Abnormal Vasoreactivity in the Pathophysiology of Persistent Pulmonary Hypertension of the Newborn

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

1. Describe the factors that modulate the transition of pulmonary circulation from in utero to after birth.
2. Delineate temporal changes in pulmonary vascular resistance during fetal life.
3. List the substances that play a role in vasoregulation of normal fetal pulmonary circulation.
4. Delineate the role of nitric oxide in increasing pulmonary blood flow at birth.
5. Describe the common physiologic characteristics of persistent pulmonary hypertension of the newborn.
6. Delineate how abnormalities in production and responsiveness to nitric oxide affect developing lung circulation.
7. Explain why inhaled nitric oxide therapy may not be effective in all cases of pulmonary hypertension.

Introduction
Successful adaptation of the newborn to postnatal conditions requires a dramatic transition of the pulmonary circulation from a high resistance state in utero to a low-resistance state within minutes after birth. This fall in pulmonary vascular resistance (PVR) allows for a nearly 10-fold rise in pulmonary blood flow that ensures that the lung can assume its postnatal role in gas exchange. Over the past 50 years, experimental studies have demonstrated that several mechanisms contribute to the normal fall in PVR at birth, including the establishment of a gas-liquid interface in the lung, increased oxygen tension, rhythmic distension of the lung (respiration), and shear stress. In addition to these physical stimuli, pulmonary vascular tone is modulated by altered production of vasoactive products, especially the release of potent vasodilator substances, such as nitric oxide (NO) and prostacyclin (PGI2). Within minutes of this vasodilator response, increased pulmonary blood flow distends the vasculature, causing a “structural reorganization” of the vascular wall that includes flattening of the endothelium and thinning of smooth muscle cells and matrix. Thus, the ability to accommodate this marked rise in blood flow requires rapid functional and structural adaptations to ensure that the normal postnatal fall in PVR is achieved.

Some infants fail to achieve or sustain the normal decrease in PVR at birth, which leads to severe respiratory distress and hypoxemia, referred to as persistent pulmonary hypertension of the newborn (PPHN). PPHN is a clinical syndrome that can occur in association with diverse neonatal cardiopulmonary disorders, such as meconium aspiration, sepsis, pneumonia, acute respiratory distress syndrome (ARDS), asphyxia, congenital diaphragmatic hernia, and lung hypoplasia. Although striking differences exist among these conditions, they can share common pathophysiologic features, including high PVR leading to extrapulmonary right-to-left shunting of blood flow across the ductus arteriosus or foramen ovale. PPHN remains a major clinical problem, contributing significantly to morbidity and mortality in both term and preterm neonates.

Mechanisms that cause severe pulmonary hypertension after birth are understood incompletely, but they can include abnormalities of pulmonary vascular tone, reactivity, growth, and structure (Fig. 1 and Table). Because PPHN represents the failure of postnatal adaptation of the lung circulation at birth, understanding basic mechanisms of normal functional and structural development of the pulmonary circulation in utero and mechanisms that contribute to pulmonary vasodilation at birth may provide insights into the syndrome of PPHN and its treatment. Although high PVR in various diseases associated with PPHN often is accompanied by hypertensive structural changes, this review will focus on mechanisms that regulate vascular tone and reactivity in the normal and hypertensive perinatal lung. Other articles in this issue review structural components and the clinical treatment of PPHN.

Vasoregulation of the Normal Fetal Pulmonary Circulation
Due to high PVR in the normal fetus, the pulmonary circulation receives less than 8% to 10% of combined ventricular output, with most of the right ventricular output crossing the ductus arteriosus to the aorta. During fetal life, pulmonary artery pressure and blood flow pro-

ABBREVIATIONS
ARDS: acute respiratory distress syndrome
cGMP: cyclic guanosine-3’,5’-monophosphate
EDHF: endothelium-derived hyperpolarizing factor
ET: endothelin
NO: nitric oxide
NOS: nitric oxide synthase
PDE: phosphodiesterase
PGI2: prostacyclin
PPHN: persistent pulmonary hypertension of the newborn
PVR: pulmonary vascular resistance
RDS: respiratory distress syndrome
sGC: soluble guanylate cyclase
gressively increase with advancing gestational age. Pulmonary vascular growth also increases dramatically during late gestation, but despite an increase in vascular surface area, PVR actually increases with gestational age when corrected for lung or body weight. Thus, pulmonary vascular tone increases during late gestation, especially prior to birth. Mechanisms that contribute to high basal PVR in the fetus are not understood completely, but they include low oxygen tension, low basal production of vasodilator products (such as PGI₂ and NO), increased production of vasoconstrictors (including endothelin-1 [ET-1] or leukotrienes), and altered smooth muscle cell reactivity (such as enhanced myogenic tone). The pulmonary vasculature can respond to vasoactive stimuli relatively early in the developing sheep fetus, but such reactivity increases during late gestation. For example, the pulmonary vasoconstrictor response to hypoxia and the vasodilator response to increased fetal PO₂ or acetylcholine increase with gestation in the ovine fetus. These findings suggest that in addition to structural maturation and growth of the developing lung circulation, the vessel wall also undergoes functional maturation, leading to enhanced vasoreactivity during fetal life.

Mechanisms that contribute to progressive changes in pulmonary vasoreactivity during development are unknown, but may include maturation of pulmonary endothelial cell function, especially in regard to the NO-cyclooxygenase-3',5'-monophosphate (cGMP) cascade (Fig. 2). NO is produced primarily by vascular endothelium during the conversion of L-arginine to L-citrulline by the enzyme NO synthase (NOS). Once produced, NO rapidly diffuses to underlying smooth muscle cells and causes vasodilation by stimulating soluble guanylate cyclase and increasing cGMP production. Elevated cGMP levels stimulate cGMP kinase, which then opens calcium-activated K⁺ channels and causes membrane hyperpolarization. This lowers intracellular calcium in the smooth muscle cell by decreasing calcium entry through L-type channels and causes vasodilation. In some experimental settings, NO has been shown to stimulate K⁺ channels or voltage-gated Ca²⁺ channels directly independent of increased cGMP.

NOS expression and activity are affected by multiple factors, including oxygen tension, hemodynamic forces, hormonal stimuli, substrate and cofactor availability, and superoxide production (which inactivates NO). Lung endothelial NOS mRNA and protein are present in the early fetus and increase with advancing gestation in utero and during the early postnatal period in rats. In fetal sheep, lung endothelial NOS mRNA, protein, and activity increase markedly at 113 to 118 days (term = 147 d). The timing of this increase in lung endothelial NOS content coincides with the capacity to respond to endothelium-dependent vasodilator stimuli, such as oxygen and acetylcholine. In contrast, fetal pulmonary arteries are more responsive to exogenous NO earlier in gestation. Thus, the ability of exogenous NO to dilate fetal pulmonary arteries is greater at less mature gestational ages than respon-

### TABLE. Potential Mechanisms Leading to Failure of Pulmonary Vasodilation at Birth

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<tr>
<th>Failure to Release or Sustain Release of Endogenous Vasodilators:</th>
<th>Endothelium-derived hyperpolarizing factor</th>
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<tr>
<td>Nitric oxide</td>
<td>Adenosine</td>
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<td>Prostacyclin</td>
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<td>Others (adrenomedullin?)</td>
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<th>Increased Production of Vasoconstrictors:</th>
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<tr>
<td>Endothelin-1</td>
<td>Thromboxane</td>
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<tr>
<td>Leukotrienes</td>
<td>Platelet-activating factor</td>
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<th>Altered Vascular Smooth Muscle Cell Responsiveness:</th>
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<tr>
<td>Enhanced myogenic tone</td>
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<tr>
<td>Failure to respond to dilator stimuli (eg, decreased soluble guanylate cyclase, cGMP kinase, or K⁺ channel expression; increased phosphodiesterase activity)</td>
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<th>Hypertensive Structural Remodeling:</th>
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<tr>
<td>Smooth muscle hyperplasia and hypertrophy</td>
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<td>Altered extracellular matrix production</td>
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<td>Adventitial thickening</td>
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siveness to vasodilator stimuli that require the endothelium to release endogenous NO. These findings suggest that the ability of the endothelium to produce or sustain production of NO in response to specific stimuli during maturation lags behind the capacity of fetal pulmonary smooth muscle to relax to NO. This may account for clinical observations that extremely preterm newborns are highly responsive to inhaled NO.

Vascular responsiveness to NO also depends on several smooth muscle cell enzymes, including soluble guanylate cyclase, cGMP-specific (types V) phosphodiesterase (PDE5), and cGMP kinase. Several studies have shown that soluble guanylate cyclase, which produces cGMP in response to NO activation, is active before 70% of term gestation in the ovine fetal lung. Similarly, PDE5, which limits cGMP-mediated vasodilation by hydrolysis and inactivation of cGMP, is active in utero. Infusions of selective PDE5 antagonists, including zaprinast, diprydamol, E4021, and DMPPO, cause potent and sustained fetal pulmonary vasodilation. In the fetal lung, PDE5 expression has been localized to vascular smooth muscle, and PDE5 activity is high compared with the postnatal lung. Thus, PDE5 activity appears to play a critical role in pulmonary vasoregulation during the perinatal period and must be considered when assessing responsiveness to endogenous NO and related vasodilator stimuli.

Functionally, the NO-cGMP cascade plays several important physiologic roles in vasoregulation of the fetal pulmonary circulation. These include: 1) modulating basal PVR in the fetus; 2) mediating the vasodilator response to specific physiologic and pharmacologic stimuli; and 3) opposing the strong myogenic tone in the normal fetal lung. Past studies in fetal lambs have demonstrated that intrapulmonary infusions of NOS inhibitors increase basal PVR by 35%. Because inhibition of NOS increases basal PVR at least as early as 75% of gestation (112 d) in the fetal lamb, endogenous NOS activity appears to contribute to vasoregulation throughout late gestation. NOS inhibition also selectively blocks pulmonary vasodilation to such stimuli as acetylcholine, oxygen, and shear stress in the normal fetus. In addition, more recent studies have suggested that NO release plays a role in modulating high intrinsic or myogenic tone in the fetal pulmonary circulation. The myogenic response commonly is defined by the presence of increased vasoconstriction caused by acute elevation of intravascular pressure or “stretch stress.” Past in vitro studies demonstrated the presence of a myogenic response in sheep pulmonary arteries and greater myogenic activity in fetal pulmonary arteries than neonatal or adult arteries. More recent studies of intact fetal lambs have demonstrated that high myogenic tone operates normally in the fetus and contributes to maintaining high PVR in utero. In addition, these studies demonstrated that NO inhibition further unmasks a potent myogenic response, suggesting that downregulation of NOS, as observed in experimental models of pulmonary hypertension, may increase myogenic activity further, adding to the risk for unopposed vasoconstriction in response to stretch stress at birth.

Although other vasodilator products, including PGI2, are released when the fetal lung is stimulated (eg, by increased shear stress), basal release of PGI2 appears to play a less important role than NO in fetal pulmonary vasoregulation. For example, cyclo-oxygenase inhibition has minimal effect on basal PVR and does not increase myogenic tone in the fetal lamb. The physiologic roles of other dilators, including adrenomedullin, adenosine, and endothelium-derived hyperpolarizing factor (EDHF), are uncertain. EDHF is a short-lived, diffusible factor 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 PVR and vasodilator responses to shear stress and increased oxygen tension in the fetal lung, but whether this is partly related to EDHF activity is unknown.

Vasoconstrictors long have been considered as having the potential to maintain high PVR in utero. Several candidate products, including lipid mediators (thromboxane A2, leukotrienes C4 and D4, and platelet-activating factor) and ET-1, have been studied extensively. Thromboxane A2, a potent pulmonary vasoconstrictor that has been implicated in animal models of group B streptococcal sepsis, does not appear to influence PVR in the normal fetus. In contrast, inhibition of leukotriene
production causes fetal pulmonary vasodilation, although questions have been raised regarding the specificity of these agents, and additional studies with newer and more selective inhibitors are needed. Similarly, inhibition of platelet-activating factor may influence PVR during the normal transition, but data from recent experimental studies are difficult to interpret because of extensive nonspecific hemodynamic effects.

ET-1, a potent vasoconstrictor and comitogen that is produced by vascular endothelium, plays a key role in fetal pulmonary vasoregulation. PreproET-1 mRNA (the precursor to ET-1) was identified in fetal rat lung early in gestation, and high circulating ET-1 levels are present in umbilical cord blood. Although ET-1 causes an intense vasoconstrictor response in vitro, its effects in the intact pulmonary circulation are complex. Brief infusions of ET-1 cause transient vasodilation, but PVR progressively increases during prolonged treatment. The biphasic pulmonary vascular effects during pharmacologic infusions of ET-1 are explained by the presence of at least two different ET receptors. The ET B receptor, localized to the endothelium in the sheep fetus, mediates the ET-1 vasodilator response through the release of NO. A second receptor, the ET A receptor, is located on vascular smooth muscle, and when activated, causes marked constriction. Although capable of both vasodilator and constrictor responses, ET-1 is more likely to play an important role as a pulmonary vasoconstrictor in the normal fetus. This is suggested in extensive fetal studies showing that inhibition of the ET A receptor decreases basal PVR and augments the vasodilator response to shear stress-induced pulmonary vasodilation. Thus, ET-1 is likely to modulate PVR through the ET A and B receptors, but its predominant role is as a vasoconstrictor through stimulation of the ET A receptor.

Mechanisms of Pulmonary Vasodilation at Birth

Within minutes after delivery, pulmonary artery pressure falls and blood flow increases in response to birth-related stimuli, such as ventilation, increased P02, and shear stress. Physical stimuli, including increased shear stress, ventilation, and increased oxygen, cause pulmonary vasodilation in part by increasing production of vasodilators, NO, and Pgl2. Pretreatment with the NOS inhibitor, nitro-L-arginine, attenuates pulmonary vasodilation after delivery by 50% in near-term fetal lambs. These findings suggest that a significant part of the rise in pulmonary blood flow at birth may be related directly to the acute release of NO. Each of the birth-related stimuli can stimulate NO release independently, followed by vasodilation through cGMP kinase-mediated stimulation of K+ channels. Although the endothelial isoform of NOS (type III) has been presumed to be the major contributor of NO at birth, recent studies suggest that other isoforms (inducible [type II] and neuronal [type I]) may be important sources of NO release in utero and at birth. Early studies were performed in term animals, but NO also contributes to the rapid decrease in PVR at birth in preterm lambs, at least as early as 112 to 115 days (70% of term). Other vasodilator products, including Pgl2, also modulate changes in pulmonary vascular tone at birth.

Rhythmic lung distension and shear stress stimulate both Pgl2 and NO production in the late-gestation fetus, but increased O2 tension triggers NO activity and overcomes the effects of Pgl2 inhibition at birth. Thus, although NO does not account for the entire fall in PVR at birth, NOS activity appears important in achieving postnatal adaptation of the lung circulation. Adenosine release also may contribute to the fall in PVR at birth, but its actions may be partly through NO release.

Abnormal Vasoreactivity in Experimental PPHN

As a clinical syndrome, PPHN includes diverse cardiac and pulmonary disorders or it can be an idiopathic disorder. Although these diverse diseases have features that are distinct from each other, they share a common pathophysiologic characteristic: high PVR leading to right-to-left shunting of blood across the ductus arteriosus or foramen ovale and marked hypoxemia. The central hallmarks of PPHN include sustained elevation of PVR, abnormal vasoreactivity, and at least in fatal cases, structural remodeling of the pulmonary vascular bed. Mechanisms leading to the failure of postnatal adaptation are poorly understood. The inability to lower PVR effectively during the first days of life in neonates who have PPHN may be lead to further abnormalities in vasoreactivity and structure. Early changes in reactivity due to decreased dilator production, increased vasoconstrictors, or altered smooth muscle cell responsiveness can elevate PVR. Within hours to days, hypertension itself can accelerate pulmonary vascular injury, and with sustained elevation of PVR, disease may progress rapidly to become more refractory to therapy.

Diseases associated with the syndrome of PPHN often are characterized as fitting into one of three categories: 1) Maladaptation, in which vessels are presumably of normal structure but have abnormal vasoreactivity; 2) Excessive muscularization, in which smooth muscle cell thickness is increased and muscle extends distally to vessels that usually are nonmuscular; and 3) Underdevelopment, in which lung hypoplasia is associated with decreased numbers of pulmonary arteries. Clinically, many conditions are characterized by changes in both structure and function. For example, congenital diaphragmatic hernia includes abnormal reactivity, hypertensive structural remodeling, and altered vascular growth. Probably not all newborns who have PPHN have structural lung vascular lesions; altered pulmonary vasoreactivity in some cases can be due to an acute insult (eg, group B streptococcal sepsis, meconium aspiration, acute asphyxia).

Several experimental models have been studied to explore the pathogenesis and pathophysiology of PPHN. Such models include acute or chronic hypoxia exposure in utero and after birth, placement of meconium into the airways of neonatal animals, and sepsis. Although each model demonstrates interesting
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Physiologic changes that may be especially relevant to particular clinical settings, most 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 who have severe PPHN and 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 decreased lung blood flow, changes in substrate or hormone delivery to the lung, chronic hypoxia, chronic hypertension, or inflammation, have the potential to alter lung vascular function and structure, thereby contributing to abnormalities of postnatal adaptation.

Several investigators have examined the effects of chronic intrauterine stresses, such as hypoxia or hypertension, in animals in an attempt to mimic the clinical problem of PPHN. Whether chronic hypoxia alone can cause PPHN is controversial. An early report that maternal hypoxia in rats increases pulmonary vascular smooth muscle thickening in newborns has not been reproduced in maternal rats or guinea pigs with more extensive studies. However, animal studies suggest that hypertension due to either renal artery ligation or partial or complete closure of the ductus arteriosus can cause structural and physiologic changes that resemble features of clinical PPHN.

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. In this model, partial closure of the ductus arteriosus acutely increases pulmonary artery pressure and flow, but blood flow returns toward the baseline value after 1 hour. Over days, pulmonary artery pressure and PVR increase progressively, but flow remains low and PaO₂ is unchanged. Thus, this model illustrates the effects of chronic intrauterine hypertension, but not high flow, on intrauterine lung vascular structure and function. Marked right ventricular hypertrophy and structural remodeling of small pulmonary arteries develop after 8 days of hypertension. After delivery, these lambs have persistent elevation of PVR despite mechanical ventilation with high oxygen concentrations. Thus, physiologic and structural studies suggest that this experimental model of PPHN mimics many of the abnormalities found in severe idiopathic PPHN in the human newborn.

To determine whether changes in the NO-cGMP system contribute to pulmonary vascular abnormalities in PPHN, investigators have studied endothelial and smooth muscle cell function in this experimental model (Fig. 3). That chronic hypertension can alter NO production or activity was suggested initially in physiologic studies of pulmonary vasodilation in hypertensive and control lambs. Pulmonary vasodilator responses to acetylcholine and increased oxygen, which act in part by stimulating NO release, were impaired after chronic hypertension. Responsiveness to atrial natriuretic peptide, which causes vasodilation by directly increasing smooth muscle cGMP content independent of NO release by vascular endothelium, remained relatively intact. These findings suggested that intrauterine hypertension impairs endothelial function and that the ability to produce NO may be limited. Chronic pulmonary hypertension decreases lung eNOS mRNA and protein expression and total NOS activity. As predicted from studies of NOS inhibition in normal fetal lambs, myogenic tone is elevated in this model of PPHN. Thus, these studies support the hypothesis that vascular injury in utero can decrease vasodilator responsiveness to birth-related stimuli by reducing lung eNOS content and NO production. Whether impaired NOS activity in utero also contributes to hypertensive structural remodeling of pulmonary arteries (including smooth muscle hypertrophy or hyperplasia) is uncertain.

Pulmonary vasodilation following endogenous administration of NO depends on several other factors, including smooth muscle soluble guanylate cyclase (sGC) and cGMP-specific phosphodiesterase (type 5; PDE5) activities. Recent studies have examined sGC and PDE5 activities after chronic ductus arteriosus closure in this experimental model of PPHN. sGC activity was impaired in hypertensive lambs, as reflected by decreased generation of cGMP and reduced vascular relaxation to NO stimulation in vitro. In addition, lung PDE5 activity was increased markedly in this model, suggesting that rapid cGMP hydrolysis may limit cGMP-dependent pulmonary vasodilation after chronic hypertension. Thus,
decreased lung eNOS protein and activity in the presence of decreased sGC and elevated PDE5 activities limits the ability to sustain smooth muscle cGMP, favoring vasoconstriction and high PVR in experimental PPHN. These observations may have clinical implications for potential strategies to enhance responsiveness to vasodilator therapy of PPHN.

Alterations in the NO-cGMP cascade appear to play an essential role in the pathogenesis and pathophysiology of experimental PPHN. Abnormalities of NO production and responsiveness contribute to altered structure and function of the developing lung circulation, leading to failure of postnatal cardiorespiratory adaptation. Insights into mechanisms underlying altered vasoreactivity may provide new treatment strategies for clinical PPHN.

In addition to changes in the NO pathway, upregulation of ET-1 contributes to altered vascular tone and structure in experimental PPHN. Acute and chronic treatment with an ET A receptor blocker improves pulmonary blood flow and decreases hypertensive remodeling in lambs that have experimental PPHN.

**Clinical Implications**

Inhaled NO therapy was studied in newborns who had severe PPHN after early reports demonstrated its potent and selective pulmonary vasodilator effects in adults who had primary pulmonary hypertension and perinatal animals. Two recent multicenter randomized studies have demonstrated the success of inhaled NO therapy in improving oxygenation and decreasing the need for extracorporeal membrane oxygenation therapy (see accompanying article by Kinsella).

Although clinical improvement during inhaled NO therapy occurs with many disorders that are associated with PPHN, not all neonates who have acute hypoxemic respiratory failure and pulmonary hypertension respond well to this therapy. Several mechanisms may explain this clinical variability in response. An inability to deliver NO to the pulmonary circulation due to poor lung inflation is the major cause of poor response. In some settings, administration of NO with high frequency oscillatory ventilation has improved oxygenation compared with conventional ventilation in the same patient. In addition, a poor response to NO therapy may be related to myocardial dysfunction, systemic hypotension, severe pulmonary vascular structural disease, or unsuspected or missed anatomic cardiovascular lesions (eg, total anomalous pulmonary venous return, coarctation of the aorta, alveolar capillary dysplasia). Another mechanism responsible for poor response to inhaled NO may be altered responsiveness of smooth muscle cells. As described from animal studies, decreased sGC or increased PDE5 activities may limit the vasodilator response to NO. For example, inhibition of PDE5 activity with dipyridamole or zaprinast may augment the vasodilator response to inhaled NO in experimental studies.

Although the primary physiologic abnormality in preterm neonates is respiratory distress syndrome (RDS) with surfactant deficiency or dysfunction, severe RDS is associated with pulmonary hypertension. The presence of high PVR is associated with severe lung disease and poor outcome. Pulmonary hypertension in this setting may be due to the mechanical effects of low lung volumes, but pulmonary vasoconstriction contributes to high PVR in some patients. As suggested by the marked vasodilator responsiveness to inhaled NO in preterm animals, low-dose inhaled NO therapy (5 ppm) can improve oxygenation in selected preterm neonates who have severe RDS. In addition to lowering PVR and improving pulmonary blood flow, low-dose inhaled NO may improve oxygenation further in the absence of severe pulmonary hypertension by reducing intrapulmonary shunt, as demonstrated in ARDS. Whether inhaled NO can improve oxygenation safely and reduce mortality without adverse sequelae, such as increased risk of chronic lung disease or intracranial hemorrhage, is under study. Although NO may prove toxic to the preterm lung, recent studies suggest that inhaled NO may decrease lung inflammation in experimental RDS in preterm lambs.

Finally, circulating ET-1 levels are increased markedly in human newborns who have severe PPHN and decrease during recovery. ET blockers currently are being investigated clinically in adult patients who have congestive heart failure and systemic hypertension; whether this will prove to be an effective clinical intervention for PPHN is unknown.

**Conclusion**

Experimental studies clearly have shown the important role of the NO-cGMP cascade and the ET-1 system in regulating the vascular tone and reactivity of the fetal and transitional pulmonary circulation. In addition, abnormalities in these systems contribute to abnormal pulmonary vascular tone and reactivity in an experimental model of PPHN. Although inhaled NO therapy can improve oxygenation dramatically in sick neonates who have severe PPHN and preterm neonates who have RDS, responsiveness is poor in some patients. Further studies of the NO-cGMP cascade may provide helpful insights into novel clinical strategies for more successful treatment of neonatal pulmonary vascular disease. In addition, because studies of vascular growth suggest important functions of NO in angiogenesis, we speculate that fetal NO production may contribute to normal lung vascular development. Mechanisms linking abnormal lung growth, the risk for pulmonary hypertension, and regulation of the NO-cGMP cascade may have important therapeutic implications in the clinical setting.

**SUGGESTED READING**


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