Advances in the Diagnosis and Management of Persistent Pulmonary Hypertension of the Newborn

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KEYWORDS

- Pulmonary hypertension • Respiratory failure in the newborn
- Nitric oxide • Extracorporeal membrane oxygenation
- Outcomes of persistent pulmonary hypertension of the newborn

Persistence of pulmonary hypertension leading to respiratory failure in the neonate has been recognized for 40 years since its original description by Gersony and colleagues[1] in 1969. Fox and colleagues[2] reported suprasystemic pulmonary artery pressures and systemic desaturation in a group of neonates who had perinatal aspiration syndrome and absence of congenital heart disease (CHD) documented by cardiac catheterization. The hypoxemia in these neonates was attributable to right-to-left extrapulmonary shunting of blood across a patent foramen ovale (PFO) or patent ductus arteriosus (PDA).[1,2] The term originally used to describe this syndrome was *persistent fetal circulation*,[1] which was subsequently changed to *persistent pulmonary hypertension of the newborn* (PPHN) because it describes the pathophysiology more accurately.

PPHN occurs when the pulmonary vascular resistance (PVR) fails to decrease at birth. Affected neonates fail to establish adequate oxygenation during postnatal life and may develop multiorgan dysfunction. The condition usually presents at or shortly after birth. Although high pulmonary artery pressure and an oxygen tension of 20 to 30 mm Hg are normal during fetal life, they are poorly tolerated after birth. The severity of PPHN can run the full spectrum from mild and transient respiratory distress to severe

This article was supported by grant RO1 HL57268 from the National Heart, Lung, and Blood Institute and grants from the Advancing Healthier Wisconsin Foundation and Children's Research Institute of Wisconsin.
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Pediatr Clin N Am 56 (2009) 579–600
doi:10.1016/j.pcl.2009.04.004 **pediatric.theclinics.com**
0031-3955/09/$ – see front matter

hypoxemia and cardiopulmonary instability requiring intensive care support. Prompt diagnosis and management, including a timely referral to a tertiary care center, can dramatically improve the chances of survival. Although mortality for PPHN was reported as 11% to 34% during 1980s,[3–5] current mortality is lower than 10% at most tertiary care centers.[6] Most cases of PPHN are associated with lung parenchymal disease, such as meconium aspiration syndrome (MAS) and respiratory distress syndrome (RDS); however, some present without known lung disease as primary PPHN. Some infants who have PPHN have lethal causes of respiratory failure, such as alveolar-capillary dysplasia (ACD),[7] genetic defects in surfactant synthesis,[8] or severe lung hypoplasia secondary to oligohydramnios or congenital anomalies.

VASCULAR BIOLOGY OF NORMAL TRANSITION

Translational biology studies in animal models have led to rapid advances in our understanding and management of PPHN. PPHN represents a failure of the unique adaptations that occur at birth in the pulmonary circulation. The fetal lung is a fluid-filled organ that does not participate in gas exchange and offers high resistance to blood flow.[9] Fetal lungs receive only 5% to 15% of the right ventricular output, with the remainder shunted across the PDA to the descending aorta and placental circulation.[10] Low oxygen tension present during fetal life and release of the endogenous vasoconstrictors endothelin-1 and thromboxane facilitate the maintenance of high PVR.[11] Fetal pulmonary circulation becomes more responsive to the vasodilator effect of oxygen with maturation, acquiring this response after 31 weeks of gestation in the human fetus and at a comparable time point in fetal sheep.[12,13] PVR undergoes a dramatic decrease as the lungs take over gas exchange function at birth. The decrease in PVR results in a 50% decrease in pulmonary artery pressure and a nearly 10-fold increase in pulmonary blood flow during the first few minutes of this transition.[10] The increase in pulmonary blood flow facilitates gas transport across the air-blood interface in the lung. The physiologic stimuli that initiate pulmonary vasodilation include the clearance of lung liquid, distention of air spaces, increase in oxygen tension, and shear stress from increased blood flow.[13–16] Oxygen is the most important stimulus for pulmonary vasodilation, although a decrease in $Paco_2$ and increase in pH also contribute to this response.[13] Together, these physiologic stimuli promote the release of several vasodilators, including endothelium-derived mediators, nitric oxide (NO), and vasodilator prostaglandins (PGs) (**Fig. 1**).[16–19]

Endothelial nitric oxide synthase (eNOS) plays a critical role in the transition of pulmonary circulation by releasing NO. eNOS converts l-arginine to l-citrulline and NO in the presence of oxygen. Oxygen stimulates NO release directly[18] and indirectly by an increase in oxidative phosphorylation and release of ATP from oxygenated fetal red blood cells.[20,21] A maturational increase in the eNOS protein level at term gestation occurs[22] and is critical to this adaptation, because NO is not stored in the cell and its increased synthesis at birth requires high expression of the enzyme. NO initiates rapid vasodilation by stimulating soluble guanylate cyclase in the vascular smooth muscle cell, which, in turn, converts the nucleotide guanosine triphosphate to cyclic guanosine monophosphate (cGMP) (see **Fig. 1**). An increase in intracellular cGMP levels leads to a decrease in Ca^{2+} influx and relaxation of the vascular smooth muscle cell. Type 5 phosphodiesterase (PDE-5) in the vascular smooth muscle cell breaks down cGMP and limits the duration of vasodilation. In addition to the vasodilator effect, NO plays a major role in promoting the growth of blood vessels in the pulmonary circulation in utero in response to vascular endothelial growth factor (VEGF).[23] Loss of NO and inhibition of VEGF receptors in utero cause decreased growth of