

Role of Nitric Oxide in the Pathophysiology and Treatment of the Neonatal Pulmonary Hypertension

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Postnatal survival is dependent upon the successful transition of the fetal pulmonary circulation from its high resistance state *in utero* to a low resistance, high flow vascular bed within minutes after delivery. Mechanisms that contribute to the normal fall in PVR at birth include increased oxygen tension, ventilation, and shear stress, and altered production of several vasoactive products, especially the enhanced release of nitric oxide (NO) and prostacyclin (P_gI₂). Some infants fail to achieve or sustain the normal decrease in PVR at birth, leading to severe respiratory distress and hypoxemia, which is referred to as *persistent pulmonary hypertension of the newborn* (PPHN). PPHN is a major clinical problem, contributing significantly to high morbidity and mortality in both full-term and premature neonates. This review will briefly describe mechanisms underlying the physiology of the perinatal lung circulation, the pathophysiology of PPHN, and clinical strategies that utilize a physiologic approach to the treatment of newborns with severe PPHN.

Pulmonary vascular resistance (PVR) is high throughout fetal life, especially in comparison with the low resistance of the systemic circulation. Mechanisms that contribute to high basal PVR in the fetus include low oxygen tension, relatively low basal production of vasodilator products (such as P_gI₂ and NO), increased production of vasoconstrictors (including endothelin-1 (ET-1)), and altered smooth muscle cell reactivity (such as enhanced myogenic tone). Maturation changes in endothelial cell function, especially with regard to NO production, contribute to progressive changes in pulmonary vasoreactivity during development. Lung endothelial NOS (eNOS) mRNA and protein is present in the early fetus and increases with advancing gestation *in utero* and during the early postnatal period in rats and sheep. Developmental changes in eNOS expression and activity are regulated by several factors, including oxygen tension, hemodynamic forces, hormonal stimuli (e.g., estradiol), paracrine factors (including vascular endothelial growth factor; VEGF), substrate and cofactor availability, superoxide production (which inactivates NO), and others. NO causes vasodilation by stimulating soluble guanylate cyclase in vascular smooth muscle, which increases smooth muscle cGMP content. Cyclic GMP-specific phosphodiesterases (PDE₅) inactivate cGMP, thereby playing a critical role in the regulation of vasodilation in the fetal lung.

Within minutes after delivery, pulmonary artery pressure falls and blood flow increases in response to birth-related stimuli. Mechanisms contributing to the fall in PVR at birth include establishment of an air-liquid interface, rhythmic lung distension, increased oxygen tension, and altered production of vasoactive substances. Physiologic stimuli, such as increased shear stress, ventilation and increased oxygen, cause pulmonary vasodilation in part by increasing production of endogenous vasodilators, such as NO and P_gI₂. Inhibition of NOS activity attenuates the decline in PVR after delivery of fetal lambs, and suggest that about 50% of the rise in pulmonary blood flow at birth may be directly related to the acute release of NO. Strong experimental and clinical data further suggest that ET-1 contributes to the pathophysiology of PPHN.

Several factors can contribute to high pulmonary artery pressure in neonates with PPHN-type physiology.

Pulmonary hypertension can be due to vasoconstriction or structural lesions that directly increase PVR. Changes in lung volume in neonates with parenchymal lung disease can also be an important determinant of PVR. PVR increases at low lung volumes due to dense parenchymal infiltrate and poor lung recruitment, or with high lung volumes due to hyperinflation associated with overdistension or gas-trapping. Cardiac disease is also associated with PPHN. High pulmonary venous pressure due to left ventricular dysfunction can also elevate PAP (eg, asphyxia, sepsis), causing right-to-left shunting, with little vasoconstriction. In this setting, enhancing cardiac performance and systemic hemodynamics may lower PAP more effectively than achieving pulmonary vasodilation.

In general, management of the newborn with PPHN includes the treatment and avoidance of hypothermia, hypoglycemia, hypocalcemia, anemia and hypovolemia; correction of metabolic acidosis; diagnostic studies for sepsis; serial monitoring of arterial blood pressure, pulse oximetry (pre- and post-ductal); and transcutaneous PCO₂, especially with the initiation of high frequency oscillatory ventilation (HFOV). Therapy includes aggressive management of systemic hemodynamics with volume and cardiotoxic therapy (dobutamine, dopamine, and milrinone), in order to enhance cardiac output and systemic O₂ transport. In addition, increasing systemic arterial pressure can improve oxygenation in some cases by reducing right-to-left extrapulmonary shunting. Failure to respond to medical management, as evidenced by failure to sustain improvement in oxygenation with good hemodynamic function, often leads to treatment with extracorporeal membrane oxygenation (ECMO).

Inhaled nitric oxide (iNO) therapy at low doses (5-20 ppm) improves oxygenation and decreases the need for ECMO therapy in patients with diverse causes of PPHN. Multicenter clinical trials support the use of iNO in near-term (>34 weeks gestation) and term newborns, and the use of iNO in infants less than 34 weeks gestation remains investigational. Studies support the use of iNO in infants who have hypoxemic respiratory failure with evidence of PPHN, who require mechanical ventilation and high inspired oxygen concentrations. In selected newborns with severe lung disease, HFOV is frequently used to optimize lung inflation and minimize lung injury. In clinical studies using iNO, the combination of HFOV and iNO caused the greatest improvement in oxygenation in some newborns who had severe PPHN complicated by diffuse parenchymal lung disease and underinflation (e.g. RDS, pneumonia). This response to combined treatment with HFOV + iNO likely reflects both improvement in intrapulmonary shunting in patients with severe lung disease and PPHN (using a strategy designed to recruit and sustain lung volume, rather than to hyperventilate) and augmented NO delivery to its site of action. Although iNO may be an effective treatment for PPHN, it should be considered only as part of an overall clinical strategy that cautiously manages parenchymal lung disease, cardiac performance, and systemic hemodynamics.

More recent studies have evaluated the experimental role of NO in the development of bronchopulmonary dysplasia (BPD), as well as the potential therapeutic use of inhaled NO in premature newborns. Experimental models of BPD suggest that impaired NO production may contribute to pulmonary hypertension in BPD. In addition, decreased endogenous NO production may inhibit angiogenesis in the lung and contribute to decreased alveolarization and lung growth. In neonatal rats, inhaled NO (5-10 ppm) improves vessel growth and alveolarization in animal models of BPD after exposure to hyperoxia or inhibition of VEGF receptors. Multicenter randomized clinical trials are currently underway to determine whether early treatment of premature newborns with inhaled NO can decrease the risk of BPD without impairing neurodevelopmental outcomes.