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Advances in the Diagnosis and Management of Persistent Pulmonary Hypertension of the Newborn (PPHN)

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Synopsis

Rapid evaluation of a neonate who is cyanotic and in respiratory distress is essential for achieving a good outcome. Persistent pulmonary hypertension of the newborn (PPHN) can be a primary cause or a contributing factor to respiratory failure, particularly in neonates born at 34 weeks gestation. PPHN represents a failure of normal postnatal adaptation that occurs at birth in the pulmonary circulation. Rapid advances in therapy in recent years have led to a remarkable decrease in mortality for the affected infants. However, infants who survive PPHN are at a significant risk for long term hearing and neuro-developmental impairments. This review focuses on the diagnosis, recent advances in management and recommendations for the long term follow-up of infants with PPHN.

Keywords

Pulmonary hypertension; Respiratory failure in the newborn; nitric oxide; ECMO; outcomes of PPHN

Introduction

Persistence of pulmonary hypertension leading to respiratory failure in the neonate has been recognized for 40 years since its original description by Gersony et al in 1969 (1). Fox et al reported supra-systemic pulmonary artery (PA) pressures and systemic desaturation in a group of neonates with perinatal aspiration syndrome and absence of congenital heart disease documented by cardiac catheterization (2). The hypoxemia in these infants was due to right to left extra-pulmonary shunting of blood across a patent foramen ovale or patent ductus arteriosus (1, 2). The term originally used to describe this syndrome was persistent fetal circulation (PFC) (1) which was subsequently changed to persistent pulmonary

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hypertension of the newborn (PPHN) since it describes the pathophysiology more accurately.

PPHN occurs when the pulmonary vascular resistance (PVR) fails to decrease at birth. The affected infants fail to establish adequate oxygenation during postnatal life and may develop multi-organ dysfunction. The condition usually presents at or shortly after birth. Although high pulmonary artery pressure and an oxygen tension of 20–30 torr 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 hypoxemia and cardio-pulmonary instability that require 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 rates for PPHN were reported as 11–34% during 1980s (3–5), current mortality rates are <10% at most tertiary care centers (6). The majority of cases of PPHN are associated with lung parenchymal disease, such as meconium aspiration syndrome and respiratory distress syndrome; however, some present without known lung disease as primary PPHN. Some infants with PPHN have lethal causes of respiratory failure, such as, alveolar-capillary dysplasia (ACD) (7), genetic defects in surfactant synthesis (8) and severe lung hypoplasia secondary to oligohydramnios or congenital anomalies.

Vascular biology of normal transition

Translational biology studies in animal models have lead 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 5–15% of the right ventricular output with the remainder shunted across the patent ductus arteriosus (PDA) to descending aorta and placental circulation (10). Low oxygen tension present during fetal life and release of 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 tenfold 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, distension 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 PaCO₂ and increase in pH also contribute to this response (13). These physiologic stimuli together promote the release of a number of vasodilators, including endothelium derived mediators, nitric oxide (NO) and vasodilator prostaglandins (16–19) (Figure 1).

Endothelial nitric oxide synthase (eNOS) plays a critical role in the transition of pulmonary circulation by releasing NO. Endothelial NOS converts L-arginine to L-citrulline and NO in the presence of oxygen. Oxygen stimulates NO release both directly (18) and indirectly by an increase in oxidative phosphorylation and release of ATP from oxygenated fetal RBC (20–21). A maturational increase in the eNOS protein level at term gestation occurs (22) and is critical to this adaptation since 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, GTP to cGMP (Figure 1). An increase in intra-cellular cGMP levels leads to a decrease in Ca²⁺ 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 pulmonary vessels and air spaces, suggesting a coordinated development of the vasculature and parenchyma during fetal life (24). The intra-cellular cGMP levels in the smooth muscle can be also augmented by the natriuretic peptides- atrial (ANP) and B-type natriuretic peptide (BNP) which stimulate the particulate guanylate cyclase, an isoform of soluble guanylate cyclase. Although the role of ANP and BNP in the perinatal transition has not been delineated, they dilate pulmonary arteries in the newborn lung (25). The natriuretic peptide-cGMP system may offer redundancy to the NO-cGMP system in the pulmonary circulation.

The prostaglandin (PG) system is also activated by birth related stimuli in the fetal lung (26) and mediates pulmonary vasodilation in a complementary fashion to the NO-cGMP system (Figure 1). Prostacyclin (PGI₂) is the most potent of the vasodilator PG and activates the enzyme, adenylate cyclase in the vascular smooth muscle cell, which converts ATP to cAMP. Increase in intra-cellular cAMP also results in the relaxation of vascular smooth muscle cell by decreasing Ca²⁺ influx. Type 3 phosphodiesterase (PDE-3) breaks down cAMP and limits the duration of vasodilation. Therefore, pulmonary vasodilation can be achieved by increasing the levels of oxygen and arginine which are substrates for eNOS, providing NO or PGI₂ or by inhibition of their corresponding cyclic nucleotide PDEs - type 5 by sildenafil or type 3 by milrinone (Figure 1). Vascular smooth muscle cells in the pulmonary artery also show independent responses to oxygen and hypoxia, via activation of specific potassium channels (27, 28). Despite decades of investigation, the fundamental mechanisms involved in the opposing effects of oxygen, hypoxia and acidosis on the pulmonary and systemic vessels remain unknown. Understanding the nature of these differences in basic physiology of pulmonary and systemic vessels may provide additional targeted therapies to selectively decrease the pulmonary artery pressure in PPHN.

Altered vascular biology in PPHN

Failure of postnatal vasodilation may result from inadequate oxygenation/lung expansion and/or failure of NO or PG release at birth. Infants with meconium aspiration or respiratory distress syndrome may present with reversible pulmonary hypertension due to a failure of alveolar expansion or oxygenation. Biochemical alterations in the NO-cGMP pathway reported in infants with PPHN include decreased expression of eNOS (29), decreased availability of arginine (30) and decreased NO production reflected by lower NO metabolites in the urine (30). The fetal lamb model of PPHN shows a consistent decrease in the eNOS expression in pulmonary arteries (31–32). The naturally occurring arginine analog, asymmetric dimethyl arginine (ADMA) can induce competitive inhibition of eNOS and decrease the NO production (Figure 1), as previously reported in animal models of PPHN (33) and adult patients with pulmonary hypertension (34). Increase in endothelin-1 peptide levels in PPHN (35) can cause pulmonary hypertension both by inhibition of eNOS and constriction of the vascular smooth muscle (36). Superoxide, a free radical present in vascular cells can scavenge NO and cause pulmonary vasoconstriction (Figure 1). Increased superoxide levels have been demonstrated in the pulmonary arteries obtained from fetal lambs with PPHN (37, 38). A decrease in the expression of soluble guanylate cyclase which leads to decreased availability of cGMP in the pulmonary artery smooth muscle also occurs in this model (39). In summary, one or several of the steps in NO-cGMP signaling may be altered and contribute to impaired pulmonary vasodilation in PPHN.

Inhibition of PG synthesis by prenatal exposure to non-steroidal anti-inflammatory drugs (NSAID) which inhibit cyclo-oxygenase also increases the risk of PPHN (40, 41). PPHN occurs in these babies due to prenatal constriction of PDA from maternal intake of NSAID (42). Prenatal ductal constriction consistently reproduces the clinical and structural features of PPHN in fetal lambs (43, 44). Constriction of the PDA leads to sustained elevation of pulmonary artery pressure in utero (45) and persistence of right to left shunts postnatally. Studies in this animal model have led to major advances in the understanding of altered vascular biology in PPHN. Pulmonary arteries in this PPHN model show decreased NO release and increased levels of reactive oxygen species- superoxide, hydrogen peroxide and peroxynitrite (31, 32, 37 & 38). Scavengers of superoxide improve the vasodilation and oxygenation in lambs with PPHN (46). Recent studies demonstrated that in utero pulmonary hypertension from ductal constriction leads to impaired development of both pulmonary vasculature and alveoli (47). These data suggest that pressure elevation at a critical phase in the lung development leads to structural alterations in the fetal lung.

Incidence

PPHN primarily affects full term and near term neonates, although some premature infants < 32 weeks gestation show echocardiographic evidence of PPHN (48). The incidence of PPHN in term and near term newborn infants is estimated to be 2 per 1000 live births, based on an observational study by Walsh Sukys et al that included neonatal ICUs at 12 large academic centers during 1993–1994 (49). This study and subsequent large multi-center trials of inhaled nitric oxide (iNO) demonstrated that meconium aspiration syndrome (MAS) is the most common underlying diagnosis of PPHN, followed by primary PPHN (Figure 2). Other diagnoses include respiratory distress syndrome (RDS), pneumonia and/or sepsis, pulmonary vasoconstriction from asphyxia and pulmonary hypoplasia secondary to congenital diaphragmatic hernia or oligohydramnios. The incidence of lung diseases associated with PPHN has changed over the last 8 years. The overall incidence of MAS has declined, coinciding with a decrease in the number of post-term pregnancies (50). In contrast, RDS in preterm neonates delivered by elective or indicated Cesarean section at 34–37 weeks gestation has become a more frequent cause of PPHN. Yoder et al compared the incidence of MAS over two time periods- 1990–92 with 1997–98. The incidence of MAS declined by four fold from 5.8% to 1.5% of all the meconium stained infants in the second time period. They attribute this to a 33% reduction in the number of deliveries at >41 weeks (50). They observed a reciprocal 33% increase in deliveries at 38–39 weeks and an increase in deliveries at 34–36 weeks over the same time period (51). The median age at delivery decreased from 40 weeks to 39 weeks (51). These recent secular trends should be factored into the changing demographics of PPHN babies with important implications for their management and long term outcome. The incidence of lung diseases associated with PPHN from a multi-center trial of early inhaled NO therapy (6) is shown in Figure 2.

Meconium aspiration syndrome (MAS)

Although meconium staining of amniotic fluid occurs in 10–15% of pregnancies, MAS occurs infrequently, in up to 5% of infants born through meconium stained fluid. As noted above, the incidence of MAS among meconium stained infants has declined in recent years (50) with the drop in post-term pregnancies. This observation suggests that MAS is often a result of in utero stress with aspiration of meconium by a compromised fetus. Meconium can cause respiratory failure from a number of mechanisms. Meconium causes mechanical obstruction to the airways, particularly during exhalation, resulting in air trapping, hyperinflation and increased risk of pneumothorax. Meconium components also inactivate surfactant (52), incite an inflammatory response with release of cytokines and increase the production of vasoconstrictors- endothelin and thromboxane (53). MAS can result in PPHN

by the same mechanisms that were just described. Recent advances in the management of PPHN resulted in an excellent outcome for babies with MAS (54).

Primary PPHN

Infants with primary PPHN usually have hypoxemia in the absence of a recognizable parenchymal lung disease. The cause of primary PPHN remains elusive; however, prenatal constriction of ductus arteriosus has been identified as an important contributor. Association of PPHN with maternal intake of NSAID has been recognized in case reports since 1970s (40–41). In a controlled prospective study, NSAID were detected in 88% of babies with PPHN delivered in an urban population by meconium drug analysis, indicating prenatal exposure (42). The concentration of NSAID in the meconium correlated with the incidence and severity of PPHN in this study. A strong causal association is also suggested by the consistent reproduction of hemodynamic and structural features of PPHN by fetal ductal constriction (43, 44). Recently an epidemiologic study suggested an increased incidence of PPHN with prenatal exposure to selective serotonin re-uptake inhibitors (SSRI) during the third trimester of pregnancy (55). However, another study (56) that compared the incidence of PPHN among mothers exposed to SSRI during third trimester and control mothers without exposure found no such association (incidence among SSRI exposed 2.14/1000 and controls 2.72/1000). There are methodological differences between the two studies that may account for these different study findings. Larger population based studies are needed to define the risk of SSRI exposure in causing PPHN. The potential mechanism of the effect of SSRI on the fetal pulmonary circulation also requires further investigation. Both for NSAID and SSRI, some control babies with prenatal exposure did not develop PPHN, suggesting that a biological susceptibility to these drugs plays a role in the pathogenesis. Some neonates delivered through meconium stained amniotic fluid develop PPHN without radiographic evidence of MAS. This observation suggests that the intra-uterine stress which leads to meconium passage *in utero* also may result in PPHN; however, the nature of this stress is unknown.

Pneumonia and/or sepsis

PPHN can be a complication of pneumonia or sepsis secondary to common neonatal pathogens- Group B Strep and gram negative organisms (57). Bacterial endotoxin causes pulmonary hypertension from several mechanisms including the release of thromboxane, endothelin and a number of cytokines such as TNF- α (58, 59). Sepsis also leads to systemic hypotension from activation of inducible NOS with excess NO release in the systemic vascular beds, impaired myocardial function and multi-organ failure. Addressing pulmonary hypertension should be a component of the overall management of septic shock and prevention of multi-organ failure in the affected infants.

Respiratory distress syndrome

PPHN can occur as a complication of RDS in near term premature infants, often delivered by elective or indicated C-section at 34–37 weeks gestation (60). The increasing reactivity of pulmonary arteries at this gestation predisposes these infants to pulmonary hypertension when gas exchange is impaired due to surfactant deficiency.

Pulmonary hypoplasia

Congenital diaphragmatic hernia (CDH) and oligohydramnios secondary to renal anomalies or premature rupture of membranes lead to pulmonary hypoplasia. Pulmonary hypertension often occurs as a complication due to the decreased number of blood vessels and increased reactivity of the vessels in the hypoplastic lungs. PPHN is usually more chronic and less

responsive to vasodilator therapy in these babies. The outcome of these babies is related to the degree of lung hypoplasia, associated anomalies and duration of pulmonary hypertension (61). The outcome for infants with CDH has improved since gentle ventilation and permissive hypercapnia have been incorporated into the management with many centers reporting 75% survival in recent years (61, 62)

Lethal causes of PPHN

Alveolar capillary dysplasia (ACD) can present at birth or several days after birth with progressive cyanosis and severe pulmonary hypertension (7, 63). The diagnosis is made by lung biopsy or post mortem lung sections that show characteristic features of abnormal air-blood interface with increased distance between alveolar epithelium and capillaries (64). Misalignment of pulmonary veins also occurs as they appear next to the bronchus and pulmonary artery in a broncho-vascular bundle instead of their usual location in the interlobular septum. Recurrence of ACD in some families, some times by autosomal recessive inheritance has been reported (7, 63). In some case series, 50% of infants with ACD have associated renal, gastrointestinal and cardiac anomalies (63).

PPHN was also reported in association with respiratory failure in term infants caused by inherited defects in surfactant components. Mutations in surfactant protein B (SP-B) gene that lead to defective synthesis or processing can cause severe respiratory failure and PPHN (65). Originally referred to as congenital alveolar proteinosis, the most common defect in SP-B synthesis is due to a mutation in the codon 121 of SP-B gene (65). These infants present with signs of hyaline membrane disease that shows only short term improvement with surfactant replacement therapy. The outcome is poor despite support with surfactant, iNO and extra corporeal membrane oxygenation (ECMO). Lung transplantation is offered by some centers for the affected infants. Diagnosis is usually made in suspected infants by blood DNA analysis for the common mutations (65). A related series of neonates with fatal respiratory failure due to ATP-binding cassette protein member A3 (ABCA3) deficiency, an inborn error in surfactant synthesis has also been reported (66). The affected infants can develop severe PPHN unresponsive to iNO (8).

Diagnosis of PPHN

A term or late preterm infant with symptoms of respiratory distress shortly after delivery may have a variety of pulmonary diseases described above or simply a delayed transition to extra-uterine life. However, if the infant has respiratory distress complicated by labile oxygenation and hypoxemia out of proportion to the degree of lung disease, PPHN should be suspected. Physical exam of an infant with PPHN usually reveals tachypnea, retractions, grunting and cyanosis. Abnormal cardiac sounds such as a systolic murmur of tricuspid regurgitation or a prominent S₂ may be heard; however these are not diagnostic for PPHN. Many of these clinical signs are also found in infants with cyanotic congenital heart disease (CHD) and the differentiation between lung disease, PPHN or cyanotic CHD can be difficult.

A systematic approach to the hypoxemic infant with serial interventions and tests is needed for a timely and accurate diagnosis of PPHN. The initial studies obtained in symptomatic neonates are a chest radiograph (CXR) and arterial blood gas (ABG) analysis. The CXR can be normal in primary PPHN since most affected infants have minimal or no parenchymal lung disease (Figure 3A). However, it is more common for PPHN to be secondary to parenchymal lung disease which is evident on CXR. Apparent lung disease on CXR does not rule out a cardiac defect as shown in the example in Figure 3B. The CXR in Figure 3B was obtained in a 36 week gestation preterm infant that presented with signs of RDS, had poor response to surfactant therapy and a transient improvement in PO₂ with inhaled NO

therapy. After the infant was transferred to our center for evaluation of severe PPHN, Echocardiogram revealed total anomalous infra-diaphragmatic pulmonary venous return to inferior vena cava. An atypical course with poor response to surfactant therapy and hypoxemia that is out of proportion to ventilation problem should lead the clinician to suspect cyanotic heart disease or severe PPHN. Response to supplemental oxygen has been traditionally used to differentiate lung disease from CHD. Oxygen is a potent and selective pulmonary vasodilator. A PaO_2 increase > 20 mm Hg, or saturation increase $> 10\%$ in response to O_2 suggests that hypoxemia is secondary to lung disease or mild PPHN. Higher pre-ductal PaO_2 and oxygen saturation compared to post-ductal location indicates presence of right to left shunt at PDA which occurs in approximately half of the babies with PPHN (67). However, ductal dependent left sided cardiac defects are also associated with right to left shunt at PDA and lower post-ductal O_2 saturation. Response to inhaled Nitric oxide (iNO) may help differentiate PPHN from cyanotic CHD. Majority of the infants with PPHN respond rapidly to iNO with an increase in PaO_2 and oxygen saturations. However, some infants with severe PPHN and infants with cyanotic CHD may experience a small or no increase in oxygenation with iNO. It is important to recognize that the use of high oxygen concentrations or pulmonary vasodilator therapy can adversely affect systemic perfusion in an infant with ductal dependent, left sided CHD such as coarctation of aorta or hypoplastic left heart syndrome. An echocardiogram is therefore needed to make an accurate diagnosis and initiate PG therapy for ductal dependent CHD. Echocardiography can also document the presence of right-left or bidirectional shunts at the level of PDA/PFO and estimate the pulmonary artery pressure from Doppler velocity measurement of tricuspid regurgitation jet.

Management of PPHN

Infants with PPHN require supportive care tailored to the degree of hypoxemia and physiologic instability. The overall approach should focus on restoring the cardio-pulmonary adaptation while avoiding lung injury and adverse effects on systemic perfusion. Prolonged exposure to 100% oxygen and aggressive ventilation can be avoided by judicious application of newer therapies, such as iNO, surfactant replacement and inotropic support. The traditional practice of targeting a high PO_2 (> 100 torr) and low PCO_2 to achieve pulmonary vasodilation has not been shown to improve outcome and is potentially harmful to the developing lung and cerebral perfusion. While achieving a normal PaO_2 of 60–90 torr is important for the postnatal adaptation, there is no evidence that a $\text{PaO}_2 > 100$ causes a greater reduction in PVR.

Since PPHN is often associated with parenchymal lung disease or systemic illness, therapy should target the underlying disease. Infants with mild and transient respiratory distress may respond well to supplemental oxygen alone or the use of nasal CPAP. Infants with moderate respiratory distress and hypoxemia may need ventilator support and monitoring of blood gases. Management of moderate to severe PPHN requires a comprehensive approach to optimize cardiac function, achieve uniform lung expansion and pulmonary vasodilation. It is important to recognize that the heart and lungs are connected, interdependent and function as an integrated system while undergoing critical adaptation at birth. Reversal of right-left extra-pulmonary shunts requires both a reduction in pulmonary artery pressure and maintaining the systemic blood pressure. Sedation may be necessary to provide comfort and decrease oxygen consumption from agitation in hypoxemic infants. Finally, infants that fail to respond to optimum medical management may require extra-corporeal membrane oxygenation (ECMO). These supportive measures are discussed in sequence with the evidence presented where available to favor each approach for a critically ill infant with PPHN.

Optimum lung expansion

Mechanical ventilation facilitates alveolar recruitment and lung expansion, potentially improving ventilation/perfusion (VQ) match. The ventilator strategy should target recruitment of the atelectatic segments while avoiding over distension which leads to lung injury and increased resistance to pulmonary blood flow. The application of surfactant therapy facilitates alveolar expansion in the parenchymal lung disease. Surfactant therapy has been shown to decrease the need for ECMO in full term infants with severe respiratory failure (68). The beneficial effect of surfactant was seen particularly in babies with MAS and sepsis (68). The use of surfactant in PPHN has increased over the recent years with nearly 80% of babies with moderate to severe respiratory failure currently receiving this therapy (6, 69). High frequency oscillation (HFO) may help to optimize lung expansion in babies with PPHN secondary to lung disease. Kinsella et al reported that HFO improves the oxygenation response to iNO when used in babies with MAS and RDS (70).

Use of sedatives and skeletal muscle relaxation

Although widely used to minimize fluctuations in oxygenation and facilitate ventilation, these approaches have not been tested in randomized trials. These drugs have significant adverse effects and commonly induce hypotension, generalized edema and deterioration of lung function with prolonged use. Hypotension is more common when a combination of sedatives and muscle relaxants are used. The use of skeletal muscle relaxation has been linked to increased incidence of hearing impairment in survivors of PPHN; however, the mechanism of this association is unclear (71). Diuretics, often used to treat edema secondary to skeletal muscle relaxation also increase the risk of hearing loss (72). Although sedation may be needed for comfort in ventilated infants, we do not recommend the routine use of skeletal muscle relaxation and limit its use when necessary for <48 hours. Pulmonary vasodilation with iNO can ameliorate the fluctuations in pulmonary artery pressure and oxygenation and its safety has been demonstrated in randomized trials as described below.

Hyperventilation/alkalosis

These therapies were widely used in the management of PPHN before the introduction of iNO. Studies in the animal models and limited studies in babies with PPHN demonstrated that low PaCO₂ and increase in pH cause pulmonary vasodilation (73–75). However, these studies demonstrated only short term improvements in pulmonary hypertension and oxygenation. The effect of hyperventilation on the pulmonary circulation appears to be primarily related to its effect on increasing pH (75). Hypocarbica and alkalosis decrease cerebral perfusion and have been associated with hearing loss and neurologic injury in the follow-up studies of infants that survived PPHN (76, 77). They induce hypocalcemia, myocardial dysfunction and systemic hypotension. Alkalosis also decreases the unloading of oxygen from hemoglobin (Hb) which can potentially decrease oxygen delivery to the tissues. Use of high tidal volumes to induce hypocarbica also leads to lung injury and can prolong the hospital stay for these infants. The development of new and specific pulmonary vasodilators has lead to the decreased use of these therapies. While correction of respiratory and metabolic acidosis facilitates pulmonary vasodilation, we do not advocate the use of hypocarbica and metabolic alkalosis in neonates with PPHN.

Cardiotonic therapy

Dopamine, dobutamine and epinephrine have been widely used in the management of PPHN, primarily to optimize cardiac function, stabilize systemic blood pressure and reduce right-left shunting. Recently, norepinephrine has been shown to increase systemic pressure and oxygenation in babies with PPHN (78). An increase in systemic pressure, however, may

not reflect an improvement in cardiac output. The use of vasopressor support should be considered one component of an overall approach to PPHN.

Inhaled nitric oxide (iNO) therapy

The introduction of iNO therapy has been the most significant milestone in the era of vasodilator therapy for PPHN. Development of this approach for PPHN is a remarkable example of the bench-to-bedside translational biology research done by several investigators. A short time after the discovery of NO as the endogenous vasodilator released by blood vessels, iNO was shown to cause selective pulmonary vasodilation at doses <100 ppm in a sheep model of pulmonary hypertension (79). NO gas given by inhalation reaches the alveolar space and diffuses to the vascular smooth muscle of the adjacent pulmonary artery from the ab-luminal side (Figure 4). Inhaled NO causes vasodilation by increasing the intracellular cGMP levels in the smooth muscle. As NO continues to diffuse into the lumen of pulmonary artery, it is rapidly bound and inactivated by Hb, limiting its effect to the pulmonary circulation. Inhaled NO is also preferentially distributed to the ventilated segments of the lung, resulting in increased perfusion of the ventilated segments, optimizing VQ match (Figure 4). The effect of iNO on pulmonary circulation is not limited by the presence of extra-pulmonary right-left shunts, which often resulted in hypotension with intravenously given vasodilators. These properties make iNO the ideal pulmonary vasodilator in neonatal respiratory failure. Recent studies demonstrated that NO levels in the nasal cavity of premature infants can reach 50–100 parts per billion (80, 81). Significant exhaled NO concentrations are measured in these infants, suggesting that inhalation of NO occurs physiologically during tidal respiration (80). Pilot studies in neonates with PPHN reported a rapid and sustained improvement in oxygenation with iNO (82, 83). The improvement in oxygenation is usually evident within a few minutes of starting iNO, which facilitates the rapid stabilization of a severely hypoxic and compromised neonate. Several large randomized clinical trials demonstrated that iNO therapy decreases the need for ECMO/mortality in full term and near term infants with hypoxic respiratory failure and pulmonary hypertension (67, 84–87). Inhaled NO improves oxygenation in 70% of the infants with PPHN with the best responses observed in idiopathic PPHN (6, 67, 86). Inhaled NO therapy has been approved for clinical use in term/near term newborn infants (>34 wks gestation) with hypoxic respiratory failure since 2000 by FDA (88). Previous clinical trials suggested that the ideal starting dose for iNO is 20 parts per million (ppm) with the effective doses between 5 and 20 ppm (6). Doses > 20 ppm did not increase the efficacy and were associated with more adverse effects in these infants (67, 89). The timing of initiation of iNO therapy is an important consideration in the management of PPHN. Based on a review of the previous clinical trials (Figure 5), we recommend initiation of iNO therapy when the respiratory failure progresses and oxygenation index (OI) reaches 20 on at least 2 blood gases. The severity of respiratory failure, assessed by OI, differed widely at the time of initiation of iNO in these 6 trials. The ECMO rates observed for iNO treated infants in these trials correlate well with the OI at the time of initiation of iNO and range from 40% (84) to 11% (6). The optimum time for initiation of iNO is before the infant develops severe respiratory failure secondary to progression of lung disease and/or lung injury. The randomized controlled studies of iNO also demonstrated both short term and long term safety of this therapy in infants with PPHN. Inhaled NO therapy can lead to 3 potential adverse events- methemoglobinemia generated by oxidation of Hb by NO, exposure to NO₂ generated by reaction of NO and O₂ and inhibition of platelet aggregation by NO. Previous iNO trials reported low methemoglobin levels and no significant exposure to NO₂ when doses <20 ppm are used. Davidson et al reported that at doses of 80 ppm, the average methemoglobin levels peak at >5% with up to a third of babies having levels >7% (89). Significant levels of NO₂ were also measured at the 80 ppm dose (89). Although altered

platelet function is a potential complication, Christou et al found no difference in platelet activation by ADP in babies receiving 40 ppm of iNO and placebo group (90).

Exposure to iNO even for a brief period can sensitize the pulmonary circulation to rebound vasoconstriction during discontinuation of iNO therapy. A significant drop in PaO₂ during withdrawal of iNO can be avoided by weaning the dose gradually in steps from 20 ppm to the lowest dose possible (0.5 -1 ppm) for a period of time before its discontinuation (91). Even in babies that show no response to iNO, sudden discontinuation can precipitate pulmonary vasoconstriction and rapid deterioration (92). When iNO therapy is used in non-ECMO centers, it should be continued during transport of the infant to ECMO center (88). Non-ECMO centers should establish treatment failure criteria for iNO in collaboration with the nearest ECMO center so that transfer of an ill infant is not delayed while waiting for a response to iNO. Based on the efficacy and safety of iNO from controlled clinical trials, we recommend using this therapy before prolonged exposure to high FiO₂ or maximal ventilator support. Exposure to 100% O₂ even for a brief period can induce vascular dysfunction, increase oxidative stress and impair subsequent response to iNO (93). Inhaled NO facilitates rapid weaning of FiO₂ and decreases oxidative stress from O₂ in an animal model of PPHN (46).

Alternatives to iNO therapy in PPHN

Inhaled NO therapy has not been as effective in babies with congenital diaphragmatic hernia, despite clinical and echocardiographic evidence of PPHN in majority of these infants (94). Inhaled NO does not reduce the mortality or ECMO rate in babies with CDH (94). In addition, nearly 30% of PPHN babies in randomized trials of iNO did not show an improvement in oxygenation (6, 67). As shown in Figure 1, inhibition of PDE-5 by sildenafil to preserve cGMP, activation of cAMP by PGI₂ or PDE-3 inhibition by milrinone offer additional tools to achieve pulmonary vasodilation. These therapies have been tested in limited clinical trials so far in patients that did not respond to iNO or when iNO was not available. After the introduction of sildenafil for erectile dysfunction, it was tested in adults with pulmonary hypertension since pulmonary circulation has a high expression of type - 5 PDE. The initial promising results lead to randomized clinical trials that demonstrated the efficacy and relative safety of oral sildenafil in adult primary pulmonary hypertension. Studies in the fetal lamb model of PPHN demonstrated an increased expression of type- 5 PDE in pulmonary arteries, which contributes to impaired vasodilation (95). Sildenafil has been shown to decrease the pulmonary artery pressure and prevent rebound pulmonary hypertension after iNO withdrawal during the post-operative period, following repair of congenital heart defects (96). A randomized placebo controlled trial of oral sildenafil in PPHN was halted early after 5 out of 6 infants in the placebo group died compared to 1 out of 7 infants in the sildenafil group (97). A significant improvement in oxygenation occurred in the sildenafil treated infants 6–12 hours after the first dose. Systemic hypotension was not observed in these studies with oral sildenafil. These data suggest a beneficial effect of oral sildenafil used as primary therapy for PPHN when iNO is not available. Intravenous sildenafil, which is currently not available for clinical use, has been reported to cause systemic hypotension (98). We currently use oral sildenafil for PPHN in iNO non-responders. An alternative to sildenafil is inhaled prostacyclin (PGI₂) which can be used in conjunction with iNO therapy. The effects of inhaled PGI₂ can be complementary to iNO since they stimulate different cyclic nucleotides. Kelly et al demonstrated an additive effect of inhaled PGI₂ (Flolan) given with iNO in four babies with severe PPHN unresponsive to iNO therapy alone (99). While inhaled PGI₂ requires continuous administration due to short half life, a more stable analog, Iloprost (Ventavis) can be given by intermittent nebulization. Although no clinical trials have been reported with inhaled Iloprost in neonates, our preliminary experience suggests an effect similar to inhaled PGI₂ in infants with CDH. The

PDE-3 inhibitor, milrinone ameliorates post-operative pulmonary hypertension and improves cardiac function after surgical repair of CHD (100). Milrinone infusion has been tested as a pulmonary vasodilator in PPHN in uncontrolled studies (101, 102). McNamara et al and Bassler et al reported an increase in PaO₂ and decrease in OI in response to milrinone infusion in neonates with PPHN who are unresponsive to iNO. Whether the improvement is related to milrinone or gradual resolution of underlying disease can only be determined by a randomized trial. The effect of milrinone on cAMP may be additive to inhaled PGI₂ and complementary to iNO therapy to amplify the vasodilation.

Extra-corporeal membrane oxygenation (ECMO)

ECMO was introduced as a rescue therapy to support neonates in severe respiratory failure with >80% predicted mortality during 1970s by Bartlett et al (103). ECMO has significantly improved the survival of babies with severe but reversible lung disease (104, 105). ECMO provides both respiratory and cardiac support to facilitate the postnatal adaptation to occur while allowing the lungs to recover from barotraumas and O₂ toxicity. However, ECMO requires cannulation of right carotid artery and jugular vein for veno-arterial bypass or jugular vein alone for veno-venous bypass. The infants on ECMO support also require anti-coagulation with heparin to prevent clotting in the bypass circuit. In view of their vulnerability to intra-ventricular hemorrhage, ECMO is generally not used in premature infants <34 weeks of gestation in most centers. Despite the obvious concerns about ligation of carotid artery and/or jugular vein during cannulation, ECMO support did not have an adverse impact on the outcome of neonates with PPHN. The 1 year outcomes for babies in severe respiratory failure treated with ECMO are comparable to infants that survived without ECMO support (104). The increasing application of newer therapies such as iNO, HFO and surfactant over the last 10 years has greatly reduced the need for ECMO in babies with PPHN secondary to parenchymal lung disease or primary PPHN (69, 106). Currently fewer than 5% of babies with PPHN at our center receive ECMO. Most of the babies that require ECMO support at our center for PPHN have CDH with pulmonary hypoplasia as the underlying diagnosis.

Pulmonary hypertension in premature infants

PPHN has been demonstrated by echocardiography in some premature newborns <30 weeks gestation with hypoxemia unresponsive to surfactant therapy (48). Prolonged rupture of membranes, pulmonary hypoplasia and intra-uterine growth retardation have been identified as risk factors for hypoxemia secondary to PPHN in premature infants (48). Although iNO has been shown to improve oxygenation in premature infants with RDS, its efficacy in improving long term outcome has not been demonstrated (107). Pulmonary hypertension (PH) is also being increasingly recognized as a component of chronic lung disease (CLD) in survivors of extreme prematurity (108). A decrease in the number of pulmonary vessels, altered lung architecture and episodes of hypoxemia and hypercarbia together may contribute to development of PH in CLD. A retrospective observational study of 42 infants with CLD and PH by Khemani et al demonstrated severe PH, defined as systemic or supra systemic right ventricular pressure in 43% of these babies (108). PH was diagnosed at a median postnatal age of 4.8 months. Survival for this cohort was 64% at 6 months after the diagnosis of PH and severe PH was a significant risk factor for mortality. However, the overall prevalence of PH in survivors of extreme prematurity with CLD remains unknown. It is important to recognize that PH can develop as a complication of CLD in extremely low birth weight infants after their discharge from NICU. Both iNO and sildenafil have been reported to be beneficial in these infants in decreasing the pulmonary artery pressure. Although the long term safety of sildenafil is unclear, it has been used for as long as 1–2 years without adverse effects in isolated case reports and uncontrolled trials (109). A case

report of severe retinopathy of prematurity (ROP) that developed in a premature infant treated at 29 weeks gestational age with sildenafil raises concerns about the safety of this drug during the window of vulnerability for ROP (110). Whether iNO or sildenafil improve survival and stimulate angiogenesis and lung growth in infants with CLD remains unknown, although these beneficial effects were suggested in animal models (107).

Long term outcomes for survivors of PPHN

A number of randomized trials of iNO evaluated the neuro-developmental status of survivors of PPHN at 18–24 months of age. These studies identified a significant risk of hearing loss and neuro-developmental impairments among survivors of PPHN (111–114). Late onset hearing loss has been identified in infants that initially pass their hearing screen prior to discharge from the NICU (113). This observation highlights the need for close follow-up of these infants following discharge from NICU. Two recent follow-up trials at 18–24 months of age reported on the outcome for babies with moderate and severe PPHN respectively (111, 112). The 299 babies enrolled in the early iNO therapy trial presented with moderate degree of respiratory failure. Among the 234 surviving infants seen at follow-up, 24% had hearing impairment and 26% had a neuro-developmental impairment, defined as moderate-severe cerebral palsy (CP), permanent hearing loss requiring amplification or vision loss or Bayley MDI or PDI<70. CP occurred in 7% and an abnormal neuro exam in 13% of the infants in this cohort. These data demonstrate a need for close follow-up of survivors of PPHN as they remain at a high risk for adverse outcomes, despite survival rates that exceed 90%. We currently follow all neonates admitted with PPHN severe enough to need iNO therapy at six month intervals until 2 years of age to identify these long term deficits. Future therapies to be tested in infants with PPHN should focus on improving their long term outcomes besides survival.

Future therapies for PPHN

Recent investigations in a fetal lamb model of PPHN demonstrated an increase in the oxidative stress in pulmonary arteries (37, 38). The oxidative stress contributes to impaired pulmonary vasodilation and lack of response to iNO (46). The free radical, superoxide is a vasoconstrictor and reacts with NO to reduce its bio-availability for vasodilation. Superoxide scavengers, such as recombinant human superoxide dismutase decrease the pulmonary artery pressure and improve the oxygenation response to iNO in this model (46). Antenatal administration of betamethasone also reduces the oxidative stress and improves the vasodilator response to NO in fetal lambs with PPHN (114). Prenatal correction of vascular dysfunction may facilitate normal birth-related adaptation and prevent periods of hypoxemia during postnatal life. Antenatal betamethasone is currently being investigated by the Maternal and Fetal Medicine Units network of NICHD in a randomized controlled trial to reduce respiratory morbidity for late preterm deliveries at 34–37 weeks gestation. Future studies will determine the potential role of these new approaches for the prevention and management of PPHN.

In summary, rapid advances in our understanding of the postnatal adaptation of pulmonary circulation have lead to newer therapeutic approaches for PPHN. Many of these advances resulted from the translational biology investigations in animal models of PPHN. Our enthusiasm over the dramatic decrease in mortality over the last 20 years should be tempered by recognition of the long term complications among survivors of PPHN. Promising new therapies that are targeted to correct the vascular dysfunction in PPHN may help prevent the periods of cardio-pulmonary instability inherent to these babies. The impact of these new approaches on the long term neuro-developmental outcome for babies with PPHN requires further investigation.

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Figure 1.

The mechanism of endothelium-dependent pulmonary vasodilation at birth. NO and PGI₂ are released in response to birth related stimuli. NO and PGI₂ increase the cGMP and cAMP levels in the smooth muscle cell. Type 5 and Type 3 phosphodiesterases (PDE) degrade these cyclic nucleotides. A decrease in intra-cellular Ca²⁺ levels leads to relaxation of vascular smooth muscle. NO levels are decreased by asymmetric dimethyl arginine (ADMA), superoxide (O₂⁻) and endothelin (ET-1). Non steroidal anti-inflammatory drugs (NSAID) inhibit cyclooxygenase (COX). PGIS=PGI₂ synthase. (Adapted from Figure 1, Berger S & Konduri GG: Pulmonary hypertension in children. *Pediatr Clin North Am* 2006; 53:961-987).

Figure 2.

Lung diseases associated with PPHN in 299 infants enrolled in the early inhaled nitric oxide study in term and near term neonates (6). Meconium aspiration syndrome (MAS) was the most frequent diagnosis, followed by primary PPHN, respiratory distress syndrome (RDS) and pneumonia and/or sepsis. Infants with congenital diaphragmatic hernia were excluded from this study.

Figure 3.

Chest X-ray obtained in an infant with primary PPHN on the left (A) shows absence of parenchymal lung disease. Chest X-ray on the right (B) was obtained in an infant with suspected RDS who did not improve with surfactant therapy. Echocardiography demonstrated total anomalous pulmonary venous return to inferior vena cava.

Figure 4.

Effect of inhaled NO on the pulmonary circulation. Inhaled NO reaches healthy alveoli, shown on the left and diffuses to the adjacent pulmonary arteries to cause vasodilation. As NO reaches the lumen of pulmonary artery, it is inactivated by hemoglobin (Hb) limiting its effect to the pulmonary circulation. NO does not reach the atelectatic alveoli shown to the right, maintaining constriction of the adjacent pulmonary arteries. Increased perfusion of the ventilated segments of the lung improves VQ match and oxygenation in parenchymal lung disease.

Figure 5.

Relationship of the severity of respiratory failure, defined by oxygenation index (OI) at the time of initiation of inhaled NO therapy and the ECMO rates observed in these babies. Data are from six randomized trials in term/near term neonates for babies assigned to the iNO arm in these trials (6, 67, 84, 86, 87 & 89). The trials are labeled by first author and are shown in the order of highest to lowest OI. NINOS=neonatal inhaled nitric oxide study group. The ECMO rate correlates with the severity of respiratory failure at the time of iNO initiation.