

## **Persistent Pulmonary Hypertension of the Newborn: Novel Mechanisms and Therapies**

Steven H. Abman

University of Colorado School of Medicine and The Children's Hospital, Denver, Colorado USA

Persistent pulmonary hypertension of the newborn (PPHN) is a clinical syndrome characterized by failure of the lung circulation to achieve or sustain the normal drop in pulmonary vascular resistance (PVR) at birth. Past laboratory studies identified the important role of nitric oxide (NO)-cGMP signaling in the regulation of the perinatal lung circulation, leading to the development and application of inhaled NO therapy for PPHN. Although iNO therapy has improved the clinical course and outcomes of many infants, pulmonary hypertension can be refractory to inhaled NO, suggesting the need for additional approaches to severe PPHN. To develop novel therapeutic strategies for PPHN, ongoing studies continue to explore basic mechanisms underlying the pathobiology of PPHN in experimental models, including strategies to enhance NO-cGMP signaling. Recent studies have demonstrated that impaired vascular endothelial growth factor (VEGF) signaling may contribute to the pathogenesis of PPHN. Other studies have shown that enhanced NO-cGMP activity through the use of cGMP-specific phosphodiesterase inhibitors (sildenafil), soluble guanylate cyclase activators (BAY 41-2272), superoxide scavengers (superoxide dismutase), and rho kinase inhibitors (fasudil) can lead to potent and sustained pulmonary vasodilation in experimental PPHN. Overall, these laboratory studies suggest novel pharmacologic strategies for the treatment of refractory PPHN.

Management of the newborn with PPHN initially includes aggressive management of systemic hemodynamics with volume and cardiotoxic therapy (dobutamine, dopamine, and milrinone), in order to enhance cardiac output and systemic O<sub>2</sub> transport. Increasing systemic arterial pressure itself often improves oxygenation by reducing right-to-left extrapulmonary shunting, the hallmark of PPHN physiology. Pulmonary vasodilator therapy with inhaled nitric oxide (iNO) has been clearly shown to improve oxygenation and decrease the need for ECMO therapy in patients with diverse causes of PPHN in several randomized, multicenter clinical trials. 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.

Although clinical improvement during inhaled NO therapy occurs with many disorders associated with PPHN, not all neonates with acute hypoxemic respiratory failure and pulmonary hypertension respond to iNO. Several mechanisms may explain the clinical variability in responsiveness to iNO therapy. An inability to deliver NO to the pulmonary circulation due to poor lung inflation is the major cause of poor responsiveness. In addition, poor responsiveness may be related to myocardial dysfunction, systemic hypotension, severe pulmonary vascular structural disease, and unsuspected or missed anatomic cardiovascular lesions (such as total anomalous pulmonary venous return,

coarctation of the aorta, and others). Prolonged need for inhaled NO therapy without resolution of disease should lead to a more extensive evaluation to determine whether previously unsuspected anatomic lung or cardiovascular disease is present (for example, pulmonary venous stenosis, alveolar capillary dysplasia, severe lung hypoplasia, surfactant protein deficiencies, or others).

Other mechanisms of poor responsiveness to therapy may be related to abnormalities in endothelial and smooth muscle cell function. Currently, sildenafil, a selective PDE5 inhibitor, has been shown to improve oxygenation in infants with PPHN especially at centers lacking inhaled NO. and has been extensively for the treatment of pulmonary hypertension in other settings. Despite extensive use of ET receptor antagonists in older patients with severe chronic pulmonary hypertension, there is limited experience with its use in infants, and whether it is effective in the acute setting is less clear. New studies indicate that scavengers of reactive oxygen species such as superoxide dismutase (SOD), sGC activators and rho-kinase inhibitors can cause pulmonary vasodilation and augment responsiveness to iNO in the laboratory, suggesting a future role for these strategies in neonates who fail to respond to other therapies.

### **References**

- Abman SH. Recent Advances in the Pathogenesis and Treatment of Persistent Pulmonary Hypertension of the Newborn. *Neonatology*. 91:283-290, 2007.