

Persistent Pulmonary Hypertension

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Introduction

- 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.

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.

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.

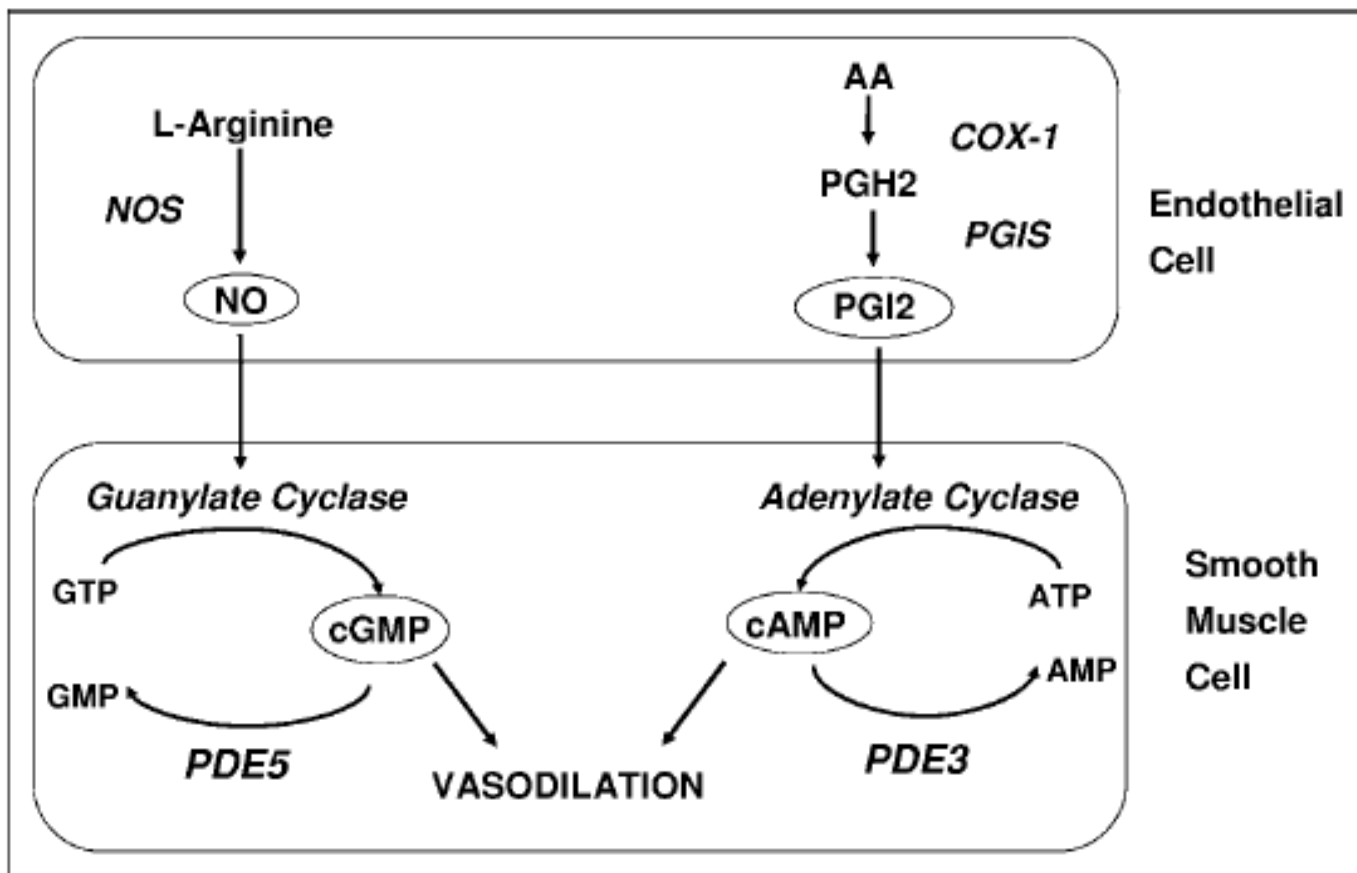


Figure. Nitric oxide (NO) and prostacyclin (PG) signaling pathways in regulation of vascular tone. NO is synthesized by nitric oxide synthase (NOS) from the terminal nitrogen group of L-arginine. NO stimulates soluble guanylate cyclase (sGC) to increase intracellular cGMP. PGH₂ is an arachidonic acid (AA) metabolite formed by cyclooxygenase (COX-1) and prostacyclin synthase (PGIS) in the vascular endothelium. PGH₂ 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, which leads to vascular dilation. Specific phosphodiesterases hydrolyze cGMP and cAMP, thus regulating the intensity and duration of their vascular effects. Inhibition of these phosphodiesterases is an attractive therapeutic target.

Table 1. Mechanisms of Persistent Pulmonary Hypertension of the Newborn

Abnormally Constricted Pulmonary Vasculature

- Meconium Aspiration Syndrome
- Pneumonia
- Respiratory Distress Syndrome

Structurally Abnormal Pulmonary Vasculature

- Idiopathic Persistent Pulmonary Hypertension (“black lung PPHN”)

Hypoplastic Pulmonary Vasculature

- Congenital Diaphragmatic Hernia
- Pulmonary Hypoplasia

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.

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.

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 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.

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

Initial Therapies

- Treat metabolic derangements: correct acidosis, hypoglycemia, hypocalcemia
- Optimize lung recruitment: mechanical ventilation, high-frequency oscillatory ventilation, surfactant
- Optimize cardiac output and left ventricular function: vasopressors, inotropic agents

Pulmonary Vasodilators

- Inhaled nitric oxide

Future Therapies

- Phosphodiesterase Inhibitors (sildenafil)
- Inhaled prostacyclin analogs (iloprost, prostacyclin)
- Recombinant superoxide dismutase

Treatment(General)

- 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.
- 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.

Treatment (Ventilation)

- 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.

Treatment (Surfactant)

- 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 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.

Treatment (Nitric Oxide)

- 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.

Treatment (Nitric Oxide)

- 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.

Contraindications to iNO

- 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.

Inhaled Nitric oxide and ECMO

- 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.
- Data from the ELSO registry between 1996 and 2003 indicate 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.

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 inhibitor, recently was relabeled and approved by the United States Food and Drug Administration for the treatment of pulmonary hypertension in adults.

Alternative and Emerging Pulmonary Vasodilators

- 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.

Alternative and Emerging Pulmonary Vasodilators

- 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

Alternative and Emerging Pulmonary Vasodilators

- 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, 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
- 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.

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Questions

- Describe fetal pulmonary vasculature and adaptation in extrauterine life.
- Describe mechanism of action of inhaled Nitric oxide on pulmonary vasculature.
- Describe the pathophysiology of PPHN
- What makes inhaled Nitric oxide an ideal pulmonary vasodilator to treat PPHN
- What is the role of Surfactant in PPHN
- List pulmonary vasodilators alternative to inhaled Nitric oxide