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Diagnosis and treatment of pulmonary hypertension in infancy

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Abstract

Normal pulmonary vascular development in infancy requires maintenance of low pulmonary vascular resistance after birth, and is necessary for normal lung function and growth. The developing lung is subject to multiple genetic, pathological and/or environmental influences that can adversely affect lung adaptation, development, and growth, leading to pulmonary hypertension. New classifications of pulmonary hypertension are beginning to account for these diverse phenotypes, and or pulmonary hypertension in infants due to PPHN, congenital diaphragmatic hernia, and bronchopulmonary dysplasia (BPD). The most effective pharmacotherapeutic strategies for infants with PPHN are directed at selective reduction of PVR, and take advantage of a rapidly advancing understanding of the altered signaling pathways in the remodeled vasculature.

INTRODUCTION

At birth, the fetal cardiopulmonary system rapidly establishes the lung as the organ of gas exchange by decreasing pulmonary vascular resistance and increasing pulmonary blood flow. Pulmonary artery pressure and vascular resistance continue to slowly decrease for another 2–3 weeks after birth. The vasoconstrictive response to hypoxia is retained into adulthood, and pulmonary hypertension can be easily triggered in the newborn period by hypoxic lung disease, apnea, or other causes. As development continues through infancy, normal lung function and growth requires maintenance of low pulmonary vascular resistance. Abnormalities of vascular development or function during this critical developmental period will result in persistent pulmonary hypertension. Pulmonary hypertension can also occur in infancy due to lung diseases such as bronchopulmonary dysplasia and congenital diaphragmatic hernia, and is a common complication of congenital heart disease.

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CLASSIFICATION AND EPIDEMIOLOGY OF PULMONARY HYPERTENSION IN INFANTS

Pulmonary hypertension is a necessary component of the fetal circulatory pattern, but sustained elevation of pulmonary arterial pressure is abnormal in the neonate and infant, and results in substantial mortality and morbidity. The classification, genetic causes, and treatment of pulmonary hypertension are strikingly different in infants vs. older children and adults. This is largely because the developing lung is subject to genetic, pathological and/or environmental influences that affect lung adaptation, development, and growth, leading to a greater complexity of phenotypes (Figure 1) [1]. The classifications of pulmonary hypertension introduced at the WHO Symposium in 1998 [2] and subsequently modified at the Venice and Dana Point Symposia [3, 4] were primarily designed for adult disease, and have been more challenging to apply to pediatric populations. The 2013 Nice WHO Symposium is expected to revise the classification to better account for pediatric diseases such as PPHN, congenital diaphragmatic hernia, and bronchopulmonary dysplasia (BPD). In addition, an expert panel convened in Panama City in 2011 provided a detailed and comprehensive classification system for pulmonary vascular disease in children [1, 5].

PATHOPHYSIOLOGY

Table 1 outlines a broad range of diseases that can be associated with PPHN or PH in infancy. Early PPHN usually presents as one of three patterns: 1) *maladaptation*: the constricted but structurally normal pulmonary vasculature, commonly associated with lung parenchymal diseases such as meconium aspiration syndrome, respiratory distress syndrome, or pneumonia; 2) *excessive muscularization*: the lung with normal parenchyma but remodeled pulmonary vasculature characterized by increased smooth muscle cell thickness and distal extension of muscle to vessels that are usually non-muscular; or 3) *the hypoplastic vasculature*, associated with underdevelopment of the pulmonary vasculature, as seen in congenital diaphragmatic hernia. However, these designations are imprecise, and many patients have respiratory failure due to changes that overlap among these categories. For example, neonates with severe, lethal meconium aspiration typically have excessive muscularization found at autopsy. Neonates with congenital diaphragmatic hernia are primarily classified as having vascular hypoplasia, yet lung histology of fatal cases typically shows marked muscularization of pulmonary arteries, and clinically, these patients frequently respond to vasodilator therapy.

Persistent pulmonary hypertension of the newborn (PPHN)

Persistent pulmonary hypertension (PPHN) describes the failure of normal pulmonary vascular adaptation at birth, and is characterized by elevated pulmonary vascular resistance and right-to-left extrapulmonary shunting of deoxygenated blood that produces severe hypoxemia [6]. PPHN complicates a wide range of neonatal cardiopulmonary diseases, and affects up to 10% of all neonates that require intensive care for respiratory failure. Moderate or severe PPHN affects up to 2–6 per 1,000 live births, and complicates the course of 10% of all infants admitted to neonatal intensive care [7]. Prior to the introduction of extracorporeal support in the late 1980's, PPHN was a disease associated more than 50%

mortality. Even with contemporary diagnostic and therapeutic modalities, the early mortality for moderate to severe PPHN remains 8–10%, and long term outcomes include high rates of neurodevelopmental impairment at 18 months of age [8, 9].

The first reports of PPHN described term newborns with profound hypoxemic pulmonary hypertension that lacked radiographic evidence of parenchymal lung disease. Idiopathic PPHN is sometimes called ‘black lung PPHN’ because of the predominant vascular disease with little or no underlying parenchymal lung disease. It can cause profound hypoxemia due to shunting of blood through the extrapulmonary channels of the foramen ovale and ductus arteriosus. Autopsy studies of fatal PPHN suggest that severe hypertensive structural remodeling with vessel wall thickening and smooth muscle hyperplasia develops *in utero*, likely as a result of chronic intrauterine stress. In addition, the vascular smooth muscle extends to the level of the intra-acinar arteries, which does not normally occur until much later in postnatal lung development. Pulmonary vascular remodeling and extrapulmonary shunting can also contribute to the severity of disease in babies with meconium aspiration syndrome and other parenchymal lung diseases.

Right ventricular dysfunction is a major contributor to poor outcomes for PPHN [10]. While pulmonary vascular resistance is high during fetal life, the right ventricle pumps against the low resistance placental circulation by directing most of its output through the ductus arteriosus. If transition occurs normally, the right ventricle continues to pump against a low resistance circuit as the pulmonary vascular resistance falls. On the other hand, if PPHN develops, the fetal right ventricle is poorly adapted to abruptly handle a high resistance circuit, and responds with a dramatic reduction in stroke volume [11].

Two recent studies indicate that the PPHN syndrome also occurs in preterm babies, particularly after oligohydramnios or prolonged rupture of membranes. Kumar retrospectively analyzed 1202 infants born at <33 weeks, and determined a PPHN incidence of 2% [12]. The 5 min Apgar score, PPROM, oligohydramnios, pulmonary hypoplasia and sepsis were independently predictive of PPHN. Aikio et al prospectively screened a cohort of 765 babies born at 32 weeks, and found an overall PPHN incidence of 2%, which rose to 12% in the group that required mechanical ventilation [13]. Premature rupture of membranes was the most significant risk factor. Even modest prematurity may increase the risk of PPHN, as late preterm (34–36 weeks gestation) and early-term infants (37–38 weeks gestation) are over-represented in infants who require ECMO [14].

Risk Factors for PPHN

Potential causes of antenatal remodeling of the pulmonary vasculature include environmental factors, toxic exposures or genetic risk factors (Figure 1). A recent case-control surveillance study reported maternal risk factors of black or Asian maternal race, elevated BMI (>27), diabetes and asthma. Neonatal risk factors included male gender, delivery by cesarean section, large for gestational age infants, and delivery before 37 weeks gestation or after 41 weeks [15].

Maternal use of salicylates was one of the earliest triggers identified for PPHN [16], and some reports suggest a strong association between clinically significant PPHN and the

maternal use of NSAIDs (aspirin, ibuprofen, naproxen) [17, 18]. However, a recent large multicenter epidemiologic study found no significant association between PPHN risk and maternal use of nonaspirin NSAIDs or ibuprofen use during third trimester [19]. It is not completely clear whether maternal SSRI use during pregnancy increases the risk of persistent pulmonary hypertension of the newborn. Brief infusions of sertraline and fluoxetine in fetal lambs directly increased PVR, and newborn rats chronically exposed *in utero* to maternal fluoxetine developed pulmonary vascular remodeling, abnormal oxygenation and higher mortality relative to controls [20, 21]. To date, six retrospective population-based studies have presented conflicting findings: three of the studies reported a positive association, but three other retrospective cohort studies found no association [22–27]. In addition, it is difficult to distinguish the impact of SSRI use as a risk factor independent of maternal depression, which may also increase rates of prematurity and PPHN [28]. The FDA currently recommends that health care professionals treat depression during pregnancy as clinically appropriate.

Unlike pulmonary hypertension in older patients, PPHN is rarely familial, and few genetic risk factors have been identified. Children with Down syndrome (Trisomy 21) commonly develop pulmonary hypertension in association with structural heart defects, but an elevated incidence of PPHN independent of cardiac disease is also evident [29, 30]. In a Dutch cohort with excellent early ascertainment, PPHN was documented in 5.2% of Down syndrome infants [31], and other studies have shown a higher need for ECMO support [32]. A recent single-center study reported the results of rigorous genotype analysis of 88 neonates with documented PPHN [33]. No differences were noted in most candidate genes, including BMPR2 and nitric oxide synthase. However, PPHN was significantly associated with genetic variants for corticotropin releasing hormone receptor-1 (*CRHR1*) and CRH-binding protein and with significantly increased levels of 17-hydroxyprogesterone. These data are supported by animal data indicating that antenatal and postnatal steroids reduce oxidant stress and normalize nitric oxide synthase and phosphodiesterase function in experimental PPHN [34, 35].

Alveolar capillary dysplasia (ACD) with misalignment of the pulmonary veins is a rare form of interstitial lung disease that presents as severe early hypoxemia and refractory, fatal PH [36]. The etiology of ACD is not well understood, but the prevailing opinion is that an early antenatal injury and/or a genetic defect leads to insufficient development of the pulmonary capillary bed, followed by remodeling and muscularization of the pulmonary arterioles and the development of congested ‘misaligned pulmonary veins’ residing in the same adventitial sheath. Approximately 10% of reported ACD cases have a familial association, and deletions in the FOXF1 transcription factor gene or deletions upstream to FOXF1 are observed in 40% of infants with ACD [37]. A murine model of FOXF1 deficiency has been described which has further demonstrated the importance of the Foxf1 protein in embryonic development of the pulmonary vasculature [38].

Genetic abnormalities of surfactant function have been reported in infants with PPHN who were refractory to iNO and ECMO. Surfactant protein B deficiency has been reported most commonly, and is characterized by early presentation, radiographic findings of ground-glass opacities, progressive respiratory failure, and early death. The most common mutation is in

codon 121 of the SP-B gene. Deficiencies in surfactant protein C also occur, but PPHN is not a known association. Mutations in the ATP-binding cassette (ABC) transporter 3 gene are now recognized to occur in neonates with severe neonatal lung disease and symptoms of surfactant deficiency and have been reported as a lethal cause of PPHN [39].

Congenital diaphragmatic hernia

Congenital diaphragmatic hernia (CDH) affects approximately 1 in 2500–3000 pregnancies when factoring in prenatal diagnosis, and represents ~8% of all major congenital anomalies. CDH includes abnormal diaphragm development, herniation of abdominal viscera into the chest, and a variable degree of lung hypoplasia. Herniation occurs most often in the posterolateral segments of the diaphragm, and 80% of the defects occur on the left side.

Severe CDH develops early in the course of lung development, and an arrest in the normal pattern of airway branching occurs in both lungs, resulting in reduced lung volume and impaired alveolarization. A similar developmental arrest occurs in pulmonary arterial branching, resulting in reduced cross-sectional area of the pulmonary vascular bed, thickened media and adventitia of small arterioles, and abnormal medial muscular hypertrophy extending distally to the level of the acinar arterioles. Although *in utero* lung compression by herniated viscera has been implicated as the primary mechanism producing the lung abnormalities of CDH, some evidence suggests that decreased pulmonary blood flow alone causes lung hypoplasia [40].

After birth, PVR often remains at suprasystemic levels, causing extra-pulmonary right-to-left shunting across the foramen ovale and ductus arteriosus and profound hypoxemia. High PVR in the newborn with CDH is related to multiple factors, including the small cross-sectional area of pulmonary arteries, structural vascular remodeling, vasoconstriction with altered reactivity and LV dysfunction causing pulmonary venous hypertension. The mediators of altered pulmonary vascular reactivity in CDH are not well understood, although substantial evidence points to disruptions in NO-cGMP and endothelin signaling [41].

Abnormalities of cardiac development and function also play an important role in the pathophysiology of CDH. The size of the left ventricle, left atrium, and intraventricular septum are hypoplastic in infants that die of CDH relative to age matched controls, perhaps due to low fetal and postnatal pulmonary blood flow and/or compression by the hypertensive right ventricle. Left ventricular hypoplasia and dysfunction will increase left atrial and pulmonary venous pressures, and the resulting pulmonary venous hypertension will diminish the clinical response to inhaled NO during the first few days of life. Some infants may have exceptionally severe left ventricular dysfunction that leads to dependence on the right ventricle for systemic perfusion; this subset may benefit from clinical strategies that maintain patency of the ductus arteriosus.

Bronchopulmonary dysplasia

Bronchopulmonary dysplasia (BPD) complicates the course of more than 30% of extremely preterm infants and has become the most common chronic lung disease of infancy. In

contrast to the classic features of fibroproliferative BPD as originally described by Northway, lung disease in today's post-surfactant era is characterized by impaired alveolarization and compromised vasculogenesis that occurs when the preterm lung attempts to adapt to air breathing.[42] These morphological vascular alterations are accompanied by functional changes, including increased pulmonary vascular tone and heightened vasoconstrictor responses to acute hypoxia.[43] Over time, reduced vascular growth limits vascular surface area and promotes high PVR, especially in response to high cardiac output at times of stress or exercise [44].

Pulmonary hypertension is now recognized as a common complication of BPD and worsens its clinical course, morbidity and mortality. Identifying BPD-associated pulmonary hypertension requires a high index of suspicion and careful longitudinal evaluation with echocardiography and cardiac catheterization. The risk for PH is not directly related to the severity of BPD, as some severe BPD infants never develop PH, while other babies with relatively mild BPD do. Risk factors for PH include extremely low gestational age, small-for-gestational age birth weight, oligohydramnios, duration of mechanical ventilation and prolonged oxygen therapy [45–47]. Preterm infants with PH should also be carefully screened for pulmonary venous stenosis, which is strongly associated with prematurity and BPD, and will predict worse outcomes [48].

Early retrospective studies suggested that up to a third of babies with BPD develop pulmonary hypertension, but were hampered by inconsistent screening practices [49–51]. Another large single-site study performed prospective echocardiographic screening in all extremely low birth weight (ELBW) babies for the presence or absence of pulmonary hypertension [52]. In this cohort, 6% of infants had evidence for PH by 4 weeks of age, and an additional 12% developed PH by the time of discharge. Babies with PH were more likely to be small for gestational age, and to require oxygen supplementation at 28 days and 36 weeks corrected gestation. PH persisted to discharge in the majority of the infants, and was associated with longer hospitalization times and higher mortality.

Numerous preclinical and clinical studies are addressing the vascular signaling abnormalities in evolving and established BPD. In sheep and primate models of prematurity, lung endothelial nitric oxide synthase (eNOS) expression is decreased and nitric oxide inhalation normalizes patterns of lung growth and vascularization [53, 54]. However, clinical trials of inhaled nitric oxide have not demonstrated a significant impact in reducing the severity of BPD [55]. Studies in preterm lambs indicate that deficient soluble guanylate cyclase activity could diminish vascular responses to nitric oxide, and that elevated activity of the cGMP-specific phosphodiesterase (PDE5) may also disrupt the cGMP response to nitric oxide,[56] but further study is needed to determine whether these findings will lead to new therapeutic insights.

CLINICAL DIAGNOSIS AND GENERAL CARE

Clinical manifestations of PPHN include labile oxygenation, differential saturation (higher SpO₂ in the right upper extremity compared to a lower extremity in most cases), or profound hypoxemia despite oxygen and mechanical ventilation. These findings are not

specific for PPHN, and echocardiography is mandatory to establish an accurate diagnosis of PPHN, identify extra pulmonary shunting and to rule-out congenital heart disease. Echocardiography also determines whether left ventricular insufficiency is present, which produces pulmonary venous hypertension that would only be aggravated by a pulmonary vasodilator. Measurements of brain type natriuretic peptide (BNP) levels may provide a biomarker that helps to differentiate infants with PPHN physiology from those with pulmonary causes of respiratory failure [57]. However, BNP levels are not sufficient to diagnose or gauge the severity of PPHN, and are better suited for serial evaluation of right ventricular strain and response to therapy [58].

General care

General management principles for the newborn with PPHN include maintenance of normal temperature, electrolytes (particularly calcium), glucose, and intravascular volume. In all infants, treatment of PH includes optimization of lung function and oxygen delivery, and support of cardiac function. Systemic blood pressure should be maintained at normal levels for age with volume and cardiotonic therapy, with the primary goal to reduce both left and right ventricular dysfunction and enhance systemic O₂ transport. Increasing blood pressure to supraphysiologic levels for the sole purpose of driving a left-to-right shunt across the PDA may transiently improve oxygenation but will not reduce pulmonary vascular resistance, and should be avoided.

Lung recruitment should be optimized, and high frequency ventilation and/or surfactant are often useful in infants with severe parenchymal lung disease. Surfactant deficiency (respiratory distress syndrome) or inactivation (eg, from meconium aspiration syndrome or pneumonia) is commonly present. Surfactant improves oxygenation, reduces airleak, and reduces need for ECMO in infants with meconium aspiration, sepsis and other parenchymal lung disease [59, 60]. However, these strategies are ineffective and run the risk of lung overdistension or acute airway obstruction in infants with idiopathic pulmonary hypertension, and should be reserved for infants with parenchymal lung disease.

Acidosis can induce pulmonary vasoconstriction, and should be avoided. Forced alkalosis by hyperventilation or infusion of sodium bicarbonate was frequently employed prior to the approval of inhaled nitric oxide [7]. While transient improvements in PaO₂ may be observed acutely, no studies have demonstrated long-term benefit. Prolonged alkalosis may paradoxically worsen pulmonary vascular tone, reactivity and permeability edema [61], and may produce cerebral constriction, reduced cerebral blood flow and worse neurodevelopmental outcomes.

Extracorporeal membrane oxygenation (ECMO) is the only therapy known to be life saving for PPHN infants who fail to sufficiently improve oxygenation and hemodynamic function [62]. No major differences have been reported in respiratory outcomes between ECMO provided by the venoarterial or venovenous routes of cannulation, although venoarterial support will usually be required for those infants with cardiac failure. Although ECMO can be life saving, it is also costly, labor intensive, and associated with potential adverse effects, such as intracranial hemorrhage and ligation of the right common carotid artery. The registry

maintained by the Extracorporeal Life Support Organization facilitates sharing of data and supports decision making for individual patients.

Therapeutic Oxygen

Oxygen is a specific and potent pulmonary vasodilator and increased oxygen tension is a central mediator of reduction in PVR at birth. Alveolar hypoxia and hypoxemia increase PVR and contribute to the pathophysiology of PPHN. As a result, high oxygen concentrations, frequently as high as 100% O₂, are commonly used to treat hypoxemia and reverse pulmonary vasoconstriction in infants with PPHN. However, hyperoxia exaggerates oxidative stress in the lung and pulmonary vasculature, and more precise oxygenation targets should be used when administering therapeutic oxygen. The use of 100% oxygen enhances markers of oxidant stress, increases pulmonary vascular contractility and impairs the pulmonary dilator responses to inhaled NO and endogenous NO. In animal studies, hypoxemia results in pulmonary vasoconstriction; normoxemia reduces PVR but hyperoxemia does not result in additional pulmonary vasodilation [63]. [64, 65]. In both normal lambs and lambs with pulmonary hypertension, the vasodilatory effects of supplemental oxygen reach a plateau at about 50% oxygen or a PaO₂ of 50–60 mm Hg [66]. Maintaining preductal oxygen saturations in the 90% to 97% range was associated with the lowest PVR in the ductal ligation model of PPHN (Figure 2), but clinical studies are still needed in infants with PPHN. The short-term pulmonary vascular benefits of hyperoxia should be weighed against the risks of increased pulmonary vascular contractility, diminished vasodilator responses, as well as potential systemic risks [67].

PHARMACOTHERAPY OF PULMONARY HYPERTENSION

The aims of pharmacotherapy for pulmonary arterial hypertension are selective pulmonary vasodilation, restoration of normal endothelial function, and reversal of remodeling of the pulmonary vasculature. All of these serve to reduce right ventricular afterload and prevent right ventricular failure. The choice of agents will often depend on the severity and acuity of illness –for instance, acute pulmonary vasodilation is needed for PPHN, but long-term therapy for CDH or BPD may focus more on vascular remodeling. The scientific understanding and therapeutic management of pulmonary hypertension are changing rapidly, but the main therapeutic avenues are currently centered around the nitric oxide (NO), prostacyclin, and endothelin pathways, as summarized in excellent recent comprehensive reviews [68–70].

Nitric oxide

Nitric oxide (NO) is synthesized from the terminal nitrogen of L-arginine by the enzyme nitric oxide synthase (NOS). Three isoforms of NOS are present in the lung, although endothelial NOS is regarded as the most important regulator of NO production in the lung vasculature. NO is a gas molecule that diffuses freely from the endothelium to the vascular smooth muscle cell. The biologic effects of NO in vascular smooth muscle are mediated primarily through activation of soluble guanylate cyclase, which converts GTP to cGMP (Figure 3). cGMP serves as a second messenger that relaxes vascular smooth muscle through activation of cGMP-gated ion channels and activation of cGMP-dependent protein

kinase. However, recent studies indicate that alternative NO signaling pathways may also exist through reaction of NO with protein thiols to form S-nitrosothiols (SNO), which may induce vasodilation or protein modification [71].

Lung eNOS mRNA and protein are present in the early fetus, but both increase toward the end of gestation, readying the lung to adapt to the postnatal need for pulmonary vasodilation. This increase in lung endothelial NOS content explains the emergence of responsiveness to endothelium-dependent vasodilators, such as oxygen and acetylcholine, in late gestation [72]. Many factors associated with pulmonary hypertension have the capacity to perturb eNOS function, even if protein levels are sufficient. Presumably, this is because the normal catalytic function of eNOS depends on numerous post-translational modifications, including association with the chaperone protein Hsp90 and availability of essential substrates and cofactors including L-arginine, tetrahydrobiopterin (BH₄), NADPH and calcium/calmodulin. Depletion of Hsp90 or biopterin will reduce production or bioavailability of NO, and will also “uncouple” eNOS, resulting in incomplete reduction of molecular oxygen with subsequent formation of superoxide, essentially turning the enzyme into a source of oxidant stress [73, 74].

Inhaled NO (iNO) has many features of an ideal pulmonary vasodilator, including inhalational delivery to the lung and a rapid onset of action. Since eNOS is decreased or dysfunctional in PPHN, iNO could provide specific replacement therapy that is delivered by inhalation directly to airspaces approximating the pulmonary vascular bed. While it is most commonly administered with mechanical ventilation, iNO can also be provided via CPAP or nasal cannula devices, although the concentration may need to be increased to account for the entrainment of room air [75]. It has been assumed that because nitric oxide is a small lipophilic molecule, inhaled NO simply diffuses from alveoli through epithelial cells to gain direct access to the vasculature. However, it is now understood that NO is a free radical that can be inactivated through interaction with reactive oxygen species found in the alveolar space or alveolar lining. Others propose that NO gas gains entry into alveolar epithelium in part by forming a nitrosothiol derivative of cysteine that enters *via* an amino acid transporter [76]. Once in the blood stream, NO binds avidly to hemoglobin, which is subsequently reduced by methemoglobin reductase.

iNO significantly decreases the need for ECMO support in newborns with PPHN, but does not reduce mortality or length of hospitalization. Starting iNO for respiratory failure that is in earlier stages of evolution (for an oxygenation index of 15 to 25) does not decrease the incidence of ECMO and/or death or improve other patient outcomes [8, 77]. On the other hand, delaying iNO initiation until respiratory failure is advanced (oxygenation index of >40) may increase length of time on oxygen [78]. In longer term follow-up, iNO did not significantly alter the incidence of chronic lung disease or neurodevelopmental impairment relative to placebo.

NO does not induce a consistent improvement in oxygenation in infants with congenital diaphragmatic hernia [79], although there appears to be a survival benefit of stabilizing infants and preventing cardiac arrest before ECMO [80]. The reasons for the poor early response to iNO is not well understood, but may be due to pulmonary venous hypertension

as a result of left ventricular hypoplasia and dysfunction. Some infants may have exceptionally severe left ventricular dysfunction that leads to dependence on the right ventricle for systemic perfusion; this subset may benefit from clinical strategies that maintain patency of the ductus arteriosus.

Up to one third of premature infants with bronchopulmonary dysplasia (BPD) will develop some degree of pulmonary hypertension or cor pulmonale, and alterations in NO signaling appear to play a role in the vascular and lung injury [54]. A recent case series indicates that iNO reduces BPD-associated pulmonary hypertension to a greater degree than oxygen alone [43], but trials are needed to determine whether this translates to clinical benefit. On the other hand, large clinical trials have not shown any consistent benefit when iNO is used to prevent BPD [81–84].

As the understanding of nitric oxide signaling evolves, strategies will emerge that enhance function of the native NOS enzyme. For instance, sufficient synthesis of L-arginine is necessary for optimal NOS function [85], and exogenous L-arginine supplementation enhances NOS activity *in vitro*. While arginine supplementation has been less successful when attempted *in vivo*, L-arginine can be endogenously synthesized from L-citrulline by a recycling pathway consisting of two enzymes, argininosuccinate synthase (AS) and argininosuccinate lyase (AL). Recent studies indicate that providing exogenous L-citrulline may reverse NOS dysfunction in animal models of neonatal pulmonary hypertension [86]. In clinical studies, oral L-citrulline increased both plasma citrulline and arginine levels in high-risk children undergoing cardiopulmonary bypass [87]. Intravenous L-citrulline has been shown to be safe and well tolerated in children undergoing cardiopulmonary bypass [88], and clinical trials are underway.

Reactive oxygen species (ROS) produced during hypoxia or hyperoxia promote vasoconstriction, in part by uncoupling and inactivating nitric oxide synthase, and altering function of its downstream receptors. Free radical scavengers may augment responsiveness to inhaled nitric oxide and restore pulmonary vasodilation. In lambs with pulmonary hypertension, ROS scavengers enhanced pulmonary vascular relaxations to nitric oxide both *in vitro* and *in vivo* [89, 90]. These were followed by pre-clinical studies in which a single intratracheal dose of recombinant human superoxide dismutase (rhSOD) was found to dilate the pulmonary circulation [89], and improve oxygenation over a 24-hour period to a degree that was similar to inhaled NO [91]. Furthermore, rhSOD administration blocked formation of oxidants such as peroxynitrite and isoprostanes, and restored normal postnatal patterns of endogenous nitric oxide synthase and phosphodiesterase expression and activity [74, 92]. Thus, use of antioxidants may have multiple beneficial effects on nitric oxide function by increasing the availability of both endogenous and inhaled NO, reducing oxidative stress and its effects on downstream targets, restoring normal patterns of enzyme expression, and limiting lung injury.

Sildenafil

Cyclic GMP is the second messenger that regulates contractility of smooth muscle through activation of cGMP-dependent kinases, phosphodiesterases and ion channels. In vascular smooth muscle cells, NO-mediated activation of soluble guanylate cyclase is a major source

of cGMP production. Because cGMP is such a central mediator of vascular contractility, its concentrations are regulated within a relatively narrow range to allow fine-tuning of vascular responses to oxygen, nitric oxide, and other stimuli.

Phosphodiesterases are a large family of enzymes that hydrolyze and inactivate cGMP and cAMP, thus regulating their concentrations and effects, as well as facilitating “cross-talk” between the two cyclic nucleotides. The type 5 phosphodiesterase (PDE5) is highly expressed in the perinatal lung, and not only uses cGMP as a substrate but also contains a specific cGMP binding domain that serves to activate its catabolic activity. As the primary enzyme responsible for regulating cGMP, PDE5 may well represent the most important regulator of NO-mediated vascular relaxation in the normal pulmonary vascular transition after birth (Figure 3) [93].

Fetal and neonatal lung development, along with commonly used therapies, will affect regulation of PDE expression and activity. In developing lambs and rats, PDE5 is expressed according to specific developmental trajectories that result in a peak of expression during late fetal life, followed by an acute fall around the time of birth [92, 94]. This drop in PDE5 activity would be expected to amplify the effects of nitric oxide produced by birth-related stimuli such as oxygen and shear stress. In contrast, in animal models of PPHN, PDE5 activity increases dramatically relative to control lambs [92, 95], an effect that is greatly amplified by hyperoxia [96]. Increased PDE5 activity would be expected to diminish responses to both endogenous and exogenous NO, and could explain why iNO does not fully reverse pulmonary hypertension in some infants. It is also interesting to note that recent reports indicate that PDE5 is highly expressed in the remodeled human right ventricle, raising the possibility that sildenafil therapy may improve right ventricular function [97].

The first clinical report of sildenafil use in infants was to facilitate weaning from iNO following corrective surgery for congenital heart disease [98]. In this initial case series, oral sildenafil increased circulating cGMP and allowed two of three infants to wean from iNO without rebound pulmonary hypertension. Subsequent case series showed that enteral sildenafil may facilitate iNO discontinuation in infants with critical illness [99], and may also reduce duration of mechanical ventilation and ICU length of stay [100]. The clinical use of enteral sildenafil has also been reported in infants with PPHN, including one small, randomized controlled trial with oral sildenafil that showed a dramatic improvement in oxygenation and survival [101].

Enteral administration of sildenafil could be compromised by inconsistent gastrointestinal absorption, particularly in critically ill patients. An open-label pilot trial of intravenous sildenafil in infants with PPHN demonstrated continuous infusions of sildenafil improved oxygenation, and were associated with low rates of complications and use of ECMO [102]. Furthermore, seven infants treated with sildenafil without prior use of iNO experienced similar improvements in oxygenation within four hours after sildenafil administration. All infants improved and survived to hospital discharge, and only one required standard therapy with iNO [102].

Sildenafil may provide an attractive therapeutic option for infants with chronic pulmonary hypertension due to congenital diaphragmatic hernia or bronchopulmonary dysplasia because it can be given orally, and over longer periods of time with apparent low toxicity. Several reports from rodent models of hyperoxic lung injury have shown that sildenafil improves lung growth and alveolarization [103, 104], and increases expression of pro-angiogenic factors such as HIF and VEGF [105]. A clinical case series examined the effect of oral sildenafil in 25 infants and children (<2 years of age) with pulmonary hypertension due to chronic lung disease (mostly BPD). Most patients showed some improvement after a median treatment interval of 40 days, and the majority of infants were able to wean off iNO [106]. Five patients died after initiation of sildenafil treatment, but none died from refractory pulmonary hypertension or right heart failure. A similar approach might benefit some infants with chronic pulmonary hypertension associated with congenital diaphragmatic hernia [107]. These important pilot studies suggest that sildenafil is well tolerated in infants with pulmonary hypertension due to chronic lung disease, and paves the way to further studies in this especially challenging population.

It is important to note that in August of 2012, the US Food and Drug Administration released an alert against the use of sildenafil (Revatio) for pediatric patients (ages 1–17) with pulmonary arterial hypertension. The FDA warning stemmed from its analysis of the long term follow-up data associated with an extension phase of the STARTS trial [108, 109], and recommends against pediatric sildenafil use that is “based on a recent long-term clinical pediatric trial showing that: (1) children taking a high dose of Revatio had a higher risk of death than children taking a low dose and (2) the low doses of Revatio are not effective in improving exercise ability.” However, the STARTS trial focused only on children who were >1 year of age and without lung disease, so by design, it could not determine the potential efficacy or safety of sildenafil for sick newborns or young infants. The STARTS trial also does not address the short-term benefits and risks of sildenafil in the NICU setting, especially since the elevated mortality signal did not emerge until after three years of therapy and was only observed at the highest dose (~3–6 mg/kg/day).

Prostanoids

A complementary vasodilatory pathway in the perinatal lung is mediated by prostacyclin (PGI₂) and cAMP (Figure 3). Prostacyclin is a metabolite of arachidonic acid that is endogenously produced by the vascular endothelium. The vascular effects of PGI₂ are mediated through its binding to a membrane IP receptor which activates adenylate cyclase and increases cAMP, which triggers smooth muscle cell relaxation through reducing intracellular calcium concentrations. Prostacyclin production increases in late gestation and early postnatal life [110, 111], indicating its importance in promoting the neonatal pulmonary vascular transition. Pulmonary hypertension in infants is characterized by an decrease in the biosynthesis of prostacyclin accompanied by increased synthesis of the vasoconstrictor thromboxane A₂ [112]. Furthermore, the PGI₂ receptor (IP) is decreased in pediatric patients with pulmonary hypertension, and animal studies point to its contribution to altered vasodilation in PPHN [113]. Prostacyclin is a potent vasodilator in both the systemic and pulmonary circulations and also has anti-platelet effects [114]. Prostacyclin was one of the earliest pulmonary vasodilators used for clinical treatment of pulmonary

hypertension, and was approved by the FDA in 1995 for the treatment of severe chronic pulmonary arterial hypertension.

Intravenous PGI₂ is front-line therapy for acute and chronic treatment of pulmonary hypertension in adults, but rapid dosage escalation is often necessary to achieve acute pulmonary vasodilation. In infants, this can produce systemic hypotension, which can further compromise circulatory function. In addition, a dedicated central venous catheter is necessary for its delivery, with associated risks of infection and other line complications. Other systemic side effects (especially pain) also limit the utility of systemic PGI₂ in the acute setting.

Inhalation of aerosolized PGI₂ produces vasodilator effects more limited to the pulmonary circulation, and has been widely adopted in adult critical care units [115]. There are fewer reports of the use of inhaled PGI₂ in infants [116–118]. Our experience suggests that inhaled PGI₂ (50–100 ng/kg/min) is well tolerated and improves oxygenation in infants with severe PPHN and inadequate response to iNO [9, 119]. Concerns include airway irritation from the alkaline solution needed to maintain drug stability, rebound pulmonary hypertension if the drug is abruptly discontinued, inconsistent drug delivery due to loss into the circuit, and alteration of characteristics of mechanical ventilation from the added gas flow needed for the nebulization. Prolonged use of continuous inhaled PGI₂ may also lead to damage of mechanical ventilator valves.

Further investigations will likely focus on preparations specifically designed for inhalation, such as iloprost or treprostinil. Because these medications are more stable than PGI₂ they do not need to be dissolved in an alkaline solution, which could decrease the risk of lung injury. In addition, their longer half-lives allow for intermittent dosing using ultrasonic nebulizers. In critically ill mechanically ventilated patients, the effective dosing of inhaled prostanoids is likely to be higher and more frequent than in spontaneously breathing patients due to loss of the medication into the humidified ventilator circuit. Treprostanil may also be suitable for systemic administration. Furthermore, the care of infants with severe pulmonary hypertension in the NICU is often complicated by limited vascular access. This problem prompted us to use subcutaneous treprostinil in a small cohort infants with severe pulmonary hypertension due to heterogeneous causes. In three extremely premature infants with severe pulmonary hypertension associated with BPD, RV size and function improved over time, and local site pain (typically a significant problem in adults) was not evident [9]. However, the use of systemic prostanoids should be approached with caution, and care must be taken to avoid excessive prostanoid doses, which may produce severe discomfort, generalized vasodilation and high output heart failure.

PDE3 Inhibition - Milrinone

Similar to the NO–cGMP pathway, prostacyclin–cAMP signaling is regulated by cAMP-hydrolyzing PDE isoforms such as PDE3 and PDE4. We recently reported that PDE3A expression and activity in the resistance pulmonary arteries increase dramatically by 24 h after birth [120]. These results were unexpected, as we would have predicted that PDE3 activity would decrease after birth to facilitate cAMP accumulation, similar to the patterns reported for PDE5 [9, 93]. We also observed that addition of inhaled nitric oxide

dramatically increased PDE3 levels, which suggests that inhibition of PDE3 activity might enhance the vasodilatory effects of iNO/cGMP signaling [113].

Milrinone is an inhibitor of PDE3 activity that is frequently used in pediatric patients to improve myocardial contractility after cardiac surgery. Milrinone may also bypass abnormalities in endogenous PGI₂ production and/or enhance availability of cAMP, which could be useful for acute treatment of pulmonary hypertension [121]. Animal studies have shown that milrinone decreases pulmonary artery pressure, acts synergistically with inhaled prostanoids [113], and acts additively with iNO [122, 123]. Clinical reports indicate that milrinone may decrease rebound pulmonary hypertension after iNO is stopped [124], and may enhance pulmonary vasodilation of infants with PPHN refractory to iNO [125, 126]. A study to better define the pharmacokinetic profile of milrinone in infants with PPHN is ongoing (NCT01088997), and should lead to clinical trials designed to test its efficacy.

Endothelin Receptor Antagonists - Bosentan

Endothelin-1 (ET-1) is a 21 amino acid protein formed by serial enzymatic cleavage of a larger prepropeptide to the vasoactive form, and is one of the most potent vasoconstrictors described in the pulmonary vasculature (Figure 3). ET-1 is principally produced in endothelial cells in response to hypoxia, and is known to promote endothelial cell dysfunction, smooth muscle cell proliferation and remodeling, as well as inflammation and fibrosis [127]. ET-1 binds to two receptor subtypes, ET receptors A and B, and the binding of ET-1 to the ETA receptor on smooth muscle cells produces vasoconstriction. Increased ET-1 production and altered ET receptor activity have been consistently reported in neonatal and adult animal models of pulmonary hypertension, and lung ET-1 expression and plasma ET levels were elevated in severe PAH in adults [128]. Endothelin-1 is believed to play a role in the pathogenesis of neonatal pulmonary hypertension, and endothelin blockade augments pulmonary vasodilation in the perinatal lung [127]. A recent prospective examination of 40 newborns with congenital diaphragmatic hernia also indicated that plasma ET-1 levels were highly correlated with the severity of pulmonary hypertension [41].

Bosentan is an oral endothelin receptor antagonist that improves exercise capacity and pulmonary vascular resistance in children with pulmonary hypertension [129, 130]. Recent case reports also suggest that bosentan may improve oxygenation in neonates with PPHN [131, 132], and a single-center randomized trial of NO-naïve PPHN patients found that oxygenation improved in 87.5% of bosentan-treated patients compared to 20% in the placebo group. [133]. A randomized controlled trial is currently underway to investigate the efficacy of bosentan in infants with severe PPHN refractory to iNO (NCT01389856). Risks of bosentan include dose-dependent hepatotoxicity, and liver function should be monitored monthly, although elevated aminotransferases and drug discontinuation rates are less common in young children compared to patients > 12 years of age [134].

Summary

No single therapeutic approach has been shown to be universally effective in the treatment of PPHN, likely due to the complexity of the signaling pathways. The future lies in combination therapy derived from a better understanding of the underlying signaling

pathways. These likely vary between disease states, age groups, and even racial and ethnic groups. A thoughtful, physiologically based approach will allow for more effective and efficient therapy, and has the best chance of minimizing side effects and lung injury.

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Figure 1.

Remodeling of the pulmonary vasculature occurs during antenatal and/or postnatal life when risk factors interact with the early developing lung. Risk factors include environmental factors (eg, maternal diabetes, smoking, fetal growth restriction), toxic exposures (eg, NSAIDs, SSRIs, hyperoxia) or genetic risk factors (eg, Down Syndrome, single gene mutations such as FOXF1).

Figure 2.

The relationship between oxygen saturation and PVR in lambs born after chronic intrauterine hypertension. Median (solid line) and 25th and 75th percentile lines (dashed lines) are shown in the figure. A saturation range of 90% to 97% is associated with the lowest PVR. (Data from reference [66]).

Figure 3.

Schematic of the nitric oxide (NO), prostacyclin (PGI₂) and endothelin (ET)-1 signaling pathways. NO stimulates soluble guanylate cyclase to increase intracellular cGMP and PGI₂ stimulates adenylate cyclase to increase intracellular cyclic AMP (cAMP). Both cGMP and cAMP indirectly decrease free cytosolic calcium, resulting in smooth muscle relaxation. Sildenafil inhibits PDE5 in vascular smooth muscle, and milrinone inhibits PDE3 in cardiomyocytes and vascular smooth muscle. ET-1 produced by endothelial cells binds endothelin A (ETA) and endothelin B (ETB) receptors on smooth muscle cells. The ET-1 receptor antagonist Bosentan augments smooth muscle vasoconstriction by blocking ET-1 effects.

Table

Disorders Associated with Pulmonary Hypertension in Infants:

PULMONARY

Idiopathic Pulmonary Hypertension

Meconium Aspiration Syndrome

Respiratory Distress Syndrome

Transient tachypnea of the newborn

Pneumonia/Sepsis

Lung Hypoplasia

Congenital Diaphragmatic Hernia

Other abnormalities in lung development:

- Alveolar-Capillary Dysplasia
- Surfactant Protein B Deficiency
- ABCA3 Deficiency
- Pulmonary lymphangiectasis
- Congenital lobar emphysema (rare association)
- Cystic adenomatoid malformation (rare association)

CARDIOVASCULAR

Myocardial dysfunction (asphyxia; infection; stress)

Pulmonary venous disease

- Pulmonary vein stenosis (isolated)
- Total anomalous pulmonary venous return

Hepatic arteriovenous malformations (AVMs)

Cerebral Arteriovascular Malformations

ASSOCIATIONS WITH OTHER DISEASES

Neuromuscular disease

Metabolic disease

Polycythemia

Thrombocytopenia

Maternal factors - NSAID use, SSRI use, maternal diabetes or smoking