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Neonatal Pulmonary Hypertension

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Abstract

When the normal cardiopulmonary transition fails to occur, the result is persistent pulmonary hypertension of the newborn (PPHN). Severe PPHN is estimated to occur in 2 per 1000 of live born term infants, and some degree of pulmonary hypertension complicates the course of more than 10% of all neonates with respiratory failure. This review article discusses the vascular abnormalities that are associated with neonatal pulmonary hypertension, including recognition of its role in severe bronchopulmonary dysplasia in preterm infants. A systematic review of the evidence for common therapies including inhaled nitric oxide, high frequency ventilation, surfactant, and extracorporeal life support is included. Finally, this field is rapidly evolving, and the rationale for promising new treatment approaches is reviewed, including inhibition of phosphodiesterases and scavengers of reactive oxygen species.

Keywords

Nitric oxide; high frequency ventilation; oxygen; phosphodiesterase reactive oxygen species

INTRODUCTION

Neonatal respiratory failure affects 2% of all live births, and is responsible for over one third of all neonatal mortality. Persistent pulmonary hypertension (PPHN) complicates the course of approximately 10% of infants with respiratory failure, and is a source of considerable mortality and morbidity in this population. A better understanding of the cellular pathophysiology of PPHN will lead to more specific and effective therapies, and eventually to prevention of this disease. This review will focus on recent progress in our understanding of the pathophysiology and treatment of neonatal pulmonary hypertension.

NORMAL FETAL PULMONARY VASCULAR DEVELOPMENT AND TRANSITION

Pulmonary hypertension is a normal and necessary state for the fetus. Because the placenta, not the lung, serves as the organ of gas exchange, most of the right ventricular output crosses the ductus arteriosus to the aorta, and only 5-10% of the combined ventricular output is directed to the pulmonary vascular bed. Even though pulmonary vascular surface area increases with fetal lung growth, PVR increases with gestational age when corrected for lung or body weight, suggesting that pulmonary vascular tone increases during late gestation. Therefore, *in utero*, pulmonary pressures are equivalent to systemic pressures due to elevated pulmonary vascular resistance. Multiple pathways appear to be involved in maintaining high pulmonary vascular

tone prior to birth. Pulmonary vasoconstrictors in the normal fetus include low oxygen tension, endothelin-1, leukotrienes and Rho kinase. Vasoconstriction is also promoted by low basal production of vasodilators such as prostacyclin and nitric oxide (NO).

A dramatic cardiopulmonary transition occurs at birth to facilitate the transition to gas exchange by the lung, characterized by a rapid fall in PVR and pulmonary artery pressure, and a 10-fold rise in pulmonary blood flow. The most critical signals for these transitional changes are mechanical distension of the lung, a decrease in carbon dioxide tension, and an increase in oxygen tension in the lungs. The fetus prepares for this transition late in gestation by increasing pulmonary expression of nitric oxide synthases and soluble guanylate cyclase (Figure 1). The importance of the NO-cGMP pathway in facilitating normal transition has been demonstrated by acute or chronic inhibition of nitric oxide synthase (NOS) in fetal lambs, which produces pulmonary hypertension following delivery (1,2). Recent data indicate that NOS dysfunction may be induced through increased levels of asymmetric dimethyl arginine (ADMA), a competitive endogenous inhibitor of NOS (3), or by decreased synthesis of the NOS substrate L-arginine (4).

The prostacyclin pathway is also a potentially important vasodilatory pathway (Figure 1). Cyclooxygenase 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 (5). This upregulation leads to an increase in prostacyclin production in late gestation and early postnatal life (6,7). Prostacyclin stimulates adenylate cyclase to increase intracellular cAMP levels, which similar to cGMP, leads to vasorelaxation through a decrease in intracellular calcium concentrations.

PATHOPHYSIOLOGY OF PPHN

When the normal cardiopulmonary transition fails to occur, the result is persistent pulmonary hypertension of the newborn (PPHN). Severe PPHN has been estimated to occur in 2 per 1000 of live born term infants (8), and some degree of pulmonary hypertension complicates the course of more than 10% of all neonates with respiratory failure. Because a patent foramen ovale and ductus arteriosus are normally present early in life, elevated pulmonary vascular resistance in the newborn will produce extrapulmonary shunting of blood, leading to severe and potentially unresponsive hypoxemia. Even with appropriate therapy, the mortality for PPHN remains between 5-10%. In addition, approximately 25% of infants with moderate or severe PPHN will exhibit significant neurodevelopmental impairment at 12-24 months (9-11). This important observation may indicate that the underlying disease and/or early therapeutic approaches are associated with early neurological injury.

PPHN can be generally characterized as one of three types: 1) the abnormally constricted pulmonary vasculature due to lung parenchymal diseases such as meconium aspiration syndrome, respiratory distress syndrome, or pneumonia; 2) the lung with normal parenchyma and remodeled pulmonary vasculature, also known as idiopathic PPHN; or 3) the hypoplastic vasculature as seen in congenital diaphragmatic hernia. While idiopathic pulmonary hypertension is responsible for only 10-20% of all infants with PPHN, severe cases are almost certainly affected by both parenchymal and vascular disease.

One cause of idiopathic PPHN is constriction of the fetal ductus arteriosus *in utero*, which can occur after exposure to non-steroidal anti-inflammatory drugs (NSAIDs) during the third trimester (12,13). Ductal constriction or ligation can be surgically performed *in utero* in lambs, and produces very rapid antenatal remodeling of the pulmonary vasculature. Findings in PPHN lambs are similar to those observed in human infants, including increased fetal pulmonary artery pressure, pulmonary vascular remodeling, and profound hypoxemia after birth.

New data suggest that exposure to selective serotonin reuptake inhibitors (SSRI) during late gestation is associated with a six-fold increase in the prevalence of PPHN (14), although it is not clear how many infants have severe disease. Newborn rats exposed *in utero* to fluoxetine develop pulmonary vascular remodeling, abnormal oxygenation and higher mortality when compared with vehicle-treated controls (15). As SSRI's have been reported to reduce pulmonary vascular remodeling in adult models of pulmonary hypertension, these findings highlight the unique nature of fetal pulmonary vascular development.

Based on work from animal models, there is strong evidence that disruptions of the NO-cGMP, prostacyclin-cAMP, and endothelin signaling pathways play an important role in the vascular abnormalities associated with PPHN. The NO-cGMP pathway has been a topic of particularly intense investigation over the last decade. Decreased expression and activity of endothelial nitric oxide synthase (eNOS) have been documented in the PPHN lamb model (16,17), and decreased eNOS expression has also been reported in umbilical venous endothelial cell cultures from human infants with meconium staining who develop PPHN (18). These important findings were rapidly followed by clinical testing of inhaled nitric oxide (iNO) as a therapy for hypoxemic respiratory failure and PPHN, as described below.

OTHER CAUSES OF PULMONARY HYPERTENSION IN INFANCY

Neonatal pulmonary hypertension differs from pediatric pulmonary hypertension in that it resolves in the majority of infants, and has not been associated with genetic factors. A notable exception is alveolar capillary dysplasia (ACD) with misalignment of lung vessels, a rare but universally lethal cause of pulmonary hypertension in the newborn (19,20). Affected infants typically present shortly after birth with cyanosis and respiratory distress refractory to all known therapies including extracorporeal support, although later presentations are increasingly recognized. The diagnosis can only be made by direct examination of lung tissue. Characteristic findings include simplification of lung architecture, widened and poorly cellular septa with a paucity of capillaries, and strikingly muscularized small arterioles accompanied by pulmonary veins within the same connective tissue sheath. Approximately 10% of ACD cases have been reported to have a familial association, indicating a potential genetic component. Unfortunately, the search for a candidate gene has not yet been fruitful.

In preterm infants, there is increasing recognition of the association of chronic lung disease with pulmonary hypertension in early infancy. While recent advances in neonatal care have led to improved survival of very low birthweight infants, they have not significantly reduced the complication of bronchopulmonary dysplasia (BPD). In the United States alone, more than 10,000 babies develop BPD each year, a disease characterized by developmental abnormalities of lung structure, including impaired alveolarization and vascularization. Altered pulmonary vascular growth and significant pulmonary hypertension frequently complicate the course of BPD (21), and increase the risk of late morbidity and death. Identifying pulmonary hypertension in this population requires a high index of suspicion and careful longitudinal evaluation. The pathogenesis of pulmonary hypertension associated with BPD is complex: while antenatal factors such as fetal inflammation appear to play a role, the disease is in large part due to postnatal injury by mechanisms including ventilator-induced lung injury and oxidant stress.

GENERAL MANAGEMENT

General management principles for the newborn with PPHN include maintenance of normal temperature, electrolytes (particularly calcium), glucose, and intravascular volume. Systemic hemodynamics should be optimized with volume and cardiotonic therapy (dobutamine, dopamine, and milrinone), in order to enhance cardiac output and systemic O₂ transport. Infants who fail to respond to medical management, as evidenced by failure to sustain improvement

in oxygenation with good hemodynamic function, may require treatment with extracorporeal membrane oxygenation (ECMO)(22). The oxygenation index (OI; calculated as (mean airway pressure * FiO₂ * 100)/PaO₂) is often used to gauge the severity of disease, with OI >40 often used as an indication for evaluation for ECMO. Although ECMO can be life saving, it is also costly, labor intensive, and associated with potential adverse effects, such as intracranial hemorrhage and ligation of the right common carotid artery.

The evidence for specific treatments is outlined in Table 2. The goal of mechanical ventilation is to improve oxygenation, achieve normal lung volumes, and to avoid the adverse effects of high or low lung volumes on PVR. Some newborns with parenchymal lung disease associated with PPHN physiology demonstrate improved oxygenation and decreased right-to-left extrapulmonary shunting with aggressive lung recruitment during high frequency oscillatory ventilation (23).

The use of surfactant therapy remains variable between centers. Single center trials have shown that surfactant improves oxygenation, reduces airleak, and reduces need for ECMO in infants with meconium aspiration (24). A multicenter trial showed benefit in infants with parenchymal lung diseases such as meconium aspiration syndrome and sepsis, and also demonstrated that the benefit was greatest for infants with relatively mild disease (Oxygenation Index of 15-22) (25). However, this trial also failed to show a reduction in ECMO utilization in the subset of newborns with idiopathic PPHN. Therefore, the use of surfactant should only be considered for infants with parenchymal lung disease.

Acidosis can act as a pulmonary vasoconstrictor, and should be avoided. The use of alkalosis was frequent prior to the approval of inhaled nitric oxide (8), based on studies that found transient improvements in PaO₂ after acute hyperventilation. However, no studies have demonstrated long-term benefit. The pulmonary vascular response to alkalosis is transient, and prolonged alkalosis may paradoxically worsen pulmonary vascular tone, reactivity and permeability edema (26). Further, alkalosis produces cerebral constriction, reduces cerebral blood flow and oxygen delivery to the brain, and may be associated with worse neurodevelopmental outcomes. Similarly, there is currently no evidence to suggest that the use of sodium bicarbonate infusions to induce alkalosis provides any short-term or long-term benefit (8).

INHALED NITRIC OXIDE FOR PPHN

The primary goal of PPHN therapy is selective pulmonary vasodilation. Intravenous dilators such as prostacyclin and tolazoline may produce non-selective effects on the systemic circulation, leading to hypotension. In contrast, inhaled NO is well suited for the treatment of PPHN (Table 2): it is a rapid and potent vasodilator, and because NO is a small gas molecule, it can be delivered as inhalation therapy to airspaces approximating the pulmonary vascular bed. Large placebo-controlled trials provide clear evidence that iNO significantly decreases the need for extracorporeal life support in newborns with PPHN (27,28). While these trials led to the FDA approval of iNO as therapy for PPHN, it is important to note that iNO did not reduce mortality, length of hospitalization, or reduce the risk of neurodevelopmental impairment. Further, beginning iNO at a milder or earlier point in the disease course (for an oxygenation index of 15-25), did not decrease the incidence of ECMO and/or death, or improve other patient outcomes, including the incidence of neurodevelopmental impairment (11,29).

The clinical trials also revealed that as many as 40% of infants will not respond or sustain a response to iNO. The reasons for an inadequate response are diverse, and require the clinician to carefully analyze the relative roles of parenchymal lung disease, pulmonary vascular disease, and cardiac dysfunction for each infant. For instance, if severe airspace disease is associated with PPHN, strategies such as high frequency ventilation that optimize lung expansion are

likely to be effective (30). Cardiac function should also be assessed longitudinally. In particular, infants with severe left ventricular dysfunction are likely to have pulmonary venous hypertension, and are unlikely to respond to pulmonary vasodilation unless there is also optimization of cardiac performance.

NEW INSIGHTS INTO PPHN PATHOPHYSIOLOGY AND TREATMENT

Alterations in downstream signaling mechanisms in pulmonary vascular smooth muscle cells may also lead to inadequate vascular responses to NO. NO mediates vasodilation by stimulating soluble guanylate cyclase in vascular smooth muscle cells, which then converts guanosine triphosphate to cGMP (Figure 1). cGMP is the central and critical second messenger that regulates contractility of the smooth muscle cell by modulating the activity of cGMP-dependent kinases, phosphodiesterases, and ion channels. Therefore, there are multiple critical points in the pathway downstream from NO production that serve as attractive targets for manipulating cellular cGMP concentrations (Table 1). For example, expression and activity of soluble guanylate cyclase are decreased in the abnormally remodeled pulmonary vessels of the PPHN lamb model, which could potentially diminish responses to both endogenous and exogenous NO. This finding would indicate that new compounds that directly stimulate sGC at a NO-independent but heme-dependent site may be helpful, a hypothesis that appears to be promising in pre-clinical testing (12).

Recent evidence indicates that the low cGMP concentrations associated with PPHN may also be associated with increased activity of cGMP-specific phosphodiesterases (PDE5). Inhibition of PDE5 activity would be expected to increase cGMP concentrations (Figure 1), dilate the pulmonary vasculature, and/or increase the efficacy of iNO. In lambs with experimental pulmonary hypertension, both enteric and aerosolized sildenafil have been shown to dilate the pulmonary vasculature and augment the pulmonary vascular response to iNO. Intravenous sildenafil was found to be a selective pulmonary vasodilator with efficacy equivalent to inhaled nitric oxide in a piglet model of meconium aspiration. When combined with iNO, sildenafil enhanced the reduction in pulmonary vascular resistance, although systemic hypotension and worsening oxygenation also resulted (31,32). Data have recently begun to emerge on the use of sildenafil in clinical populations. A recent report demonstrated that enteric sildenafil improved oxygenation and survival in human infants with PPHN compared to placebo (33). Findings from a pilot study of intravenous sildenafil in newborns with pulmonary hypertension indicate that it was generally well tolerated, with improvements in oxygenation noted in the cohorts that received higher infusion doses (34). Seven infants received sildenafil prior to initiation of iNO, and showed similar improvements in oxygenation. Of these, six survived to discharge without need for additional therapy with iNO or ECMO. These data suggest that sildenafil has the potential to independently decrease pulmonary vascular resistance and improve oxygenation in human infants with PPHN.

There is mounting evidence that oxidant stress plays an important role in the pathogenesis of PPHN. An increase in reactive oxygen species (ROS) such as superoxide and hydrogen peroxide in the smooth muscle and adventitia of pulmonary arteries has been demonstrated in the PPHN lamb model (35,36), as well as in postnatal models induced by chronic hypoxia (37). Possible sources for elevated concentrations of reactive oxygen species include increased expression and activity of NADPH oxidase, as well as a reduction in superoxide dismutase (SOD) activity. Diminished binding of the chaperone protein, heat shock protein 90 (hsp 90) to eNOS has also been demonstrated in animal models (38,39). Decreased hsp90:eNOS interactions lead to an “uncoupling” of NOS activity which results in decreased synthesis of NO and increased superoxide production. Once present in the lung, recent studies indicate that elevated concentrations of ROS promote vascular smooth muscle cell proliferation in PPHN,

and lead abnormal vascular reactivity through mechanisms that blunt cGMP accumulation (Figure 2).

Current therapeutic practices may have an effect on oxidant stress, pulmonary vascular reactivity and remodeling. In particular, the use of oxygen has recently become controversial in numerous settings. While hyperoxic ventilation continues to be a mainstay in the treatment of PPHN, we know surprisingly little about what oxygen concentrations will maximize benefits and minimize risk. The extreme hyperoxia routinely used in PPHN management may in fact be toxic to the developing lung by the formation of ROS (40). Superoxide may react with arachadonic acid to increase concentrations of isoprostanes, and may also combine with NO to form peroxynitrite (41). Both are potent oxidants with the potential to produce vasoconstriction, cytotoxicity, and damage to surfactant proteins and lipids. New data indicate that even brief periods of exposure to 100% O₂ (30 minutes) are sufficient to increase reactivity of pulmonary vessels in normal lambs (42,43), diminish the response of the pulmonary vasculature to endogenous and exogenous nitric oxide (Figure 3) (43), and increase activity of cGMP-specific phosphodiesterases (44).

If reactive oxygen species promote vasoconstriction, scavengers of reactive oxygen species such as superoxide dismutase (SOD) may augment responsiveness to iNO and promote pulmonary vasodilation. Superoxide dismutase scavenges and converts superoxide radical to hydrogen peroxide, which is subsequently 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 (45). In lambs with pulmonary hypertension, rhSOD was found to dilate the pulmonary circulation and enhance responsiveness to inhaled NO (46). A recent study went on to examine the effects of rhSOD on oxygenation over a 24-hour period in ventilated PPHN lambs (41). The results showed that a single dose of rhSOD by itself improved oxygenation to a degree that was similar to iNO. Further, rhSOD treatment appeared to block formation of oxidants such as peroxynitrite and isoprostanes, and restore activity of endogenous nitric oxide synthase (40). Thus, an antioxidant therapeutic approach may have multiple beneficial effects: Scavenging superoxide may increase the availability of both endogenous and inhaled NO, and may also reduce oxidative stress and limit lung injury (47). It is hoped that human trials of antioxidant therapy will begin soon.

CONCLUSIONS

Persistent pulmonary hypertension is a unique form of pediatric pulmonary hypertension characterized by vascular injury and remodeling that occurs before and just after birth. The approval of inhaled nitric oxide has dramatically changed treatment for PPHN, although it has not reduced mortality. Current research is focused on developing a better understanding of cellular responses in the remodeled vasculature, and will likely lead to new strategies that will enhance the vascular effects of both exogenous and endogenous NO. Many investigators are pursuing inhibition of cGMP phosphodiesterases using laboratory and clinical approaches, and it is likely a clinical role for phosphodiesterase inhibitors will emerge. New data indicate that oxidant stress is an important mechanism in pulmonary hypertension, and may reduce vascular responses to NO. Future research will better define the enzymatic and cellular sources of oxidants, delineate their role in vascular dysfunction, and determine whether anti-oxidant therapies are beneficial.

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Figure 1.

Nitric oxide (NO) and prostacyclin (PGI₂) signaling pathways in the regulation of pulmonary vascular tone. NO is synthesized by nitric oxide synthase (NOS) from the terminal nitrogen of L-arginine. NO stimulates soluble guanylate cyclase (sGC) to increase intracellular cGMP. PGI₂ is an arachidonic acid (AA) metabolite formed by cyclooxygenase (COX-1) and prostacyclin synthase (PGIS) in the vascular endothelium. PGI₂ stimulates adenylate cyclase in vascular smooth muscle cells, which increases intracellular cAMP. Both cGMP and cAMP indirectly decrease free cytosolic calcium, resulting in smooth muscle relaxation. Specific phosphodiesterases hydrolyze cGMP and cAMP, thus regulating the intensity and duration of their vascular effects. Inhibition of these phosphodiesterases with agents such as sildenafil and milrinone may enhance pulmonary vasodilation.

Figure 2.

Increased reactive oxygen species (ROS) such as superoxide and hydrogen peroxide are produced in the vascular wall of pulmonary vessels affected by persistent pulmonary hypertension of the newborn (PPHN). In addition, even brief exposures to hyperoxia elevate cellular levels of ROS in the neonatal pulmonary vasculature. Increased ROS diminish nitric oxide synthase (NOS) activity and increase type 5 phosphodiesterase (PDE5) activity, both of which blunt the normal production of cGMP.

Figure 3.

Normal lambs were ventilated with 21% or 100% oxygen for 30 minutes at the time of birth. After recovery, pulmonary vascular tone was increased with a thromboxane analog, and the lambs received 20 ppm inhaled NO or an infusion of acetylcholine (1 μ g/kg/min) to stimulate endogenous nitric oxide synthase (NOS) activity. Exposure to 30 minutes of hyperoxia blunted the responses to both exogenous and endogenous NO (43).

Table 1

Emerging Therapies for Treatment of PPHN

Enhancers of NOS Activity
Direct soluble guanylate cyclase activators
Phosphodiesterase inhibitors
Prostacyclin analogues
Rho-kinase inhibitors
Antioxidants

Table 2**Recommendations for Treatment of Neonatal Pulmonary Hypertension**

Pulmonary Vasodilators:**Inhaled Nitric Oxide:**

Inhaled Nitric Oxide should be initiated at 20 ppm for neonates with PPHN or hypoxemic respiratory failure when the oxygenation index exceeds 25. (Class I, Level A)

Sildenafil:

Limited evidence suggests that sildenafil may produce selective vasodilation in infants with PPHN. (Class IIb, Level B)

Other Supportive Modalities**Extracorporeal Life Support (ECLS or ECMO):**

Cannulation for ECMO support should be considered for term and near-term neonates with pulmonary hypertension and/or hypoxemia that remains refractory to iNO after optimization of respiratory and cardiac function. (Class I, Level A)

High Frequency Ventilation:

In neonates with parenchymal lung disease (eg, meconium aspiration syndrome, respiratory distress syndrome, pneumonia), high frequency ventilation is often useful to promote lung expansion and enhance the effect of inhaled nitric oxide in infants. (Class IIa, Level B)

Surfactant:

Administration of surfactant may promote lung expansion and reverse surfactant inactivation associated with parenchymal lung disease. (Class IIa, Level A).

Alkalosis:

Alkalosis induced by hypocarbia or infusions of alkali may result in transient improved oxygenation. However, this practice is not recommended because of the lack of demonstrated benefit, and the potential for lung and cerebral injury. (Class III, Level B).