Pulmonary Hypertension in Preterm Infants with Bronchopulmonary Dysplasia

Christopher D. Baker, MD,^{1,2} Steven H. Abman, MD,^{1,2} and Peter M. Mourani, MD^{2,3}

Bronchopulmonary dysplasia (BPD), the chronic lung disease of prematurity, is a significant contributor to perinatal morbidity and mortality. Premature birth disrupts pulmonary vascular growth and initiates a cascade of events that result in impaired gas exchange, abnormal vasoreactivity, and pulmonary vascular remodeling that may ultimately lead to pulmonary hypertension (PH). Even infants who appear to have mild BPD suffer from varying degrees of pulmonary vascular disease (PVD). Although recent studies have enhanced our understanding of the pathobiology of PVD and PH in BPD, much remains unknown with respect to how PH should be properly defined, as well as the most accurate methods for the diagnosis and treatment of PH in infants with BPD. This article will provide neonatologists and primary care providers, as well as pediatric cardiologists and pulmonologists, with a review of the pathophysiology of PH in preterm infants with BPD and a summary of current clinical recommendations for managing PH in this population.

Introduction

BRONCHOPULMONARY DYSPLASIA (BPD), the chronic lung disease associated with premature birth, was first described in infants who required mechanical ventilation and oxygen therapy for postnatal respiratory distress.¹ However, advances such as antenatal steroids, artificial surfactant, and improved ventilator strategies have resulted in the increased survival of infants born at extremely low gestational ages.^{2–4} Thus, although the incidence of BPD has remained relatively stable, both its pathophysiology and its clinical manifestations have changed dramatically over the past 45 years.^{3,5–7} Whereas classically BPD was characterized by diffuse fibroproliferative lung disease and postnatal lung injury, the “new BPD” consists more prominently of an arrest of pulmonary vascular and alveolar growth.^{1,8,9} BPD now occurs most commonly in infants born before 28 weeks gestation who typically weigh less than 1000 g at birth.^{10,11} Birth at these gestational ages results in a disruption in lung development with persistent hypoplasia of the pulmonary microvasculature and alveolar simplification.^{9,12} Dysmorphic growth and impaired function of the pulmonary vasculature can result in pulmonary hypertension (PH) in infants with BPD.^{13,14} However, even in infants without clinically apparent PH, signs of pulmonary vascular disease (PVD) such as impaired gas exchange, prolonged hypoxemia, exercise intolerance, and altered distribution of pulmonary blood flow during acute respiratory infections are commonly seen,¹⁵ suggesting that PVD may go unrecognized in many infants with BPD.

PH is associated with significant morbidity and mortality in infants with BPD.^{16–18} Two recent retrospective studies reported a 2 year mortality rate of 33–48% after PH diagnosis.^{19,20} Yet further studies are needed to understand the pathophysiology of PH in BPD better. Furthermore, standardized criteria are lacking for determining which preterm infants are at greatest risk for developing PH. Although current approaches to the treatment of PH will be reviewed here, significant gaps in our knowledge persist pertaining to the prevention and treatment of PH in this population.

Pathophysiology of PH in BPD

The factors that contribute to the development of PH in infants with BPD are numerous (Fig. 1). Disruption in vascular growth results in decreased vessel density throughout the pulmonary microcapillary network,^{21,22} which results in decreased cross-sectional area for blood flow and increased pulmonary vascular resistance (PVR). Increased PVR alters vasoreactivity and causes structural remodeling, which contribute to PVD in BPD. The pulmonary vascular bed consists of a smaller overall surface area for gas exchange that, in combination with injury to the airways and lung parenchyma, results in hypoxic vasoconstriction and impaired pulmonary blood flow particularly during exercise or respiratory infections. Chronic hypoxia in the lung tissues also contributes to pulmonary arterial vasoreactivity and ultimately leads to structural remodeling with intimal hyperplasia and increased muscularization of small pulmonary arteries.^{1,3,9,12,23,24} In its most severe form,

¹Section of Pulmonary Medicine, ²Pediatric Heart Lung Center, ³Section of Critical Care Medicine, Department of Pediatrics, University of Colorado School of Medicine, Aurora, Colorado.

FIG. 1. Pathophysiology of pulmonary hypertension (PH) in bronchopulmonary dysplasia (BPD). Prenatal and postnatal factors impair angiogenic signaling, resulting in disrupted vascular growth, abnormal vascular function, and ultimately, PH.

the PVD characterized by abnormal vascular growth, vasoreactivity, and structural remodeling can result in PH and its late morbidity and mortality.¹⁵

The mechanisms by which PVD occurs after preterm birth remain the subject of ongoing investigation. Vascular growth occurs by two distinct mechanisms: angiogenesis (the direct extension of existing vessels), and vasculogenesis (formation of vessels from primitive hemangioblasts).²⁵ Complex gene–environment interactions, as well as epigenetic influences on gene expression in the setting of prenatal and postnatal factors such as oxidative stress, regional hypoxia, inflammation, and infection, have been shown to impair angiogenesis by disrupting signaling pathways and altering growth factor expression in the developing lung.^{26–31} For example, expression of insulin-like growth factor-1 (IGF-1) is epigenetically regulated, increased in the lungs of preterm infants with severe BPD, and is affected by postnatal ventilation strategies that result in histone modification.^{32–34} In preterm infants, postnatal mechanical ventilation and oxygen therapy result in increased expression of antiangiogenic genes such as thrombospondin-1 and endoglin, as well as decreased expression of proangiogenic genes such as VEGF-B, VEGF receptor-2, and the angiotensin receptor Tie-2.^{35,36} Dysregulation of angiogenic signaling leads to impaired growth, structure, and function of the pulmonary vasculature in part through disruption of local and circulating angiogenic progenitor cells.^{37–41}

Perhaps the most studied signaling pathway associated with normal pulmonary vascular development is the vascular endothelial growth factor-nitric oxide (VEGF-NO) pathway.^{22,42–44} Animal models have shown that disruption of VEGF-NO signaling not only impairs angiogenesis, but also results in alveolar simplification in the distal lung.^{8,21,22,45} Additionally, the lungs of human infants with fatal BPD have decreased VEGF levels and markedly dysmorphic vasculature.¹² Soluble fms-like tyrosine kinase-1 (sFlt-1) inhibits this pathway by binding circulating VEGF.⁴⁶ sFlt-1 is central to the pathogenesis of pre-

eclampsia, a maternal complication of pregnancy and known contributor to BPD risk.^{47–49} A recent study in neonatal rats showed that antenatal administration of intraamniotic sFlt-1 late in gestation disrupts VEGF-NO signaling in the developing lung, impairs pulmonary vascular and alveolar growth, and leads to postnatal pulmonary hypertension.⁵⁰ VEGF signaling is also disrupted in animal models of intrauterine growth restriction (IUGR), another complication of pregnancy that has been associated with an increased risk for PH in infants with BPD.^{51,52}

Through a separate pathway, the vasoconstrictor endothelin-1 (ET-1) activates intracellular Rho-kinase and contributes to impaired pulmonary vascular growth in animal models of PH.⁵³ Many other proangiogenic and antiangiogenic mediators have been described in preclinical models (Table 1). Focused basic research is needed to investigate the complex mechanisms through which these and other growth factor signaling pathways interact to contribute to the pathobiology of PVD in BPD.

Previous studies suggest circulating and vessel wall-derived endothelial progenitor cells (EPCs) contribute to postnatal vasculogenesis.^{38,41} Two distinct EPC subsets—late-outgrowth endothelial colony-forming cells (ECFCs) and angiogenic circulating progenitor cells (CPCs)—are decreased in the umbilical cord blood of preterm infants who go on to develop moderate or severe BPD.^{39,54} Yet, it remains unclear whether cord blood ECFC or CPC levels are biomarkers that can predict BPD severity or PH in the clinical setting. Recent small animal studies have shown that ECFCs as well as mesenchymal stromal cells (MSCs) mediate a pro-angiogenic effect at least in part through paracrine mechanisms.^{55–58} However, airway-derived MSCs are increased in BPD, suggesting that the tissue of origin (e.g., blood, vascular endothelial wall, bone marrow, airway epithelium) plays a critical and yet undefined role in the pathogenesis of BPD.⁵⁹ Further studies are needed to describe more clearly how progenitor cell-mediated vasculogenesis is disrupted to cause PVD in BPD and whether

TABLE 1. LIST OF PROANGIOGENIC AND ANTIANGIOGENIC MEDIATORS

Proangiogenic mediators:

- Angiopoietin-1 (Ang-1)
- Erythropoietin
- Fibroblast Growth Factor-1, -2 (FGF-1,2)
- Hepatocyte Growth Factor (HGF)
- Kit ligand (stem cell factor)
- Matrix Metalloproteinases (MMPs)
- Nitric Oxide (NO)
- Placental Growth Factor (PlGF)
- Platelet Derived Growth Factor (PDGF)
- Prostacyclin (PGI₂)
- Soluble endoglin
- Soluble guanylate cyclase (sGC)
- Stromal Derived Factor-1 (SDF-1)
- Tumor Necrosis Factor-alpha (TNF- α)
- Transforming Growth Factor-beta (TGF- β)
- Vascular Endothelial Growth Factor (VEGF)

Antiangiogenic mediators:

- Angiopoietin-2 (Ang-2)
- Angiostatin
- Endostatin
- Endothelin-1
- Phosphodiesterase Type 5
- Soluble Flt-1 (sFlt)
- Thrombospondin-1, -2
- Tissue inhibitor of metalloproteinase (TIMP)

progenitor cell therapy will prevent or treat cardiopulmonary disease in preterm infants. Small clinical trials with the most severely affected neonates are the most likely setting in which such novel therapies will be translated into clinical practice.⁶⁰

The clinical impact of chorioamnionitis on the risk for postnatal complications of premature birth remains unclear.^{61,62} However, animal models demonstrate that uterine inflammation modulates angiogenesis in the developing lung.^{63,64} Disrupted nuclear factor kappa B (NFkB) signaling appears to contribute to this process through both inflammatory and noninflammatory pathways.^{65–67} Pulmonary dendritic cells are increased in both chorioamnionitis and BPD.⁶⁸ Although they are pro-angiogenic in nature, dendritic cells appear to promote dysmorphic vascular growth in these patients. These studies suggest that perinatal inflammation and immune modulation significantly impact pulmonary vascular development.

The pulmonary vasculature has recently been shown to contain intrapulmonary arteriovenous anastomotic vessels (IAAV) in preterm infants who died from severe BPD.⁶⁹ IAAV are small connecting vessels that shunt deoxygenated blood into the pulmonary venous circulation and thus prevent gas exchange at the alveolar–capillary interface (Fig. 2). Such vessels were known to exist during fetal development at late gestation and are similar to those described in alveolar capillary dysplasia, a frequently fatal congenital condition.^{70,71} However, IAAV are thought to disappear postnatally in healthy newborns.⁷¹ IAAV may contribute to severe hypoxemia in infants with severe BPD. It is speculated that these vessels cause regional tissue hypoxia, thus contributing to hypoxic vasoconstriction and structural remodeling in preterm infants who develop PH.

In summary, preterm birth interrupts pulmonary vascular and alveolar development resulting in decreased cross-

sectional area for blood flow and decreased surface area for gas exchange. Vascular simplification, increased vasoreactivity, and hypoxic vasoconstriction lead to increased pulmonary vascular resistance and result in structural remodeling of the pulmonary arterial circulation. Together, these complications of preterm birth contribute to a varying degree of PVD in preterm infants with BPD. Future studies will more clearly elucidate the basic mechanisms responsible for impairments in pulmonary vascular growth and function and will lead to novel therapies for these infants.

Screening and Diagnosis of PH in BPD

It is well known that pulmonary hypertension (PH) is a severe complication of BPD that is associated with high mortality.^{16,20,72} Although recent studies, both prospective and retrospective, suggest an overall incidence of PH in BPD of 18–25%, such a determination is clouded by the lack of an agreed-upon definition of PH in this context.^{15,16,73,74} Neither an absolute pulmonary arterial pressure nor a relative pulmonary arterial pressure (typically expressed as a fraction or percentage of systemic blood pressure) has been shown to result in clearly defined consequences. Such criteria, as well as the timing and methodology for screening, vary significantly between centers, and evidence to support one practice over another is lacking.

Cardiac catheterization, an invasive procedure requiring general anesthesia in young children, permits direct measurement of the pulmonary arterial pressure (PAP) and is thus the gold standard for making the diagnosis. However, noninvasive transthoracic echocardiography is more commonly used in children for its ability to estimate the systolic PAP using the tricuspid regurgitation jet velocity (TRJV) and a modified Bernoulli equation to determine the pressure gradient between the right ventricle (RV) and right atrium.^{75,76} In the absence of tricuspid stenosis or other structural anomalies, the pressure in the RV and pulmonary artery are equal during systole. Qualitative evidence of PH includes flattening of the interventricular septum and hypertrophy/enlargement of the right heart chambers. However, these are not highly predictive of PAH in the absence of a measurable TRJV and are subject to interobserver variability among echocardiographers.^{77,78} Estimations of severity have been shown to differ substantially between echocardiography and cardiac catheterization.⁷⁷ Yet, in some cases, unsedated echocardiography could yield more accurate assessments, since cardiac catheterization requires sedation and ventilatory support.

More recently, novel echocardiographic parameters have been utilized to quantify right ventricular dysfunction such as that seen in preterm infants with BPD. The myocardial performance index (or Tei index), a marker of ventricular dysfunction consisting of the sum of isovolumetric contraction and relaxation times divided by the ejection time, is elevated in primary PH, may be elevated in preterm infants with BPD, and may correlate with BPD severity.^{79–82} More recently, tissue Doppler measurements have been found to correlate with elevated end diastolic pressure in adults. The ratio of the early Doppler inflow velocity to the early myocardial tissue Doppler velocity (E/E') has been shown to correlate with the severity of BPD, but requires further study to determine if it will be a useful marker of disease.⁸² The tricuspid annular plane systolic excursion (TAPSE) is a

Adapted from Galambos 2013⁶⁹

FIG. 2. (A) In the normal perinatal lung, intrapulmonary arteriovenous anastomotic vessels (IAAV) are closed or nonexistent. Blood from a small pulmonary artery (PA) becomes oxygenated at the alveolar–capillary interface before entering a pulmonary vein (PV). (B) In infants with BPD, deoxygenated blood passes through IAAV before becoming oxygenated in the microcapillary bed causing hypoxemia in these patients.

marker of RV systolic function that correlates with gestational age, but has not been studied in relation to BPD severity.^{83–85} Thus, in spite of its limitations, echocardiography will likely remain a key clinical tool for diagnosing and monitoring PH in these children. Prospective studies with long-term follow-up are required to determine appropriate screening and diagnostic criteria for PH in BPD and to determine more clear prognostic implications of PH diagnosis.

Treatment of PH in BPD

PH therapy in the setting of significant BPD begins with optimizing the treatment of the child's chronic lung disease to improve gas exchange. Impaired gas exchange results in hypoxemic vasoconstriction and eventually structural remodeling of the vasculature. Factors contributing to hypoxemia, including bronchospasm and airway obstruction, should be treated appropriately. Flexible fiberoptic bronchoscopy may identify tracheo-bronchomalacia and other causes of airway obstruction. Each child's nutritional status should be optimized to ensure adequate somatic growth. Gastroesophageal reflux and aspiration may require treatment with the consideration of gastric fundoplication in severe cases. In the setting of chronic respiratory failure or insufficiency, long-term mechanical ventilation via tracheostomy should also be

considered with the goal of optimizing gas exchange and the neurodevelopmental potential. Once the respiratory status is optimized, selective pulmonary vasodilator therapy can improve the severity of PH in some patients (Table 2). However, randomized controlled trials for the treatment of PH in BPD are lacking to demonstrate the impact of treatment on outcomes. In cases of pulmonary veno-occlusive disease, left ventricular dysfunction, large intracardiac shunts, or collateral vessels, pulmonary vasodilators may be detrimental.^{86–88} A recent retrospective chart review of 29 infants with PH and BPD revealed that significant cardiovascular anomalies occurred in 65% of these infants, including large aortopulmonary collaterals (31%), patent ductus arteriosus (31%), pulmonary vein stenosis (24%), and others.¹⁹ Therefore, cardiac catheterization should be considered to confirm the presence of PH and exclude these other diagnoses prior to initiation of chronic pulmonary vasodilator therapy.⁸⁸

In the setting of acute PH, inhaled nitric oxide (NO), a potent vasodilator, remains the first line of therapy and is the pulmonary vasodilator with the most safety data in infants. Inhaled NO is delivered directly to the pulmonary microvasculature and thus has a very rapid onset of action.⁸⁹ This also enables the vasodilatory effects of inhaled NO to be most pronounced in well-ventilated lung regions, resulting in decreased ventilation–perfusion mismatch. Inhaled NO is

TABLE 2. LIST OF MEDICATIONS FOR THE TREATMENT OF PULMONARY HYPERTENSION

Medication	Mechanism of vasodilation	Status
Inhaled nitric oxide	sGC stimulator; increases cGMP	Clinical ^a
Prostacyclin analogues	Adenylate cyclase stimulator; increases cAMP	Clinical
Sildenafil, tadalafil	PDE-5 inhibitor; prevents cGMP breakdown	Clinical
Bosentan	Nonselective ET-1 receptor antagonist	Clinical
Ambrisentan, sitaxsentan	Selective ET _A receptor antagonist	Clinical
Riociguat ^b	sGC stimulator; increases cGMP	Experimental
Cinaciguat	sGC activator; increases cGMP	Experimental
Rosiglitazone	PPAR-gamma activator	Experimental
Experimental fasudil	Rho kinase inhibitor	Experimental

^a“Clinical” indicates medication is approved for treatment of adult PH; limited safety/efficacy data exist for children.

^bRiociguat is approved for treatment of adult PH; no safety/efficacy data exist for children.

cGMP, cyclic guanosine monophosphate.

typically administered at an initial dose of 20 ppm, as this dose provides optimal reduction of pulmonary arterial pressure with less risk of methemoglobinemia than higher doses.⁹⁰ Clinical trials of inhaled NO therapy for the prevention of BPD have shown little benefit, and it remains indicated only in the setting of PH.⁹¹

Prostacyclin (PGI₂) promotes vasodilation by stimulating the cAMP-dependent relaxation of pulmonary smooth muscle cells.⁸⁹ PGI₂ treatment should be initiated with caution, as it may also cause systemic hypotension. Analogues of PGI₂ may be aerosolized or given by either intravenous or subcutaneous infusion.^{92–94} Due to its very short half-life, the medication must be given continuously, and unplanned interruptions in delivery may be dangerous. Furthermore, the evidence for these medications to treat PH in infants with BPD is limited to case studies and small observations.^{95–97}

The off-label use of enteral phosphodiesterase-5 (PDE-5) inhibitors such as sildenafil has been increasingly used for PH pharmacotherapy in BPD. These medications minimize pulmonary arterial vasoreactivity and may prevent structural remodeling in these vessels. However, the Food and Drug Administration (FDA) has only approved its use in adults. Although some studies have suggested that sildenafil is both safe and potentially efficacious in children, a recent study reported a dose-related increase in mortality with sildenafil in children with PH secondary to idiopathic PH and congenital heart disease.^{98–100} This led the FDA to issue a warning against the use of sildenafil in children (www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm317743.htm). Importantly, the study by Barst et al. did not evaluate sildenafil therapy for secondary PH in the setting of chronic lung disease. The FDA warning applies to ages 1–17 years, but no recommendations are made for infants during the first year of life. In light of this warning, the Pediatric Pulmonary Hypertension Network (PPHNet) issued a statement emphasizing that sildenafil therapy should be initiated with much caution and high doses avoided until further studies shed more light on the subject.¹⁰¹ In Europe, while the controversy is recognized, sildenafil remains the sole oral agent for PH therapy approved by the European Medicines Agency for use in children.^{102,103} The sildenafil warning has led to increased use of similar agents such as tadalafil (a long-acting PDE-5 inhibitor). We emphasize that caution should be used with these agents as well, given the lack of long-term follow-up data in children with PH. However, the abrupt cessation of sildenafil or other PH therapies may result in clinical deterioration or death.¹⁰¹

Chronic therapy may also include use of endothelin-1 (ET-1) receptor antagonists. ET-1 acts via two G protein-coupled receptors, ET_A (promotes smooth muscle cells proliferation and vasoconstriction), and ET_B (promotes proliferation and vasoconstriction, but also mediates vasodilation by release of NO and PGI₂ from endothelial cells).^{104–107} The most commonly used agent, bosentan, a nonselective antagonist of both ET_A and ET_B receptors, has potent vasodilatory effects.¹⁰⁸ Bosentan has been shown to improve pulmonary hypertension in adults and newborns with persistent PH.^{109,110} Selective ET_A receptor blockade with agents such as ambrisentan or sitaxsentan also causes vasodilation with similar effect to nonselective ET-1 receptor antagonists.¹⁰⁴ Further study is needed to evaluate the

benefit of these medications for treating PH in infants with BPD.

The vasodilatory effects of NO are mediated through stimulation of soluble guanylate cyclase (sGC) in the smooth muscle.¹¹¹ Medications such as riociguat and cinaiguat are now being studied that cause vasodilation by direct stimulation or activation of sGC respectively.¹¹² The FDA recently approved riociguat for the treatment of adult pulmonary hypertension.¹¹³ However, these agents may cause dangerous systemic hypotension and have not been studied in infants with BPD.¹¹⁴

Activation of PPAR γ by agonists such as rosiglitazone has been shown to treat experimental PH effectively in a number of animal models.^{115–117} Rosiglitazone has also been shown to prevent experimental BPD in rodents.^{118–120} However, it is an antidiabetic agent and may have off-target effects that have not been studied.¹²¹ Rho-kinase inhibitors such as fasudil improve monocrotaline-induced PH in rats and reduce PVR after ductus arteriosus compression in fetal sheep.^{122,123} Clinically, fasudil is a potent vasodilator and may become a therapeutic option for treating PH in the future.¹²⁴ These novel experimental agents have not been studied in infants and are not approved for the treatment of PH in preterm infants. An experienced PH team should be consulted in all severe cases.

Conclusion

In an era of increased survival of the most premature infants, impaired development and function of the pulmonary vasculature play central roles in the pathogenesis of BPD. This results in PVD and secondary PH in many cases. Recent studies have identified many of the mechanisms and factors contributing to impaired pulmonary vascular development in BPD. Although much is known, further study is needed to describe better the intracellular mechanisms and pathophysiologic consequences of PVD and PH in BPD. Universally accepted guidelines for PH screening in this population have not been established. Angiogenic and vascular growth factors have potential to serve as useful biomarkers to identify preterm infants at highest risk of severe disease for targeted therapies before clinical deterioration occurs, but require further study to determine their usefulness. Although the severity of BPD and the presence of PH by current standards are associated with worse outcomes, the relationship of specific echocardiographic findings to clinical outcomes is not entirely clear. In PH secondary to BPD, therapy begins by optimizing gas exchange with the avoidance of intermittent hypoxemia. If PH persists, a number of acute and chronic therapies may help to alleviate symptoms. However, further study is needed to determine the long-term safety and efficacy of these therapies in the clinical setting of BPD.

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Address correspondence to:
 Christopher D. Baker, MD
 Pediatric Heart Lung Center
 12700 E. 19th Ave., MS 8614
 Aurora, CO 80045

E-mail: Christopher.Baker@UCDenver.edu

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