Pulmonary Vascular Phenotypes of Prematurity: The Path to Precision Medicine

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Over past decades, lung circulation in premature infants has not generally received as much clinical attention or related research as the developing airways or lung parenchyma, yet, the importance of pulmonary hypertension (PH) and related pulmonary vascular disease (PVD) has become increasingly recognized as a critical (and variably diagnosed) clinical problem and as a major determinant of outcomes after preterm birth.[1-3] In addition to the impact of abnormalities of airways and distal airspace structure and function, impaired pulmonary vascular development associated with PH can often contribute to the severity of acute and chronic respiratory disease in infants born preterm, risk for late PH and long-term cardiopulmonary outcomes.

This review explores the idea that better characterization of distinct phenotypes of in infants born preterm will provide critical insights into the variable nature of PH and mechanisms contributing to the development and severity of PH, which will have significant implications regarding diagnostic evaluations, clinical care, and personalized therapeutic strategies. Appreciation of the underlying physiology and time course of disease will better identify infants born preterm at high risk for late cardiopulmonary disease and will improve patient selection and therapeutic goals to improve the quality of future randomized clinical trials.

In this review, we (1) discuss early perinatal factors and mechanisms that disrupt normal pulmonary vascular development and cause cardiopulmonary disease after preterm birth; (2) briefly review the high incidence and general physiological features of PH in infants born preterm; (3) highlight issues regarding severe persistent PH of the newborn (PPHN) in infants born preterm; (4) present current ideas regarding the diverse phenotypes of PH in infants born preterm; and (5) discuss the clinical implications of the different phenotypes of PVD, and therapeutic strategies to optimize the care and improve early and late outcomes of infants born preterm with PH.

BPD	Bronchopulmonary dysplasia
HRF	Hypoxemic respiratory failure
iNO	Inhaled nitric oxide
LV	Left ventricular
NO	Nitric oxide
PAP	Pulmonary artery pressure
PBF	Pulmonary blood flow
PDA	Patent ductus arteriosus
PFO	Patent foramen ovale
PH	Pulmonary hypertension
PMA	Postmenstrual age
PPHN	Persistent pulmonary hypertension of the newborn
PVD	Pulmonary vascular disease
PVR	Pulmonary vascular resistance
PVS	Pulmonary venous stenosis
RV	Right ventricular
VEGF	Vascular endothelial growth factor

Mechanisms that Disrupt Normal Pulmonary Vascular Development and Increase Risk for PH in infants Born Preterm

The pathogenesis of PVD in infants born preterm is multifactorial, including interactions between diverse prenatal and postnatal factors (Figure 1). Throughout fetal life, pulmonary vascular development progresses in orchestration with accompanying airways and distal airspace growth and is dependent on the highly regulated and coordinated processes of vasculogenesis (de novo blood vessel formation from endothelial cells), and angiogenesis (extension of existing vessels through endothelial cell sprouting and intussusceptive growth).[4-10] As lung development continues, the number of small arteries, capillaries, and the microcirculation in the distal lung increase dramatically. With maturation, the early presence of a double capillary network fuses to form the microcirculation, which directly neighbors alveolar epithelium to support efficient gas exchange and has implications for coordination between vascular and alveolar growth. Laboratory studies have demonstrated that lung alveolar development is closely related to vascular development, because vascular injury and impaired angiogenesis lead to disruption of alveolar development, suggesting an important role for angiocrine signaling during normal lung growth and development.[7,11-13]

Fetal lung development is influenced by physical factors, such as intrauterine space, lung liquid volume, and fetal breathing movements. Oligohydramnios increases the risk for neonatal PVD by disrupting fetal lung airspace and vascular growth.[14] Preclinical as well as human studies have clearly shown that abnormal placental vascular structure and function, including evidence of placental

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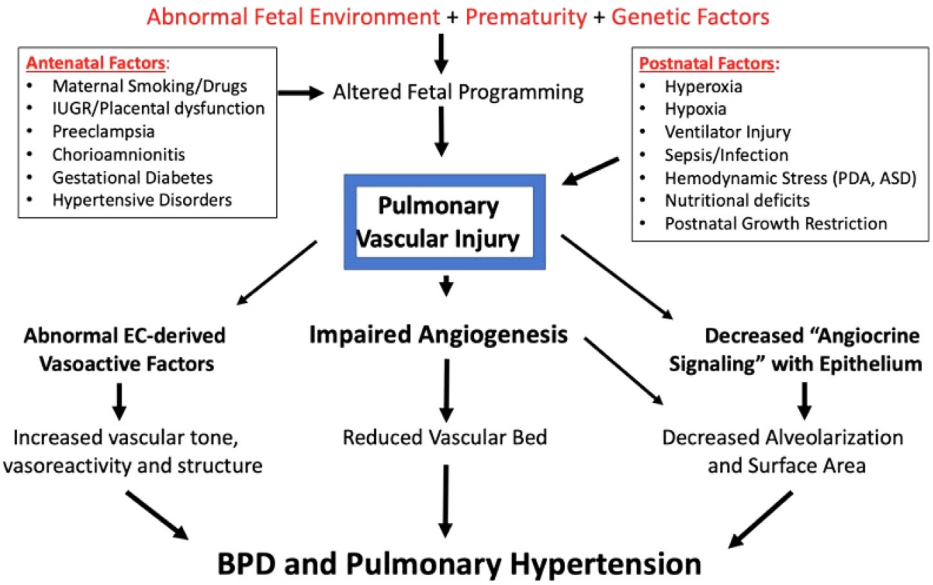

Figure 1. Mechanisms contributing to the development of early PVD and PH in premature infants. *ASD*, atrial septal defect; *EC*, endothelial cell; *IUGR*, intrauterine growth restriction.

hypoperfusion, are strongly associated with intrauterine growth restriction, neonatal PH, and death or bronchopulmonary dysplasia (BPD).[15-24] Thus, early injury that includes a variety of adverse exposures in utero that are not exclusively due to the direct effects of hypoxia alone cause sustained disruption of lung and pulmonary vascular growth and structure throughout infancy, reflecting epigenetic effects altering fetal programming.[11,20,24-26] Premature closure of the fetal ductus arteriosus can alter endothelial function and growth, favoring high pulmonary vascular resistance (PVR) and impaired angiogenesis, as well as pulmonary artery smooth muscle cell signaling that further increases the risk for PPHN.[27-29] Inflammatory mediators target lung mesenchymal cells, disrupting alveolar morphogenesis and normal pulmonary vascular development.[30] Chorioamnionitis increases the risk for neonatal PH and BPD in infants born preterm.[31,32]

In addition to premature birth, antenatal factors contribute to high risk for PH in low gestational age newborns.[18,19] Adverse exposures such as chorioamnionitis, placental insufficiency with vascular hypoperfusion, intrauterine closure of the ductus arteriosus, and oligohydramnios, especially as associated with intrauterine growth restriction or lung hypoplasia, are each strongly associated with a higher risk for PPHN in infants born preterm. However, PPHN cannot be diagnosed accurately by the severity of lung disease and hypoxemia alone. Delayed pulmonary vascular transition during the first postnatal days, even in the absence of physiologically defined PPHN by the presence of hypoxemia owing to right-to-left extrapulmonary shunt across the patent ductus arteriosus (PDA) or patent foramen ovale (PFO), is not uncommon in infants born preterm and can further reflect the presence of PVD after birth.[33] Data from preclinical studies exploring mechanisms linking antenatal inflammation to BPD and late cardiorespiratory outcomes are growing, and recent studies suggest that disruption of critical developmental signaling pathways related to hypoxia-inducible factors, insulin-like growth factor-1, vascular endothelial growth factor (VEGF), and others play overlapping and vital roles in impairing lung development, especially as related to angiogenesis.[1,2,7-13,26,34]

The pathogenesis of PVD and multifactorial risks for the development of PH in premature infants is schematically illustrated in Figure 1. Pulmonary vascular injury likely begins with impaired growth owing to extreme prematurity, adverse antenatal exposures, and placental dysfunction, which is sufficient to cause PVD with PH.[17-22] Abnormal vascular tone, vasoreactivity, and growth can further increase susceptibility for late disease, including PH and severe BPD, especially in response to persistent exposure to postnatal factors such as hypoxia, hyperoxia, inflammation, ventilator-induced vascular injury, hemodynamic stress, and other factors, which commonly occur in infants born preterm during the early postnatal period.

PVD in infants born preterm can be present in diverse clinical contexts with variable degrees of severity at different corrected gestational ages, including early, late, and chronic postnatal stages, as discussed elsewhere in this article. Overall, the presence of PVD, the diagnosis of PH and its underlying physiology and severity, and the diagnosis of PH at different clinical stages have distinct challenges and implications for both clinical management and the identification of infants at higher risk for adverse short- and long-term cardiorespiratory outcomes.

PH in Infants Born Preterm: Incidence and Physiological Features

Until relatively recently, PH was not considered a disease that commonly affects infants born preterm, but that impression has drastically changed. Naumburg et al have shown the higher risk of PH among infants born preterm born between 1973 and 2010, especially with the increasing survival of extremely low gestational age newborns.[35] In comparison with an estimated incidence of PPHN in term newborns of 1-2 per 1000 births, Nakanishi et al reported a striking incidence of PPHN of 8% of preterm newborns below 28 weeks of gestation from comprehensive registry data of the Neonatal Research Network of Japan, and that the incidence was related to the severity of prematurity, ranging from 4% in preterm neonates born at 27 weeks of gestation to 18% of those born at 22 weeks gestational age.[36-38] Striking associations of PPHN in infants born preterm from this report included more severe respiratory disease, higher rates of pneumothorax and pulmonary hemorrhage, the need for more prolonged invasive mechanical ventilation, and other comorbidities.[38] In the clinical setting, the use of echocardiography to evaluate pulmonary hemodynamics and serial changes in hemodynamics throughout the clinical course can be highly variable between neonatal intensive care units, which contributes to either under-recognition or the misdiagnosis of PH in preterm newborns with hypoxemic respiratory failure (HRF). A presumptive diagnosis of PH in infants born preterm at less than 28 weeks gestational age is often made by clinical bias, rather than through direct physiological assessment with echocardiography, limiting our understanding of PH-specific drug therapies in infants born preterm.[39]

Despite growing appreciation for the contribution of PVD in infants born preterm to the short-term clinical course and late outcomes, uncertainty exists regarding the precise nature and implications of making the diagnosis of PH within different clinical settings, and the mechanisms by which abnormalities of pulmonary vascular growth, function, and structure contribute to these outcomes (Table I). Signs of PH, such as recurrent cyanotic episodes, lability with activity, tachypnea, tachycardia, hepatomegaly, edema, and others that are present beyond the first few postnatal months in infants born preterm continue to be linked with high mortality.[40-43] In prospective studies, 25%-50% of infants with severe BPD may have late PH that is strongly associated with comorbidities and poor survival.[1,3,44-48] Currently, data regarding clinical strategies and the potential impact of therapeutic strategies to improve outcomes are largely lacking.

PVD is present at different stages after preterm birth, representing diverse pulmonary vascular phenotypes[1,48] (Table I). For example, infants born preterm may have echocardiographic evidence of PH without any clinical manifestations soon after delivery (ie, "physiological" PH) that spontaneously resolves within 72 hours after birth. In contrast, some infants born preterm with acute HRF have echocardiographic evidence of severe PH causing right-to-

Table I. Pulmonary vascular phenotypes of infants born preterm

Early PH (birth to first few weeks)*
Physiological PH
Echocardiographic evidence of PH† without hypoxemic HRF, which resolves spontaneously by 72 hours after birth.
No clear risk for late adverse outcomes or need for PH-targeted therapy.
PPHN
Echocardiographic evidence of PH owing to extrapulmonary right-to-left shunt causing with hypoxemia often with abnormal systemic hemodynamics that requires cardiorespiratory support and PH-targeted therapy.
Key role for iNO and PH-targeted drug therapies in addition to related cardiopulmonary support.
Infants with PPHN are at high risk for prolonged invasive ventilation, BPD, late PH, or death.
Delayed pulmonary vascular transition
Echocardiograph evidence of PH within 72-96 hours of birth with variable severity of HRF.
Clinical presentation less severe than PPHN yet remains associated with an increased risk for prolonged ventilation, late PH, BPD, and death.
Role of PH-specific treatment is unclear.
Acute PH
Echocardiographic evidence of PH after the normal pulmonary vascular transition.
Acute or subacute presentation may be exacerbated by large left-to-right PDA shunt and other factors.‡
Associated with the high risk for late PH, BPD or death.
PH-specific treatment may be beneficial along with the treatment of underlying triggers
Late PH (≥4 weeks to months after birth)*
Echocardiographic evidence of PH after 4 weeks of life, symptoms may be exacerbated by other triggers.‡
Associated with BPD and its severity, high risk of mortality, and hospital readmissions.
PH-specific treatment is recommended for recurrent or persistent disease.
Chronic PH (beyond 6 months of life)*
Echocardiographic evidence of ongoing PH beyond 6 months of life may have remissions or exacerbations.
High risk for mortality and hospital readmissions, PH-specific treatment is indicated.

*PH owing to excessive pulmonary blood flow or obstruction can be diagnosed at any time (early, late, or chronic) depending upon the severity of the underlying diagnosis, that is, a significant post-tricuspid shunt, mitral valve or pulmonary vein stenosis, or left ventricle dysfunction. Treatment with pulmonary vasodilators is contraindicated for these infants.
†Echocardiographic evidence of PH in the form of significant tricuspid regurgitation, septal flattening, or reverse bowing, right-to-left or bidirectional shunt at the atria level, or flow gradient across post-tricuspid shunts, such as a PDA or ventricular septal defect.
‡PH exacerbations can be triggered by hypoxemia, inadequate ventilation, suboptimal lung recruitment (VQ mismatch), or the inflammation caused by neonatal infections like pneumonia, respiratory viral infections, NEC, sepsis, UTI, and so on.

Table II. Echocardiographic parameters for the assessment of PH in BPD

Severity of PH
Interventricular septal wall motion ("septal flattening"): mild, moderate, or severe.
Eccentricity Index
Tricuspid regurgitant jet velocity
Assessment of shunt (PDA, PFO/ASD, ventricular septal defect)
Pulmonary vascular resistance
PA Doppler shape
Ratio of pulmonary artery acceleration time to RV ejection time (pulmonary artery acceleration time/right ventricular ejection time)
RV performance
Tricuspid annular plane systolic excursion
Fractional area of change
Myocardial velocities
RV strain
LV diastolic function
E:A wave (transmitral Doppler ratio)
Isovolumic relaxation time
E/ratio (to assess LV filling pressure)
Left atrium:aorta ratio
Myocardial contractility
Speckle tracking—strain and strain rate for LV and RV performance
LV and RV output
Pulmonary vein stenosis
Assessment of flow and turbulence across each of the pulmonary veins

left extrapulmonary shunt across the PDA or PFO in the hours and days after birth, defined as PPHN. The degree of hypoxemia is determined by the degree of impairment in pulmonary blood flow, rather than the specific pulmonary artery pressure (PAP). Other infants born preterm have echocardiographic evidence of PH beyond 72 postnatal hours with or without clinical symptoms owing to delayed pulmonary vascular transition. PH in infants born preterm after the first few postnatal weeks is associated with higher risk for BPD or death.[44,49–53] Late PH, associated with evolving or established BPD at 36 weeks postmenstrual age (PMA), can continue during infancy, childhood, and early adulthood (**Table I**).

The American Heart Association/American Thoracic Society Guidelines for pediatric PH recognized that formal diagnostic criteria of PH during the first 3 postnatal months remain poorly defined; specifically, as the pulmonary vascular transition from fetal to neonatal life, especially in infants born preterm, represents a very dynamic period of time.[54] As a result, current diagnostic criteria for early PH vary between centers, but generally include at least 1 of the following echocardiographic findings: the presence of mild, moderate, or severe interventricular septal flattening; estimated right ventricular (RV) systolic pressure of greater than 40 mm Hg; RV systolic pressure/systemic systolic pressure of more than 0.5, or predominantly right-to-left flow at the PDA and PFO (**Table II**).

PH can frequently be related to the presence of excessive pulmonary blood flow (eg, a large left-to-right shunt across an unrestricted PDA) or pulmonary venous hypertension, especially in infants born preterm. Because the PAP is directly proportional to the product of PVR and pulmonary blood flow (PBF) according to the equation: PAP = PVR × PBF + left atrial pressure, high PBF owing to a high volume PDA shunt (or large atrial level shunt) can markedly increase PAP, even with minimal PVD.[49,55] Similarly, elevated left atrial pressure owing to left ventricular (LV) systolic or diastolic dysfunction may also be a major contributor to PH owing to postcapillary or pulmonary venous hypertension.[56] This may be seen in the setting of a prolonged PDA shunt, sepsis, or BPD and LV diastolic dysfunction, which occurs with or without overt systemic hypertension. As a result, assessing the relative contributions of elevated PVR, high flow across an unrestricted PDA, and LV performance remain ongoing challenges in understanding the underlying pathophysiology of PH and its treatment in infants born preterm. Physiologically, an unrestrictive right-to-left shunt across the PDA as a metric of PH must further be considered in the context of absence of congenital heart disease, such as coarctation of the aorta, and in the absence of systemic hypotension, which may further augment the degree of right-to-left shunt at the PDA. Finally, predominantly right-to-left shunt at the PDA in the setting of left-to-right shunt at the atrial level is highly suggestive of LV dysfunction with pulmonary venous hypertension as a contributor to PH.

Treatment of PH is particularly challenging for infants with a moderate to large PDA. A right-to-left shunt across the PDA may provide a critical pop off valve that sustains cardiac output in the presence of high PVR, especially with RV dysfunction; treatment with pulmonary vasodilators is likely helpful for such infants. Elimination of the shunt is not advisable during the acute phase, but rather, preservation of cardiac output by maintaining ductal patency is often the basis for the use of prostaglandin E1 therapy in this setting. By echocardiogram, these patients are often characterized by right heart dilation, low RV output, pulmonary venous return, and LV output. Importantly, patients would be less likely to benefit from PH-targeted drug therapy in the setting

of a large left-to-right shunt or LV dysfunction, in which pulmonary vasodilation may worsen pulmonary edema, increase the need for respiratory support, and further impede cardiac output. Echocardiographic findings in patients with PH owing to left-to-right shunt across the PDA often show high flow in the pulmonary veins, a dilated left heart, high LV output, and compromised flow in the postductal aortic arch.

Some infants born preterm with prolonged exposure to a moderate to large PDA (or other post-tricuspid valve shunt) may have PH that is more strongly related to high flow and pulmonary overcirculation than PVD.[57,58] Treating these infants with selective (eg, inhaled nitric oxide [iNO]) or nonselective (milrinone) pulmonary vasodilators can further increase the left to right shunting by decreasing the PVR and inducing systemic hypotension with reduced RV perfusion, which can worsen RV performance. Infants with prolonged exposure to a hemodynamically significant PDA with left-to-right shunting are at high risk for progressive pulmonary vascular remodeling owing to ongoing hemodynamic stress and may benefit from medical or surgical elimination of the shunt. Early pharmacological or surgical closure of a hemodynamically significant PDA has the potential to decrease the risk of progressive PH and, if left untreated, the clinical course may be complicated by progressive increase in PVR in addition to high PAP and respiratory disease owing to pulmonary overflow.[58-60]

Determining the relative contributions of severe PVD with high PVR owing to high PBF with a large left-to-right shunt across an unrestricted PDA, or LV diastolic dysfunction in BPD-associated PH may be challenging. As a result, multiple echocardiographic parameters are useful to discern the underlying physiology and the relative roles of shunt, LV and RV performance, and other features. Screening echocardiographs for BPD-associated PH should be multiparametric owing to reliability issues of individual measures and should include multiple qualitative and quantitative metrics to assess severity of PH; measures of PVR; appraisal of shunts across the PDA, PFO or atrial septal defect, and ventricular septal defect; assessment of RV and LV performance; and others. Standardizing the echocardiograph may enhance the ability to differentiate these phenotypes. Despite careful clinical and echocardiographic evaluations, determination of underlying pathophysiological mechanisms and responsiveness to therapy may require a low threshold for early cardiac catheterization to better define management strategies.[61-64]

Pulmonary venous stenosis (PVS) is an additional, severe and very challenging contributor to PH in infants born preterm.[65-70] PVS can be congenital or acquired in origin, and can be associated with severe necrotizing enterocolitis.[65] PVS may present with or without BPD as PH in infants born preterm.[66] Diagnosis of acquired PVS in infants born preterm with BPD is usually delayed beyond 36 weeks PMA, and is characterized as abrupt late onset or progressive PH, often with increased pulmonary edema and worsening respiratory disease.[67] Many infants have concurrent precapillary PH, along with PVS, and even cautious treatment with pulmonary vasodilators can worsen the pulmonary edema that may require concurrent diuretic therapy. Current treatment approaches include mechanical PVS dilation and stenting with close monitoring with serial echocardiograms, computed tomography scans, and cardiac catheterization to assess disease course. In some centers, sirolimus therapy has been used to abate progressive pulmonary venous obstruction after anatomic interventions.[69,70]

Understanding the relative roles of cardiopulmonary interactions are important in managing PH in infants born preterm. Optimizing lung recruitment without overdistension improves PH by reducing mechanical factors that elevate PVR and worsen ventilation/perfusion mismatch in the setting of parenchymal lung disease. Furthermore, rigorous management of ongoing airways and lung disease, including monitoring and treating infections with appropriate antibiotics, the judicious use of corticosteroids, aggressive airway clearance, and managing aspiration risks may further improve PH by reducing lung inflammation and enhancing respiratory function.[61]

Potential treatment strategies for PH include targeting lung, heart, and pulmonary vascular dysfunction. Strategies typically include the use of supplemental oxygen therapy, optimized respiratory support to provide adequate and uniform lung volume with optimized gas exchange, correction of acidosis, surfactant administration, enhancing cardiac performance with cardiotonic therapies, and selective or nonselective pulmonary vasodilators such as iNO, sildenafil, bosentan, and prostanoids. As noted, the use of PH-targeted drug therapies, such as iNO, sildenafil, and others, may be counterproductive for infants with a large PDA and high left-to-right shunting, infants with PVS, or in the presence of LV dysfunction.[64]

Thus, the use of treatment strategies for PH in infants born preterm depends on understanding the PH phenotype, its underlying and evolving physiology over time, and closely monitoring disease course with serial echocardiograms, beginning early in the postnatal course, in addition to the use of serum biomarkers (eg, N-type pro brain natriuretic peptide levels), chest radiographs, and other respiratory assessments, to best define changes in clinical course and the impact of therapies on overall cardiopulmonary dynamics.

Specific Pulmonary Vascular Phenotypes of Prematurity

Physiological PH

Infants born preterm are at high risk for surfactant deficiency that requires surfactant administration, respiratory support, or supplemental oxygen. In the presence of HRF, it is difficult to differentiate the relative contribution of primary lung disease vs PVD. However, in the absence of HRF, echocardiographic evidence of PH within the first 72 postnatal hours of life is considered physiological PH, because these infants are going through normal fetal to neonatal transition of pulmonary circulation. In physiological PH, increased PVR is not enough to cause hypoxemia as the shunt across the

PDA is typically predominantly left-to-right PBF is preserved. Physiological PH in infants born preterm is not associated with poor clinical outcomes and spontaneously resolves within 72 hours.[33]

Persistent PH in Infants Born Preterm

The normal fetal lung circulation is characterized by low blood flow owing to vasoconstriction with high myogenic tone. At birth, the pulmonary circulation rapidly responds to birth-related stimuli during the transition from its high resistance state in utero to a high-flow, low-resistance circulation immediately at birth.[53] Removal of fetal lung liquid at birth, rhythmic stretch with distension of the lung, and increased alveolar oxygen tension promote the production of endogenous vasodilators, including NO and prostacyclin, and decrease the production of such potent vasoconstrictors, as endothelin-1.[71–75] PPHN is characterized by disruption of this normal transitional physiology: PVR remains high and leads to inadequate pulmonary blood flow owing to right-to-left shunting of blood through the PDA or PFO.

Clinically, these infants present with profound HRF owing to the magnitude of compromise to pulmonary blood flow. Numerous studies have explored the diverse mechanisms that contribute to high PVR in PPHN, which include the inability to generate or sustain production of NO and prostacyclin with marked increases in endothelin-1 expression.[68,69,71] Basic and translational studies regarding the mechanisms that regulate pulmonary vascular tone and vasoreactivity during the perinatal period contributed to the development of current drug therapies for PPHN in term newborns, including iNO, sildenafil, endothelin-1 receptor blockers, and prostacyclin analogues. In term infants, PH-specific drug therapies improve oxygenation in PPHN by reducing the right-to-left extrapulmonary shunt owing to high PVR and enhancing RV function and cardiac performance, thereby decreasing the need for extracorporeal membrane oxygenation support.[76–80] Infants who fail PH-targeted therapies often have underlying problems such as impaired RV or LV contractility, high pulmonary venous pressures owing to left heart dysfunction, and suboptimal oxygenation and ventilation owing to inadequate respiratory support, especially as related to lung recruitment or overdistention, or the severity of underlying lung disease (eg, severe RDS or lung hypoplasia and others). With unresponsive or severe disease, the diagnosis of genetic developmental lung disorders such as alveolar capillary dysplasia, TBX4, NKX 2.1, surfactant protein disorders, and others, should be explored with genetic studies and perhaps lung biopsy.

Studies of physiological mechanisms leading to the disruption of pulmonary transition after preterm birth have primarily focused on surfactant insufficiency and the need to optimize lung recruitment with noninvasive or invasive strategies without inducing ventilator-induced lung injury. However, it has become clear that the failure of adaptation of the lung circulation can contribute significantly to failed or delayed postnatal transition in preterm newborns.[32,38] PPHN in infants born preterm is markedly increased in comparison with near-term or term neonates, and its incidence is associated directly with the degree of prematurity.[38] In contrast with term neonates, extracorporeal membrane oxygenation is not an option for infants born preterm owing to the higher risk of complications and technical limitations, making the management of PPHN in infants born preterm even more challenging.

Past studies have demonstrated that vasodilation or vasoconstriction of the pulmonary circulation in response to high and low levels of oxygen, respectively, increases with advancing gestational age.[39,81] However, these findings are often misinterpreted as indicating that the pulmonary vasculature does not play a role in HRF in infants born preterm. For example, extremely preterm lambs are capable of regulating basal and stimulated pulmonary vascular tone through production of NO during midgestation and are highly responsive to inhaled NO during mechanical ventilation after preterm delivery.[82,83]

Clinical studies have further demonstrated that iNO often acutely improves oxygenation in human preterm newborns with HRF with PPHN, especially in the setting of suspected lung hypoplasia often with oligohydramnios, suggesting that high pulmonary vascular tone can contribute to elevated PVR in this setting.[83,84] In addition, respiratory severity in babies born preterm has been strongly associated with hypertensive pulmonary vascular remodeling as shown by histopathology in fatal disease, further supporting the contributions of early PVD to some infants with severe respiratory failure shortly after birth.[85] Numerous observational reports of marked improvement in oxygenation in infants born preterm with PPHN led to consensus recommendations for iNO use in infants born preterm with echocardiogram-proven PPHN physiology from a joint American Heart Association and American Thoracic Society guidelines and from the Pediatric Pulmonary Hypertension Network.[54,86] However, evidence from multicenter randomized trials are lacking; none of the past studies examining the effects of iNO therapy for the prevention of BPD enrolled patients based on a strict echocardiography diagnosis of PH and did not differentiate between infants born preterm with or without PPHN as part of their study design.[87–89]

As a result, our understanding of the potential benefits of iNO or other PH-targeted drug therapies for the management of severe hypoxemia with PPHN in infants born preterm remains limited. Although imperfect, one retrospective study based on a search of diagnostic billing codes through medical records at several institutions compared the outcomes of infants born preterm who were identified as having lung hypoplasia with or without PH.[90] These findings confirmed high mortality in babies born preterm who had suspected lung hypoplasia without an improvement in survival in those who received iNO therapy. However, when the data were further analyzed between infants with suspected lung hypoplasia with or without PPHN, the use of iNO was associated with a nearly 30% improvement in survival, although this subgroup analysis was not statistically

significant.[90] In addition, evidence from a single site demonstrated that an a priori echocardiography diagnosis of PH was associated with an 8-fold increased likelihood of response to iNO, independent of gestational age.[91] We speculate that the early identification and intervention in babies born preterm with PPHN physiology may improve survival in this subgroup.

Clearly, not all infants born preterm with severe hypoxemia have PPHN physiology with reduced pulmonary blood flow and/or severe RV dysfunction contributing to poor oxygenation. Routine administration of pulmonary vasodilator therapies, such as iNO, is unlikely to be helpful in the management of infants with HRF caused by severe parenchymal lung disease without PPHN (especially with insufficient lung recruitment), pulmonary venous hypertension with left heart dysfunction, structural heart disease, ductus-dependent lesions, and in the setting of developmental lung disorders such as alveolar-capillary dysplasia, TBX4, and others. Failure to appreciate the underlying physiological phenotypes that distinguish mechanisms of acute HRF has led to confusion regarding the potential usefulness for iNO therapy or other PH-targeted therapies, such as sildenafil, bosentan, milrinone or prostacyclin analogues in infants born preterm.[23,86]

Delayed Pulmonary Vascular Transition

Normal pulmonary vascular transition is expected by 24 hours in term infants or up to 72 postnatal hours in infants born preterm.[33] Unlike infants with PPHN, infants with delayed pulmonary vascular transition do not present with severe HRF. Recent work from Mirza et al showed the natural history of neonatal transition of pulmonary circulation in infants born preterm, based on serial echocardiograms performed every 24-48 hours for the first 2 postnatal weeks (Figure 2). In this study, infants were classified broadly in two categories of normal and delayed pulmonary vascular transition. Pulmonary vascular transition was considered

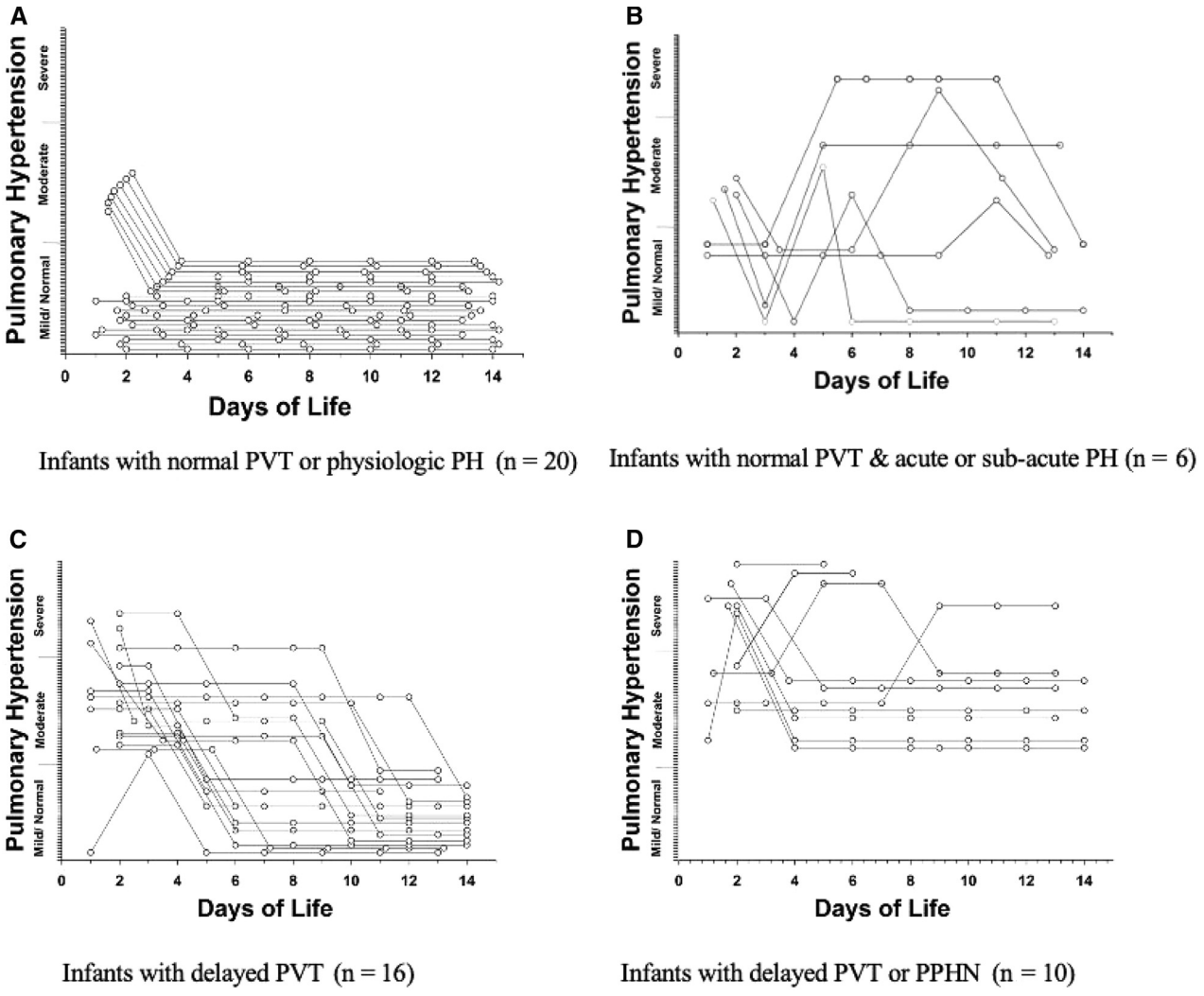

Figure 2. Different patterns of pulmonary vascular transition of the premature infant. (From[33] with permission.)

normal if there was no echocardiographic evidence of PH by 72-96 hours, even if the initial echocardiograph at 24-48 hours showed signs of PH (physiological PH). Most infants (70%) with normal pulmonary vascular transition had no echocardiographic evidence of PH until postnatal day 14, although some were noted to develop PH by postnatal day 14 day (acute or subacute PH). Infants with delayed pulmonary vascular transition had 3 different temporal profiles. In 20% of infants, PH was resolved within 24-48 hours and remained normal subsequently; in 50%, PH fully resolved by postnatal day 14; and approximately one-third of the infants with delayed pulmonary vascular transition continued to have elevated PAP until 14 days of life or later.[33]

Infants with delayed pulmonary vascular transition or early PH are at risk to develop recurrent or late PH associated with BPD.[33,43-45,52] It is not clear if targeted PH treatment with iNO or sildenafil can improve the clinical outcomes for infants with delayed pulmonary vascular transition or early PH. A randomized clinical trial is underway to determine the effects of early iNO treatment for these infants. (NCT03576885).

Some infants born preterm may have echocardiographic evidence of intermittent or transient PH that is triggered by pneumonia or other severe neonatal infections, persistent hypoxia, or suboptimal lung recruitment on mechanical ventilation (atelectasis or hyperinflation).[92] (See Acute PH category in **Table I**). For these infants, targeted treatment of the underlying etiology can help to resolve the associated PH.

Early PH and the Risk for Late PH, BPD, and Respiratory Disease in Childhood

BPD is characterized by an arrest of vascular and alveolar growth. As proposed in **Figure 1**, disruption of angiogenesis during lung development not only reduces vascular growth, which contributes to the development of PH, but it also impairs alveolarization or growth of the distal airspaces, which has been defined as the vascular hypothesis of BPD.[7-9] Animal studies have demonstrated that early disruption of lung vascular growth owing to hemodynamic stress in utero or with treatment with antiangiogenesis agents, including VEGF antagonists and nonspecific inhibitors, during the early postnatal period causes PH and decreases alveolarization, suggesting that vascular growth and endothelial signaling plays an important role for normal development of the alveoli beyond vascular growth alone.[11-13]

Human autopsy studies have shown that decreased lung VEGF expression is strongly associated with histologic evidence of lung simplification and a dysmorphic vasculature from human infants born preterm dying with BPD, suggesting that abnormal angiogenesis is linked with the pathobiology of clinical BPD.[93] Animal studies further demonstrated that endothelial-derived products enhance alveolar epithelial growth and septation, highlighting the important role of angiocrine signals from the vascular endothelium during normal lung development, as well as support for the hypothesis that early therapeutic strategies that preserve lung endothelial survival and function may decrease the risk for BPD. Epidemiological findings have shown strong associations of antenatal complications that impair placental function with a high risk for developing BPD with PH in the setting of preterm birth. Furthermore, animal models that mimic fetal stresses, as in chorioamnionitis and preeclampsia, are sufficient to impair lung vascular growth, induce sustained PH, and reduce alveolar growth independent of such classic postnatal factors as hyperoxia and ventilator-induced lung injury.[34] In addition, prospective studies have shown that in maternal pre-eclampsia, cord blood biomarkers reflecting impaired angiogenesis and early echocardiographic findings of PH shortly after birth are strongly linked to the risk of BPD, PH, prolonged hospitalization, and late respiratory outcomes in childhood.[15,18,20,21,94-98] Whether any therapeutic intervention for early PH such as iNO can decrease the risk for death or BPD remains speculative.

As discussed, early PH can be due to high PVR with right-to-left or bidirectional shunt, as in PPHN, or high flow associated with increased left-to-right flow across the PDA. A recent study described late outcomes based on physiological characterization of early PH by echocardiogram in a cohort of infants born preterm (<30 weeks of gestation) studied between postnatal day 3-10.[49] In this cohort, 55% of infants were diagnosed with early PH. These infants were then defined as having 1 of 3 distinct physiological phenotypes: PPHN, as based on the presence of predominantly right-to-left shunt; PH owing to high flow as defined by left-to-right shunting across a nonrestricted PDA; and PH without evidence of a significant shunt. Early PH owing to PPHN and PH owing to high flow, but not PH without shunt, were strongly associated with the diagnosis of severe BPD or death before 36 weeks corrected age. These findings highlight the potential usefulness of physiological phenotyping to better characterize key features underlying PH beyond the presence or absence of early PH alone. Most important, differentiation of resistance from flow-driven PH is highly relevant for clinicians. Although the former may benefit from pulmonary vasodilators, the latter may be harmed and require specific management of the excessive pulmonary blood flow (eg, PDA treatment).

Late PH

Late PH in infants born preterm with BPD is usually diagnosed if there is echocardiographic evidence of PH after 4 weeks of life and has been associated with poor survival. In 1967, Northway et al[98] conducted an original study of BPD and reported that late deaths in BPD had marked cardiomegaly and RV hypertrophy, "but the pathogenesis of cor pulmonale is puzzling." The presence of PH beyond the first few postnatal months was linked with mortality rates as high as 40%-50% in 1980, which is similar to mortality rates described in a subsequent study in 2007.[40,41] This study further showed that BPD infants with severe PH as demonstrated by right heart catheterization had

higher mortality than those with mild to moderate disease.[41] Recent prospective studies using echocardiography to define PH have shown that the incidence of late PH is between 14% and 25% at 36 weeks PMA, with the highest rates of PH identified in infants with severe BPD in comparison with none, mild or moderate BPD.[43-47,52]

Clinically, the ongoing need for high levels of respiratory support, and the presence of recurrent cyanotic episodes (BPD spells) are signs of late, severe PH. In some infants, the presence of PH with milder lung disease at the time of neonatal intensive care unit discharge can be associated with respiratory problems such as intermittent hypoxemia, obstructive sleep apnea, recurrent infections, chronic aspiration, and other issues on lung vascular injury. Major improvements in clinical care have led to increased survival and decreased the severity of BPD, yet the diagnosis of late PH and its management continue as a major clinical challenge. Guidelines from the American Heart Association, American Thoracic Society, and the Pediatric Pulmonary Hypertension Network provide consensus recommendations for the monitoring, evaluation and care of BPD-associated PH, but acknowledge the need for further studies to enhance outcomes.[54,86]

Chronic PH

For infants born preterm, there is growing evidence of late echocardiographic markers of PH that persist throughout infancy, childhood, and early adulthood.[99,100] It is considered chronic PH or PVD across the lifespan. These children and young adults with chronic PH are at high risk for developing abnormal cardiac structure and function over the years. The clinical presentation of chronic PH may be complicated by an acute on chronic course, but clinical manifestations are subtle at baseline, often with only mild signs of exercise-induced symptoms. Echocardiographic metrics, such as pulmonary artery acceleration time, can indicate the presence of PVD without striking PH throughout childhood in former infants born preterm with or without BPD. By adolescence, mild elevations in mean PAP can be detected, which are highest in prematurely born adults.[99] Ongoing studies are needed to better understand the late natural history of PVD into adulthood, along with its associated problems of cardiac structural abnormalities.

Conclusions

The purpose of this review was to highlight the importance of defining and characterizing distinct phenotypes of PH in infants born preterm. Understanding pulmonary vascular phenotypes and the overall context and physiological impact of PH has significant implications regarding diagnostic evaluation, selecting therapeutic strategies and identifying infants born preterm at risk for late cardiopulmonary disease. In addition to providing a guidance for precision medicine, it will also enhance the quality of randomized clinical trials to identify optimal therapies in the future. ■

Declaration of competing interest

The authors declare no conflicts of interest.

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References

1. Mourani PM, Abman SH. Pulmonary hypertension and vascular abnormalities in bronchopulmonary dysplasia. Clin Perinatol 2015;42:839-55.
2. Abman SH. Pulmonary hypertension: the hidden danger for newborns. Neonatology 2021;118:211-7.
3. An HS, Bae EJ, Kim GB, Kwon BS, Beak JS, Kim EK, et al. Pulmonary hypertension in preterm infants with bronchopulmonary dysplasia. Korean Circ J 2010;40:131-6.
4. Peng T, Morrisey EE. Development of the pulmonary vasculature: current understanding and concepts for the future. Pulm Circ 2013;3:176-8.
5. Groenman F, Unger S, Post M. The molecular basis for abnormal human lung development. Biol Neonate 2005;87:164-77.
6. Gao Y, Cornfield DN, Stenmark KR, Thebaud B, Abman SH, Raj JU. Unique aspects of the developing lung circulation: structural development and regulation of vasomotor tone. Pulm Circ 2016;6:407-25.
7. Abman SH, Abman SH. Bronchopulmonary dysplasia: a vascular hypothesis. Am J Respir Crit Care Med 2001;164:1755-6.
8. Stenmark KR, Abman SH. Lung vascular development: implications for the pathogenesis of bronchopulmonary dysplasia. Annu Rev Physiol 2005;67:623-61.
9. Thebaud B, Abman SH. Bronchopulmonary dysplasia: where have all the vessels gone? Roles of angiogenic growth factors in chronic lung disease. Am J Respir Crit Care Med 2007;175:978-85.
10. Baker CD, Alvira CM. Disrupted lung development and bronchopulmonary dysplasia: opportunities for lung repair and regeneration. Curr Opin Pediatr 2014;26:306-14.
11. Grover TR, Parker TA, Zenge JP, Markham NE, Kinsella JP, Abman SH. Intrauterine hypertension decreases lung VEGF expression and VEGF inhibition causes pulmonary hypertension in the ovine fetus. Am J Physiol Lung Cell Mol Physiol 2003;284:L508-17.
12. Jakkula M, Le Cras TD, Gebb S, Hirth KP, Tuder RM, Voelkel NF, et al. Inhibition of angiogenesis decreases alveolarization in the developing rat lung. Am J Physiol Lung Cell Mol Physiol 2000;279:L600-7.
13. Le Cras TD, Markham NE, Tuder RM, Voelkel NF, Abman SH. Treatment of newborn rats with a VEGF receptor inhibitor causes pulmonary hypertension and abnormal lung structure. Am J Physiol Lung Cell Mol Physiol 2002;283:L555-62.
14. Wu CS, Chen CM, Chou HC. Pulmonary hypoplasia induced by oligohydramnios: findings from animal models and a population-based study. Pediatr Neonatol 2017;58:3-7.
15. Mathias M, Bitar M, Aldulescu M, Birkett R, Perez M, Mestan K. Placental vascular maldevelopment, intrauterine growth restriction, and pulmonary hypertension. Pulm Circ 2020;10:2045894020970056.
16. Abbas G, Shah S, Hanif M, Shah A, Rehman AU, Tahir S, et al. The frequency of pulmonary hypertension in newborn with intrauterine growth restriction. Sci Rep 2020;10:8064.
17. Taglauer E, Abman SH, Keller RL. Recent advances in antenatal factors predisposing to bronchopulmonary dysplasia. Semin Perinatol 2018;42:413-24.

18. Check J, Gotteiner N, Liu X, Su E, Porta N, Steinhorn R, et al. Fetal growth restriction and pulmonary hypertension in premature infants with bronchopulmonary dysplasia. J Perinatol 2013;33:553-7.
19. Mestan KK, Check J, Minturn L, Yallapragada S, Farrow KN, Liu X, et al. Placental pathologic changes of maternal vascular underperfusion in bronchopulmonary dysplasia and pulmonary hypertension. Placenta 2014;35:570-4.
20. Mandell EW, Abman SH. Fetal vascular origins of bronchopulmonary dysplasia. J Pediatr 2017;185:7-10.e1.
21. Pierro M, Villamor-Martinez E, van Westering-Kroon E, Alvarez-Fuente M, Abman SH, Villamor E. Association of the dysfunctional placentation endotype of prematurity with BPD: a systemic review, meta-analysis and meta-regression. Thorax 2022;77:268-75.
22. Bose C, van marter LJ, Laughon M, O'Shea TM, Allred EN, Karna P, et al. Fetal growth restriction and chronic lung disease among infants born before 28th week of gestation. Pediatrics 2008;124:e450-8.
23. Laughon M, Bose C, Allred EN, O'Shea TM, Ehrenkranz RA, van Marter LJ, et al. Antecedents of chronic lung disease following 3 patterns fo early respiratory disease in preterm infants. Arch Dis Child Fetal Neonatal Ed 2011;96:F114-20.
24. Morrow L, Wagner B, Ingram DA, Poindexter BB, Schibler K, Cotton M, et al. Antenatal determinants of increased risk for bronchopulmonary dysplasia and late respiratory disease in preterm infants. Am J Respir Crit Care Med 2017;196:364-74.
25. Tang JR, Seedorf G, Muehlethaler V, Walker DL, Markham NE, Balasubramaniam V, et al. Moderate hyperoxia accelerates lung growth and attenuates pulmonary hypertension in infant rats after exposure to intra-amniotic endotoxin. Am J Physiol Lung Cell Mol Physiol 2010;299:L735-48.
26. Wallace B, Peisl A, Seedorf G, Nowlin T, Kim C, Bosco J, et al. Anti-sFlt-1 monoclonal antibody therapy preserves lung alveolar and vascular growth in antenatal models of BPD. Am J Respir Crit Care Med 2018;197:776-87.
27. Abman SH, Shanley PF, Accurso FJ. Failure of postnatal adaptation of the pulmonary circulation after chronic intrauterine pulmonary hypertension in fetal lambs. J Clin Invest 1989;83:1849-58.
28. Resnik E, Herron J, Keck M, Sukovich D, Linden B, Cornfield DN. Chronic intrauterine pulmonary hypertension selectively modifies pulmonary artery smooth muscle cell gene expression. Am J Physiol Lung Cell Mol Physiol 2006;290:L426-33.
29. Ishida H, Kawazu Y, Kayatani F, Inamura N. Prognostic factors of premature closure of the ductus arteriosus in utero: a systematic literature review. Cardiol Young 2017;27:634-8.
30. Medal RM, Im AM, Yamamoto Y, Lakhdari O, Blackwell TS, Hoffman HM, et al. The innate immune response in fetal lung mesenchymal cells targets VEGFR2 expression and activity. Am J Physiol Lung Cell Mol Physiol 2017;312:L861-72.
31. Watterberg KL, Demers LM, Scott SM, Murphy S. Chorioamnionitis and early lung inflammation in infants in whom bronchopulmonary dysplasia develops. Pediatrics 1996;97:210-5.
32. Thebaud B, Thebaud B, Laughon M, Whitsett J, Abman S, Steinhorn R, et al. Neonatal lung injury and bronchopulmonary dysplasia. Nat Rev Dis Primers 2019;198:187-93.
33. Mirza H, Garcia JA, Crawford E, Pepe J, Zussman M, Wadhawan R, et al. Natural history of postnatal cardiopulmonary adaptation in infants born extremely preterm and risk for death or bronchopulmonary dysplasia. J Pediatr 2018;198:187-193 e1.
34. Hirsch K, Taglauer E, Seedorf G, Callahan C, Mandell EW, White CW, et al. Perinatal stabilization of hypoxia-inducible factor preserves lung alveolar and vascular growth in experimental BPD. Am J Repir Crit Care Med 2020;202:1146-58. https://doi.org/10.1164/rccm.202003-0601OC
35. Naumburg E, Soderstrom L. Increased risk of pulmonary hypertension following premature birth. BMC Pediatr 2019;19:288.
36. Angus DC, Linde-Zwirble WT, Clermont T, Griffin MF, Clark RH. Epidemiology of neonatal respiratory failure in the UD; projections from California to New York. Am J Respir Crit Care Med 2001;164:1154-60.
37. Steurer MA, Jelliffe-Pawlowski LL, Baer RJ, Partridge JC, Rogers EE, Keller RL. Persistent pulmonary hypertension in late preterm and term infants in California. Pediatrics 2017;139:e20161165. https://doi.org/10.1542/peds.2016-1165
38. Nakanishi H, Suenaga H, Uchiyama A, Kusuda S , Neonatal Research Network, Japan. Persistent pulmonary hypertension of the newborn in extremely preterm infants: a Japanese cohort study. Arch Dis Child Fetal Neonatal Ed 2018;103:F554-61.
39. Kumar P. Committee on fetus and newborn, American Academy of pediatrics, use of inhaled NO in preterm infants. Pediatrics 2014;133:164-70.
40. Fouron JC, Le Guennec JC, Villemant D, Perreault G, Davignon A. Value of echocardiography in assessing the outcome of bronchopulmonary dysplasia of the newborn. Pediatrics 1980;65:529-35.
41. Khemani E, McElhinney DB, Rhein L, Andrade O, Lacro RV, Thomas KC, et al. Pulmonary artery hypertension in formerly premature infants with bronchopulmonary dysplasia: clinical features and outcomes in the surfactant era. Pediatrics 2007;120:1260-9.
42. Al-Ghanem G, Shah P, Thomas S, Banfield L, El Helou S, Fusch C, et al. Bronchopulmonary dysplasia and pulmonary hypertension: a meta-analysis. J Perinatol 2017;37:414-9.
43. Arjaans S, Haarman MG, Roofghooft MTR, Fries MWF, Kooi EMW, Bos AF, et al. Fate of pulmonary hypertension associated with BPD beyond 36 weeks postmenstrual age. Arch Dis Child Fetal Neonatal Ed 2021;106:45-50.
44. Mourani PM, Sontag MK, Younoszai A, Miller JI, Kinsella JP, Baker CD, et al. Early pulmonary vascular disease in preterm infants at risk for bronchopulmonary dysplasia. Am J Respir Crit Care Med 2015;191:87-95.
45. Mirza H, Ziegler J, Ford S, Padbury J, Tucker R, Laptook A. Pulmonary hypertension in preterm infants: prevalence and association with bronchopulmonary dysplasia. J Pediatr 2014;165:909-14.e1.
46. Bhat R, Salas AA, Foster C, Carlo WA, Ambalavanan N. Prospective analysis of pulmonary hypertension in extremely low birth weight infants. Pediatrics 2012;129:e682-9.
47. Mourani PM, Mandell EW, Meier M, Younoszai A, Brinton JT, Wagner BD, et al. Early pulmonary vascular disease in preterm infants is associated with late respiratory outcomes in childhood. Am J Respir Crit Care Med 2019;199:1020-7.
48. Arjaans S, Zwart EAH, Ploegstra MJ, Bos AF, Kooi EMW, Hillege HL, et al. Identification of gaps in the current knowledge on pulmonary hypertension in extremely preterm infants: a systematic review and meta-analysis. Pediatr Perinat Epidemiol 2018;32:258-67.
49. Arjaans S, Fries MWF, Schoots MH, Schilte CFM, Roofthooft MTR, Vrijlandt EJLE, et al. Clinical significance of early pulmonary hypertension in preterm infants. J Pediatr 2022;251:74-81.e3. https://doi.org/10.1016/j.jpeds.2022.07.039
50. Lagatta JM, Hysinger EB, Zaniletti I, Wymore EM, Vyas-Read S, Yallapragada S, et al. Childrens hospital neonatal consortium severe BPD focus grop. J Pediatr 2018;203:218-24.
51. Berenz A, Vergales JE, Swanson JR, Sinkin RA. Evidence of early pulmonary hypertension is associated with increased mortality in very low birth weight infants. Am J Perinatol 2017;34:801-7.
52. Kim HH, Sung SI, Yang MS, Han YS, Kim HS, Ahn SY, et al. Early pulmonary hypertension is a risk factor for bronchopulmonary dysplasia-associated late pulmonary hypertension in extremely preterm infants. Sci Rep 2021;11:11206.
53. Lakshminrusimha S. Neonatal and postneonatal pulmonary hypertension. Children (Basel) 2021;8:131.
54. Abman SH, Hansmann G, Archer SL, Ivy DD, Adatia I, Chung WK, et al. Pediatric pulmonary hypertension: guidelines from the American Heart Association and American Thoracic Society. Circulation 2015;132:2037-99.
55. Giesinger R, Abman SH, Kinsella JP, McNamara P. Pulmonary hypertension phenotypes in the newborn. In: Dakshinamurti S, Milsom WK, Lakshminrusima S, Abman SH, Chueng PY, McNamara P, eds. Hypoxic respiratory failure in the newborn – from origins to clinical management. Lung Biology in Health and Disease Series. Oxfordshire, United Kingdom: Taylor & Francis Publishers; 2021. p. 208-16.

56. Mourani PM, Fagan T, Ivy DD, Rosenberg A, Abman SH. Left ventricular diastolic dysfunction in bronchopulmonary dysplasia. J Pediatrics 2008;152:291-3.
57. Philip R, Lamba V, Talati A, Sathanandam S. Pulmonary hypertension with prolonged patency of the ductus arteriosus in preterm infants. Children (Basel) 2020;7:139.
58. Philip R, Nathaniel Johnson J, Naik R, Kimura D, Boston U, Chilakala S, et al. Effect of patent ductus arteriosus on pulmonary vascular disease. Congenit Heart Dis 2019;14:37-41.
59. Gentle SJ, Travers CP, Clark M, Carlo WA, Ambalavanan N. Patent ductus arteriosus and development of BPD-associated pulmonary hypertension. Am J Respir Crit Care Med 2023;207:921-8.
60. McNamara PJ, Lakshminrusimha S. Maldevelopment of the immature pulmonary vasculature and prolonged patency of the ductus arteriosus-association or cause. Am J Respir Crit Care Med 2023;207:814-6.
61. Frank BS, Schafer M, Grenolds A, Ivy DD, Abman SH, Darst J. Acute vasoreactivity testing during cardiac catheterization in infants with BPD-associated pulmonary hypertension. J Pediatrics 2019;208:127-33.
62. Nawaytou H, Steurer MA, Zhao Y, Guslits E, Teitel D, Fineman JR, et al. Clinical utility of echocardiography in former preterm infants with bronchopulmonary dysplasia. J Am Soc Echocardiogr 2020;33:378-88.
63. Tai C, Hsieh A, Moon-Grady AJ, Keller RL, Teitel D, Nawaytou HM. Pulmonary artery acceleration time in young children is determined by heart rate and transpulmonary gradient but not by pulmonary blood flow: a simultaneous echocardiography—cardiac catheterization study. Echocardiography 2022;39:895-905.
64. Levy PT, Jain A, Nawaytou H, Teitel D, Keller R, Fineman J, et al. Risk assessment and monitoring of chronic pulmonary hypertension in premature infants. J Pediatrics 2019;217:199-209.e4.
65. Heching HJ, Turner M, Farkouh-Karoleski C, Krishnan U. Pulmonary vein stenosis and necrotizing enterocolitis: is there a possible link with necrotizing enterocolitis? Arch Dis Child Fetal Neonatal Ed 2014;99:F282-5.
66. Drossner DM, Kim DW, Maher KO, Mahle WT. Pulmonary vein stenosis: prematurity and associated conditios. Pediatrics 2008;122:e656-61.
67. Mahgoub L, Kaddoura T, Kameny AR, Lopez Ortego P, Vanderlaan RD, Kakadekar A, et al. Pulmonary vein stenosis of expremature infants with pulmonary hypertension and bronchopulmonary dysplasia, epidemiology, and survival from a multicenter cohort. Pediatr Pulmonol 2017;52:1063-70.
68. Xie L, Xiao T, Shen J. Primary pulmonary vein stenosis in a premature infant without bronchopulmonary dysplasia: a case report. Heart Lung 2014;43:367-70.
69. Petit JD, Briones M, Mandhani M, Jones S, Suthar D, Gray R, et al. Systemic sirolimus therapy for infants and children with pulmonary vein stenosis. J Am Coll Cardiol 2021;77:2807-18.
70. Laux D, Rocchisani MA, Boudjemline Y, Gouton M, Bonnet D, Ovaert C. Pulmonary hypertension in the preterm infant with chronic lung disease can be caused by pulmonary vein stenosis: a must-know entity. Pediatr Cardiol 2016;37:313-21.
71. Abman SH, Chatfield BA, Rodman DM, Hall SL, McMurtry IF. Maturational changes in endothelium-dependent relaxation of ovine pulmonary arteries in vitro. Am J Physiol 1991;260:L280-5.
72. Velvis H, Moore P, Heymann MA. Prostaglandin inhibition prevents the fall in pulmonary vascular resistance as a result of rhythmic distension of the lungs in fetal lambs. Pediatr Res 1991;30:62-8.
73. Ivy DD, Parker TA, Ziegler JW, Galan HL, Kinsella JP, Tuder RM, et al. Prolonged endothelin a receptor blockade attenuates chronic pulmonary hypertension in the ovine fetus. J Clin Invest 1997;99:1179-86.
74. Villamor E, Le Cras TD, Horan MP, Halbower AC, Tuder RM, Abman SH. Chronic intrauterine pulmonary hypertension impairs endothelial nitric oxide synthase in the ovine fetus. Am J Physiol 1997;272:L1013-20.
75. Rosenberg AA, Kennaugh J, Koppenhafer SL, Loomis M, Chatfield BA, Abman SH. Increased immunoreactive endothelin-1 levels in persistent pulmonary hypertension of the newborn. J Pediatr 1993;123:109-14.
76. Roberts JD, Polaner DM, Lang P, Zapol WM. Inhaled nitric oxide in persistent pulmonary hypertension of the newborn. Lancet 1992;340:818-9.
77. Kinsella JP, Neish SR, Shaffer E, Abman SH. Low-dose inhalation nitric oxide in persistent pulmonary hypertension of the newborn. Lancet 1992;340:819-20.
78. Roberts JD Jr, Fineman JR, Morin FC 3rd, Shaul PW, Rimar S, Schreiber MD, et al. Inhaled nitric oxide and persistent pulmonary hypertension of the newborn. The Inhaled Nitric Oxide Study Group. N Engl J Med 1997;336:605-10.
79. Kinsella JP, Truog WE, Walsh WF, Goldberg RN, Bancalari E, Mayock DE, et al. Randomized, multicenter trial of inhaled nitric oxide and high-frequency oscillatory ventilation in severe, persistent pulmonary hypertension of the newborn. J Pediatr 1997;131:55-62.
80. Abman SH, Kinsella JP, Schaffer MS, Wilkening RB. Inhaled nitric oxide in the management of a premature newborn with severe respiratory distress and pulmonary hypertension. Pediatrics 1993;92:606-9.
81. Rudolph AM. High PVR after birth: 1. Pathophysiologic considerations and etiologic classification. Clin Pediatr 1980;19:585-90.
82. Kinsella JP, Ivy DD, Abman SH. Ontogeny of NO activity and response to inhaled NO in the developing ovine pulmonary circulation. Am J Physiol 1994;267:H1955-61.
83. Kinsella JP, Ivy DD, Abman SH. Inhaled nitric oxide improves gas exchange and lowers pulmonary vascular resistance in severe experimental hyaline membrane disease. Pediatr Res 1994;36:402-8.
84. Aikio O, Metsola J, Vuolteenaho R, Perhomaa M, Hallman M. Transient defect in nitric oxide generation after rupture of fetal membranes and responsiveness to inhaled nitric oxide in very preterm infants with hypoxic respiratory failure. J Pediatr 2012;161:397-403.e1.
85. Chandrasekharan P, Kozielski R, Kumar VH, Rawat M, Manja V, Ma C, et al. Early use of inhaled nitric oxide in preterm infants: is there a rationale for selective approach? Am J Perinatol 2017;34:428-40.
86. Krishnan U, Feinstein JA, Adatia I, Austin ED, Mullen MP, Hopper RK, et al. Evaluation and management of pulmonary hypertension in children with bronchopulmonary dysplasia. J Pediatr 2017;188:24-34.e1.
87. Van Meurs KP, Wright LL, Ehrenkranz RA, Lemons JA, Ball MB, Poole WK, et al. Inhaled nitric oxide for premature infants with severe respiratory failure. N Engl J Med 2005;353:13-22.
88. Ballard RA, Truog WE, Cnaan A, Martin RJ, Ballard PL, Merrill JD, et al. Inhaled nitric oxide in preterm infants undergoing mechanical ventilation. N Engl J Med 2006;355:343-53.
89. Kinsella JP, Cutter GR, Walsh WF, Gerstmann DR, Bose CL, Hart C, et al. Early inhaled nitric oxide therapy in premature newborns with respiratory failure. N Engl J Med 2006;355:354-64.
90. Ellsworth KR, Ellsworth MA, Weaver AL, Mara KC, Clark RH, Carey WA. Association of early inhaled nitric oxide with the survival of preterm neonates with pulmonary hypoplasia. JAMA Pediatr 2018;172:e180761.
91. Rallis D, Deierl A, Atria G, Chaban B, Banerjee J. The efficacy of inhaled nitric oxide treatment in premature infants with acute pulmonary hypertension. Early Hum Dev 2018;127:1-5.
92. Abman SH, Collaco JM, Keszler M, Welty SE, Lynch S, Truog WE, et al. Interdisciplinary care of children with severe bronchopulmonary dysplasia. J Pediatr 2017;181:12-28.
93. Bhatt AJ, Pryhuber GS, Huych H, Watkins RH, Metlay LA, Maniscalco WM. Disrupted pulmonary vaculature and decreased VEGF, Flt-1, and TIE-2 in human infants dying with BPD. Am J Respir Crit Care Med 2001;164:1971-81.
94. Hansen AR, Barnes CM, Folkman J, McElrath TF. Maternal preeclampsia predicts the development of bronchopulmonary dysplasia. J Pediatr 2010;156:532-6.
95. Baker CD, Balasubramaniam V, Mourani PM, Sontag MK, Black CP, Ryan SL, et al. Cord blood angiogenic progenitor cells are decreased in bronchopulmonary dysplasia. Eur Respir J 2012;40:1516-22.
96. Mestan KK, Gotteiner N, Porta N, Grobman W, Su EJ, Ernst LM. Cord blood biomarkers of placental maternal vascular underperfusion Predict bronchopulmonary dysplasia-associated pulmonary hypertension. J Pediatr 2017;185:33-41.

97. Seth SA, Soraisham AS, Harabor A. Risk factors and outcomes of early pulmonary hypertension in preterm infants. J Matern Fetal Neonatal Med 2018;31:3147-52.
98. Northway WH Jr, Rosan RC, Porter DY. Pulmonary disease following respirator therapy of hyaline-membrane disease. Bronchopulmonary dysplasia. N Engl J Med 1967;276:357-68.
99. Goss KN, Beshish AG, Barton GP, Haraldsdottir K, Levin TS, Tetri LH, et al. Early pulmonary vascular disease in young adults born preterm. Am J Respir Crit Care Med 2018;198:1549-58.
100. Mulchrone A, Bellofiore A, Douwes JM, Duong N, Beshish AG, Barton GP, et al. Impaired right ventricular-vascular coupling in young adults born preterm. Am J Respir Crit Care Med 2020;201:615-8.