and COX-1. Finally, shear stress is believed to be an important factor regulating the synthesis of NO and PGI2. During transition, the initial increase in pulmonary blood flow in response to ventilation or oxygenation leads to increased vascular shear stress. In vitro studies show that abrupt increases in flow stimulate the release of both NO and PGI2 in cultured endothelial cells. There is evidence that the NO-cGMP pathway is a more potent modulator of pulmonary vascular tone following shear stress and that NO may, in part, mediate PGI2-induced pulmonary vasodilation.

Pathophysiology of PPHN
PPHN can be categorized primarily as three types: 1) the abnormally constricted pulmonary vasculature due to parenchymal diseases such as meconium aspiration syndrome (MAS), respiratory distress syndrome, and sepsis; 2) the structurally abnormal vasculature, also known as idiopathic PPHN; or 3) the hypoplastic vasculature as seen in congenital diaphragmatic hernia (CDH) (Table 1). The pathophysiology of each type depends on the point in gestation when the normal transition to extrauterine life fails.

Parenchymal Lung Disease: MAS
The most common cause of PPHN is MAS, which affects 25,000 to 30,000 infants, causing 1,000 deaths annually in the United States. Approximately 13% of all live births are complicated by meconium-stained fluid, although only 5% of affected infants subsequently develop MAS. The traditional belief is that aspiration occurs with the first breath after birth, but more recent data suggest that for the more severely affected infants, aspiration more likely occurs in utero. In either case, meconium aspiration injures the lung through multiple mechanisms, including mechanical obstruction of the airways, chemical pneumonitis due to inflammation, activation of complement, inactivation of surfactant, and vasoconstriction of pulmonary vessels. Meconium acts as an airway obstruction with a “ball-valve” effect, preventing adequate ventilation in the immediate postnatal period. The subsequent air trapping is associated with a 15% to 30% risk of pneumothorax.

Meconium also appears to have toxic effects in the lungs that are mediated by inflammation. Within hours of the meconium aspiration event, neutrophils and macrophages are found in the alveoli and lung parenchyma. The release of cytokines such as tumor necrosis factor-alpha, interleukin 1-beta (IL-1-beta), and IL-8 may injure the lung parenchyma directly and lead to vascular leakage that causes pneumonitis with pulmonary edema. There is also evidence that meconium injury may trigger directly the postnatal release of vasoconstrictors such as ET-1, TXA2, and PGE2. It has been recognized recently that in addition to its obstructive and proinflammatory effects, meconium inactivates surfactant, in part due to the presence of surfactant inhibitors such as albumin, phosphatidylserine, and phospholipase A2. The pneumonitis and surfactant inactivation impair adequate ventilation immediately after birth, which is a key mediator of normal pulmonary transition. Such impairment of normal transition in combination with the postnatal release of vasoconstrictors ultimately leads to the pulmonary hypertension seen in conjunction with MAS.

### Table 1. Mechanisms of Persistent Pulmonary Hypertension of the Newborn

<table>
<thead>
<tr>
<th>Abnormally Constricted Pulmonary Vasculature</th>
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<tbody>
<tr>
<td>Meconium Aspiration Syndrome</td>
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<tr>
<td>Pneumonia</td>
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<td>Respiratory Distress Syndrome</td>
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<tr>
<th>Structurally Abnormal Pulmonary Vasculature</th>
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<tr>
<td>Idiopathic Persistent Pulmonary Hypertension (“black lung PPHN”)</td>
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<th>Hypoplastic Pulmonary Vasculature</th>
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<tr>
<td>Congenital Diaphragmatic Hernia</td>
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<td>Pulmonary Hypoplasia</td>
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respiratory disorders persistent pulmonary hypertension of the newborn
Idiopathic PPHN

Idiopathic (or “black lung”) PPHN is most common in term and near-term (≥34 weeks’ gestation) newborns. Evaluation of these infants at autopsy reveals significant remodeling of the pulmonary vasculature, with vessel wall thickening and smooth muscle hyperplasia. Further, the smooth muscle extends to the level of the intra-acinar arteries, which normally does not occur until much later in the postnatal period. As a result, affected infants do not vasodilate their pulmonary vasculature appropriately in response to birth-related stimuli, and they present with profound hypoxemia and clear, hyperlucent lung fields on radiography, thus the term “black lung” PPHN.

The pathophysiology of this abnormally remodeled pulmonary vasculature is a subject of intense investigation. One cause of idiopathic PPHN is constriction of the fetal ductus arteriosus in utero from exposure to nonsteroidal anti-inflammatory drugs (NSAIDs) during the third trimester. Ductal constriction or ligation can be performed surgically in utero in lambs. Findings in PPHN lambs are similar to those observed in human infants: an increase in fetal pulmonary artery pressure, pulmonary vascular remodeling, and profound hypoxemia. Recent studies have demonstrated that NSAIDs such as ibuprofen and naproxen frequently are found in the meconium of infants suffering PPHN (even with a negative maternal history). Further, the concentration of the drugs in the meconium correlated with the incidence of PPHN lambs. This suggests that production of the vasoconstrictor arachidonic acid metabolite thromboxane increases in pulmonary hypertension resulting from hypoxia.

Circulating concentrations of the potent vasoconstrictor ET-1 are elevated in lambs and newborns who have PPHN. The release of ET-1 can be stimulated by hypoxia. ET-1 effects are mediated through two receptors: ET-A receptors on smooth muscle cells that mediate vasoconstriction and ET-B receptors on endothelial cells that mediate vasodilation. In addition, endothelin may affect vascular tone by increasing production of ROS such as superoxide and hydrogen peroxide, which also act as vasoconstrictors.

Together, these findings indicate that idiopathic PPHN is the result of complex pathologic processes that include structural remodeling of the pulmonary vasculature as well as disruption of multiple signaling pathways, most notably endothelin and NO. Because multiple pathways are involved, it is almost certain that effective treatment will require multiple therapeutic agents.

Pulmonary Hypoplasia (CDH)

CDH occurs in 1 of every 2,000 to 4,000 live births and accounts for 8% of all major congenital anomalies. CDH is a developmental abnormality of diaphragmatic devel-
development that results in a defect that allows abdominal viscera to enter the chest and compress the lung. Herniation occurs most often in the posterolateral segments of the diaphragm, and 80% of the defects occur on the left side. Although in utero compression of the lung typically is believed to produce lung hypoplasia, there is some evidence that the lung hypoplasia may be a primary event that occurs independently of the diaphragmatic defect. Because severe CDH develops early in the course of lung development, airway divisions are limited in both the affected and contralateral lungs. Therefore, CDH is characterized by a variable degree of pulmonary hypoplasia associated with a decrease in cross-sectional area of the pulmonary vasculature.

Development of the pulmonary arterial system parallels development of the bronchial tree. Therefore, fewer arterial branches are observed in CDH. Further, abnormal medial muscular hypertrophy is observed as far distally as the acinar arterioles. In very severe cases, left ventricular hypoplasia is observed. Pulmonary capillary blood flow is decreased because of the small cross-sectional area of the pulmonary vascular bed, and flow may be decreased further by abnormal pulmonary vasoconstriction.

The reported survival rate for CDH varies widely, depending on whether the disease is studied before or after birth. Some tertiary referral centers with extracorporeal membrane oxygenation (ECMO) capability report that 75% or more of infants who have CDH survive. In contrast, population-based studies based on antenatal diagnosis have consistently reported lower survival rates and have not demonstrated a beneficial effect of therapeutic modalities such as ECMO and inhaled NO. CDH no longer is believed to require immediate surgery because the primary problem after birth is not herniation of abdominal viscera into the chest but severe pulmonary hypoplasia and associated pulmonary hypertension. However, the medical management of CDH remains a major challenge for the clinician.

### Treatment of PPHN

The initial treatment of the newborn who has PPHN includes correction of factors that may promote vasoconstriction, such as hypothermia, hypoglycemia, hypocalcemia, anemia, and hypovolemia (Table 2). Although the use of alkalinizing agents is controversial, correction of metabolic acidosis is standard. Cardiac function should be optimized as needed with volume expansion and inotropic agents (dobutamine, dopamine, and milrinone) to enhance cardiac output and systemic oxygen transport.

The goal of mechanical ventilation is to achieve optimal lung volume to allow for lung recruitment while minimizing the risk for lung injury. Failure to achieve adequate lung volumes at or above functional residual capacity contributes to hypoxemia and high PVR in newborns who have PPHN. For example, some newborns who have parenchymal lung disease associated with PPHN improve oxygenation and decrease right-to-left extrapulmonary shunting in response to lung recruitment during high-frequency oscillatory ventilation (HFOV). A favorable response to HFOV is most likely in infants who have homogenous lung disease due to respiratory distress syndrome or pneumonia. It is important to remember that the goal is optimal, not maximal, lung volume. Mechanical ventilation using excessive pressures can produce acute lung injury, pulmonary edema, decreased lung compliance, and lung inflammation due to increased cytokine production as well as lung neutrophil accumulation. Further, overexpansion of the lung paradoxically may worsen pulmonary hypertension because overdistended alveoli may compress capillaries and small arterioles.

Parenchymal lung disease of the term and near-term infant often is associated with surfactant deficiency or inactivation. Single-center trials have shown that surfactant improves oxygenation in infants who have MAS, and a large multicenter trial demonstrated that surfactant treatment decreased the need for ECMO. The reduction in need for ECMO was most apparent for infants who had MAS or sepsis. In contrast, a recent report indicates

### Table 2. Medical Treatment of Persistent Pulmonary Hypertension of the Newborn

<table>
<thead>
<tr>
<th>Initial Therapies</th>
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<tbody>
<tr>
<td>Treat metabolic derangements: correct acidosis, hypoglycemia, hypocalcemia</td>
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<tr>
<td>Optimize lung recruitment: mechanical ventilation, high-frequency oscillatory ventilation, surfactant</td>
<td></td>
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<tr>
<td>Optimize cardiac output and left ventricular function: vasopressors, inotropic agents</td>
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<tr>
<td>Pulmonary Vasodilators</td>
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<tr>
<td>Inhaled nitric oxide</td>
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<tr>
<td>Future Therapies</td>
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<tr>
<td>Phosphodiesterase Inhibitors (sildenafil)</td>
<td></td>
</tr>
<tr>
<td>Inhaled prostacyclin analogs (iloprost, prostacyclin)</td>
<td></td>
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<tr>
<td>Recombinant superoxide dismutase</td>
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Downloaded from [http://neoreviews.aappublications.org](http://neoreviews.aappublications.org) by J Michael Coleman on August 19, 2010
that surfactant therapy does not reduce death or need for ECMO in infants who have CDH. Thus, surfactant may be an important tool in optimizing lung inflation in infants who have parenchymal lung disease, but not idiopathic PPHN or CDH.

**Inhaled Nitric Oxide**

Before the availability of inhaled NO (iNO), selective pulmonary vasodilatation was not clinically possible. iNO has many of the characteristics of an ideal selective pulmonary vasodilator. It has a rapid and potent vasodilator effect. Because it is a small gas molecule, NO can be delivered through a ventilator directly to airspaces approximating the pulmonary vascular bed. Once in the bloodstream, NO binds avidly to hemoglobin, limiting its systemic vascular activity and increasing its selectivity for the pulmonary circulation.

Large placebo-controlled trials demonstrated that iNO significantly decreased the need for ECMO in newborns who had PPHN, although iNO did not reduce mortality or length of hospitalization. Several large randomized trials had sufficient patient entry to assess response as a function of the underlying lung disease. The most consistent finding was that iNO did not reduce the need for ECMO in infants who had unrepaired CHD. Follow-up studies to 12 to 24 months have shown that iNO did not alter the incidence of chronic lung disease or adverse neurodevelopmental sequelae significantly. This is an interesting and likely important observation that may indicate that the underlying disease is associated with early neurologic injury.

In general, iNO should be begun when the oxygenation index (OI) exceeds 25, the entry criteria for the multicenter studies noted previously. The OI is a commonly used calculation to describe the severity of pulmonary hypertension and is calculated as:

\[
OI = \left( \frac{\text{mean airway pressure} \times \text{FiO}_2}{\text{postductal PaO}_2} \right) \times 100
\]

A recent study demonstrated that beginning iNO earlier in the disease course at an OI of more than 15 did not change the incidence of ECMO use or death or improve other patient outcomes. There are few contraindications to iNO therapy. An initial echocardiographic evaluation is essential to rule out structural heart lesions and establish the presence of pulmonary hypertension. The use of iNO is contraindicated in congenital heart disease that is dependent on right-to-left shunting across the ductus arteriosus (eg, critical aortic stenosis, interrupted aortic arch, and hypoplastic left heart syndrome). In addition, iNO may worsen pulmonary edema in infants who have obstructed total anomalous pulmonary venous return due to the fixed venous obstruction.

Up to 40% of infants do not experience improved oxygenation or maintain a response to iNO. Therefore, the ability to sustain iNO delivery during emergency medical transport to an ECMO center is vital. Recent reports show that iNO therapy can be applied safely during transport. Measurements made in the cabin of various transport vehicles (including helicopters) demonstrated that ambient NO and NO\(_2\) concentrations remained within safe ranges during transport with iNO therapy—an important consideration for the medical personnel and pilots.

Following the introduction of high-frequency ventilation (HFV), surfactant, and iNO in the early 1990s, the patient demographic for neonatal ECMO changed. Neonatal Extracorporeal Life Support (ELSO) Organization registry data indicate that the use of such therapies has increased steadily over the last 10 years, accompanied by a greater than 40% reduction in the number of neonates cannulated for ECMO. However, some physicians have speculated that the new treatment modalities may delay ECMO cannulation and negatively affect infants who continue to require ECMO. For example, use of high fractions of inspired oxygen and high ventilator settings could lead to oxidative stress and lung injury, and prolonged use of aggressive respiratory support could lead to chronic lung injury. We recently examined data from the ELSO registry between 1996 and 2003. We found that NO, HFV, and surfactant use were not associated with any adverse outcomes during ECMO, including increased hours on ECMO or increased time to extubation. Further, NO use was associated with a decreased risk of cardiac arrest prior to cannulation, and both surfactant and NO use were associated with lower ECMO mortality. Because ECMO is proven therapy for severe respiratory failure, it is reassuring that these new therapies have not had a negative impact on the most severely affected infants.

**Alternative and Emerging Pulmonary Vasodilators**

Because the response to iNO is believed to be mediated primarily by activation of sGC and cGMP-dependent protein kinase, it is logical to pursue other mechanisms that might enhance cGMP accumulation. Inhibition of cGMP-metabolizing PDE5 activity may increase cGMP concentrations and may result in pulmonary vasodilation or increased efficacy of iNO.

Sildenafil, a potent and highly specific PDE5 inhibi-
tor, recently was relabeled and approved by the United States Food and Drug Administration for the treatment of pulmonary hypertension in adults. In lambs that had experimental pulmonary hypertension, both enteric and aerosolized sildenafil diluted the pulmonary vasculature and augmented the pulmonary vascular response to iNO. Intravenous sildenafil was found to be a selective pulmonary vasodilator that had efficacy equivalent to iNO in a piglet model of meconium aspiration, although hypertension and worsening oxygenation resulted when it was used in combination with iNO. Sildenafil may attenuate rebound pulmonary hypertension after withdrawal of iNO in newborn and pediatric patients. Use of sildenafil in PPHN has been limited by its availability only as an enteric form, although a recent report indicates that it improved oxygenation and survival in human infants who had PPHN compared with placebo. An intravenous preparation recently was investigated in newborns who had pulmonary hypertension, and data should be available soon.

Similar to cGMP, cAMP also stimulates vasodilatation. One potential approach that takes advantage of this mechanism is use of milrinone to inhibit PDE3, the phosphodiesterase that metabolizes cAMP. Milrinone has been shown to decrease pulmonary artery pressure and resistance and to act additively with iNO in animal studies. A recent report indicates that it may decrease rebound pulmonary hypertension after discontinuation of iNO.

PGI₂ stimulates membrane-bound adenylate cyclase, increases cAMP, and inhibits pulmonary artery smooth muscle cell proliferation in vitro. Although the use of systemic infusions of PGI₂ may be limited by systemic hypotension, inhaled PGI₂ has been shown to have vasodilator effects limited to the pulmonary circulation. Reports in children have been positive, but to date there have been few reports of inhaled PGI₂ use in neonates who have PPHN. The actions of inhaled PGI₂ and iNO appear to be additive in humans and even synergistic in some studies. Rebound pulmonary hypertension following withdrawal of iNO has been mitigated by intravenous PGI₂ in children who had pulmonary hypertension following congenital heart disease. A recent report indicates that brief inhalations of another prostaglandin mediator, PGE₁, also may improve oxygenation in newborns who have severe hypoxicemic respiratory failure.

New studies indicate that scavengers of ROS such as superoxide dismutase (SOD) may augment responsiveness to iNO. Because iNO usually is delivered with high concentrations of oxygen, there is the potential for enhanced production of free radicals such as superoxide and peroxynitrite. Further, as described previously, increased production of superoxide is noted in experimental models of PPHN. SOD scavenges and converts superoxide radical to hydrogen peroxide, which subsequently is converted to water by the enzyme catalase. Administration of recombinant human superoxide dismutase (rhSOD) has been tested in preterm infants without adverse effects and with trends toward decreased pulmonary morbidity. In lambs that have pulmonary hypertension, rhSOD dilates the pulmonary circulation, and recent studies show it improves oxygenation similar to iNO. This therapeutic approach may have multiple beneficial effects: Scavenging superoxide may make both endogenous and inhaled NO more available to stimulate vasodilatation and may reduce oxidative stress and limit lung injury. It is hoped that human trials will begin soon.

Suggested Reading


Murphy JD, Rabinovitch M, Goldstein JD, Reid LM. The structural basis of persistent pulmonary hypertension of the newborn infant. *J Pediatr.* 1981;98:962–967


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**NeoReviews Quiz**

1. When a newborn fails to achieve or sustain the normal decrease in pulmonary vascular resistance at birth, the result is hypoxemic respiratory failure or persistent pulmonary hypertension of the newborn (PPHN). Of the following, the mediator most responsible for normal pulmonary vascular transition at birth is:
   A. Asymmetric dimethylarginine.
   B. Endothelin-1.
   C. Leukotriene.
   D. Nitric oxide.
   E. Thromboxane.

2. Idiopathic PPHN is characterized by pathologic remodeling of the pulmonary vasculature, with vessel wall thickening and smooth muscle hyperplasia. Disruptions of the nitric oxide, prostacyclin, and endothelin signaling pathways contribute to the pathogenesis of idiopathic PPHN. Of the following, the mediator most likely to be decreased in expression in the pulmonary vasculature in idiopathic PPHN is:
   A. Endothelial nitric oxide synthase.
   B. Endothelin-1.
   C. Peroxynitrite.
   D. Phosphodiesterase-5.
   E. Reactive oxygen species.

3. Inhaled nitric oxide (iNO) has many of the characteristics of an ideal selective pulmonary vasodilator and, therefore, is used widely in the treatment of PPHN. Large randomized clinical trials have been conducted to assess the response to iNO as a function of the underlying lung disease. Of the following, the lung disease most resistant to iNO is:
   A. Bacterial pneumonia.
   B. Congenital diaphragmatic hernia.
   C. Idiopathic PPHN.
   D. Meconium aspiration syndrome.
   E. Respiratory distress syndrome.
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