Pulmonary Hypertension and Vascular Abnormalities in Bronchopulmonary Dysplasia

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Abstract

Advances in the care of preterm infants have improved survival of infants born at earlier gestational ages. Yet, these infants remain at risk for the chronic lung disease of infancy, bronchopulmonary dysplasia (BPD), which results in prolonged need for supplemental oxygen, recurrent respiratory exacerbations, and exercise intolerance. Recent investigations have highlighted the important contribution of the developing pulmonary circulation to lung development, demonstrating that these infants are also at risk for pulmonary vascular disease (PVD), including pulmonary hypertension (PH) and pulmonary vascular abnormalities, which contributes significantly to morbidity and mortality. In the past few years, several epidemiological studies have delineated the incidence of PH in preterm infants and the impact on outcomes. However, these studies have also highlighted gaps in our understanding of PVD in BPD, including universally accepted definitions, approaches to diagnosis and treatment, and patient outcomes. Associated pulmonary vascular and cardiac abnormalities are increasingly recognized complications contributing to PH in these infants, but incidence of these lesions and degree of contribution to disease remains unknown. Therapeutic strategies for PVD in BPD are largely untested, but recent evidence presents the rationale for the approach to diagnosis and treatment of BPD infants with PH that can be evaluated in future studies.

Keywords

bronchopulmonary dysplasia; pulmonary vascular disease; pulmonary hypertension; echocardiogram; inhaled nitric oxide

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Introduction

Bronchopulmonary dysplasia (BPD) is the chronic lung disease that occurs in preterm infants who require mechanical ventilation and oxygen therapy for postnatal respiratory distress.[1] BPD is characterized by persistent pulmonary disease with a prolonged need for supplemental oxygen, recurrent respiratory exacerbations with frequent emergency department visits hospitalizations,[2,3] exercise intolerance, and associated respiratory problems that can extend into adulthood.[4] Improved respiratory support strategies, antenatal steroids, surfactant therapy and other advances in clinical care have decreased the risk for death and the development of BPD in larger preterm infants. These strategies have also increased the survival of infants born earlier in gestation who then have high risk to develop BPD. Thus, the incidence of BPD has remained relatively stable over the past decade.[5,6] BPD in this "new" era most often occurs in infants born at 24–28 weeks post menstrual age (PMA), weighing   1000g, who have less severe acute respiratory symptoms and require less respiratory support than BPD patients in the era when the disease was first described.[7,8]

Maternal, genetic, and environmental factors can lead to early injury of the developing lung which impairs angiogenesis and alveolarization, resulting in simplification of the distal lung airspace and clinical manifestations of BPD. The impairments of the developing pulmonary vasculature may result in significant pulmonary vascular disease (PVD) (Figure 1). In its most severe form, PVD results in pulmonary hypertension (PH).[9–12] The impact of clinically apparent PH in the "new BPD" era suggest that morbidity[13–17] and late mortality is high, with up to 48% mortality 2 years after diagnosis of PH.[18]

Prospective studies have demonstrated that PH is common in BPD impacting 16–25% of infants.[15–17] Greater recognition of PH and its impact in this population has led to widespread treatment with pulmonary vasodilator medications. However, there are limited prospective data examining the impact of these medications on pulmonary vascular development as well as the clinical effectiveness of such medications. Thus, there is a need for greater insights into basic mechanisms of BPD and standardized clinical criteria for identifying at risk infants in order to develop better strategies for the prevention, monitoring, and treatment of preterm newborns. This review will present recent studies examining the role of the pulmonary circulation in the pathogenesis of BPD and PVD, the epidemiological studies of PH in BPD, and the rationale for the clinical approach to diagnosis and treatment of PH in BPD.

Pathogenesis of Pulmonary Vascular Disease in BPD

Pulmonary vascular growth is a dynamic process, beginning in the embryonic period and continuing throughout gestation and during postnatal life. Premature birth exposes the developing lung to an environment that can impair the normal developmental process. Histologically, the lung of preterm infants have revealed reduced numbers of both alveoli and intra-acinar arteries, leading to the description of BPD as an arrest of lung development. The pathogenesis of PVD in BPD is multifactorial, resulting from complex interactions between maternal, genetic and epigenetic susceptibility, and environmental factors (both prenatal and postnatal), including hyperoxia, hypoxia, hemodynamic stress, infection,

inflammation, and others. Clinical studies strongly suggest these complex interactions contribute to alter normal growth factor expression and signaling pathways, leading to impaired growth, structure and function of the developing pulmonary circulation after premature birth (Figure 1).[10,19–27]

Disruption of vascular growth and signaling may contribute to impaired lung structure,[28–32] leading to a marked reduction in alveolar-capillary surface area.[33–35] Abnormal growth of the pulmonary circulation in BPD is characterized by decreased vascular branching, an altered pattern of vascular distribution within the lung interstitium, and persistent intrapulmonary venous anastomoses,[31,36–39] which collectively contribute to the symptoms of BPD.[40] Several recent studies have shown pre-eclampsia is a risk factor for BPD and PVD,[41] possibly through disruption of these vascular signaling pathways.[42–45] Intrauterine growth restriction is another condition that has been associated with disruption of vascular signaling[46] and an increased risk for BPD and PH in preterm infants.[47]

The reduction in vessel number resulting from impaired vascular growth coupled with alveolar hypoxia, hyperoxia or hemodynamic stress may worsen pulmonary arterial structural remodeling in the preterm infant. Endothelial injury due to these environmental stressors[27,48,49] induces the media of small pulmonary arteries to undergo smooth muscle cell proliferation, precocious maturation of immature mesenchymal cells into mature smooth muscle cells, and incorporate fibroblasts/myofibroblasts into the vessel wall.[50] Smooth muscle proliferation also extends abnormally into the smaller peripheral arteries.[9] Such pulmonary artery remodeling and disruption of angiogenic factor expression as has been demonstrated in autopsy data from infants dying with BPD,[35,51,52] could lead to high pulmonary vascular resistance (PVR) due to narrowing of the vessel diameter and decreased vascular compliance, especially in response to respiratory infections. Persistent abnormalities of pulmonary vascular growth and/or failure of the lung vasculature to "catch-up" to infants born at term may contribute to PVD that becomes increasing symptomatic later in life.[53,54]

Diagnosis and Epidemiology of Pulmonary Vascular Disease in Preterm Infants

PH and cor pulmonale, resulting from extreme forms of PVD are recognized factors associated with high mortality in preterm infants with BPD.[18,55,56] In the past decade, patients with BPD and PH had a reported survival rates of 52% two years after the diagnosis of PH.[18] The increasing recognition of PVD and its association with poor outcomes in preterm infants born at earlier gestational ages led to renewed interest determining the incidence of PH in new era BPD and identifying high risk infants as early as possible. However, the lack of a data-derived definition of PH in this population and reliable diagnostic assessment measures to diagnose PH has limited study in this area.

Cardiac catheterization remains the gold standard for diagnosis of PH, but its invasive nature has restricted its application to those infants at highest risk. Non-invasive assessment via echocardiography, despite its significant limitations,[14] has become the most often used tool for screening and diagnosis of PH in preterm infants. The most objective measure of PH by

echocardiogram is the estimated right ventricular systolic pressure (RVSP) derived from the tricuspid regurgitant jet velocity (TRJV).[57–60] Applied from adult criteria, a threshold of RVSP > 35 mm Hg (TRJV > 3 m/s) to define PH has been used. Due to relatively low blood pressures in preterm infants, estimated pulmonary pressures >50% of the systemic pressure has also been used to define PH and appears to correlate better with measurements performed during cardiac catheterization.[14,61] Earlier studies of BPD infants with known or suspected PH revealed a measureable TRJV in only 31–61% of these infants.[14–16,62] More recent studies that have screened large groups of preterm infants have found that a measureable TRJV is more rare (6–10%)[16,17] and was the determining factor to diagnose PH in a very small proportion of infants. Further, the standards for determining the quality of the TRJV used to estimate RVSP and diagnose PH have not been thoroughly reported in some recent studies.[15,16,61,63]

Yet, the lack of a measureable TRJV does not preclude the presence of PVD or PH. Qualitative echocardiogram findings to diagnose PH, including right atrial enlargement, right ventricular hypertrophy, right ventricular dilation, pulmonary artery dilation, and interventricular septal flattening have correlated with diagnosis of PH by cardiac catheterization. Septal flattening appears to be among the more sensitive of these measures, but is vulnerable to interobserver reliability.

The right ventricular myocardial performance index (MPI; also known as the Tei index) has been used as a surrogate for increased PVR in BPD, and has been shown to remain elevated in infants with BPD compared to preterm infants without BPD.[64] Another study demonstrated that respiratory failure requiring mechanical ventilation from multiple etiologies, including BPD, was associated with significantly increased right ventricular MPI compared to controls,[65] suggesting that MPI may be a surrogate for worse respiratory disease. Further studies are needed to determine whether high right ventricular MPI is associated with BPD and/or PH.

In the past few years, several studies have attempted to determine the incidence of PH among preterm infants using echocardiograms as the screening tool, albeit with slightly different criteria to diagnose PH (Figure 2)[15–17,66] The first of these was a retrospective review at a single center in South Korea identifying 116 preterm infants born at <32 weeks postmenstrual age and diagnosed with BPD.[15] Echocardiograms performed after 2 months of age at the discretion of the primary caregivers were used to determine PH, but the number and timing of echocardiograms performed were not reported. PH criteria were based on clinical interpretation of echocardiograms and included a TRJV ≥ 3 m/s in the absence of pulmonary stenosis, and/or a flat or left-deviated interventricular septal configuration with RVH and chamber dilation. These authors identified 29 (25%) of BPD infants with PH at a median postnatal age of 65 days, and the diagnosis of PH was significantly correlated with severity of BPD (Figure 2). All patients diagnosed with PH were reported to have some degree of tricuspid regurgitation (trivial in 27.6%, mild in 44.8%, and moderate 27.6%), but the proportion meeting PH threshold was not reported.

The second study was a prospective analysis of preterm infants at the University of Alabama at Birmingham (USA) with birth-weight < 1000g who survived to 28 days.[16] All patients

underwent echocardiogram between 4–6 weeks of age and subsequent echocardiograms were performed if severe lung disease or clinical signs suggestive of right-sided heart failure were present. PH was diagnosed if at least one of the following findings was present: 1) right ventricular hypertrophy, 2) flattening of interventricular septum, 3) presence of tricuspid regurgitation in the absence of pulmonary stenosis, and 4) elevated right ventricular pressures as estimated by Doppler studies of tricuspid regurgitation jet (although the threshold for elevated pressure was not provided). Of 145 eligible patients, 9 (6.2%) were identified by the initial echocardiogram. Another 17 (11.7%) infants were diagnosed by subsequent echocardiograms; median age of diagnosis was 112 days. Of the patients diagnosed with PH, tricuspid regurgitation was identified in 58%, an elevated estimated systolic pulmonary pressure in 69%, right ventricular hypertrophy in 42%, and a flattened interventricular septum in 54%. Fifty-eight percent of infants had persistent signs of PH at NICU discharge, and 3 patients died from complications of PH.

The third study was a prospective evaluation at hospitals affiliated with two academic centers in the US. Two hundred seventy-seven preterm infants with gestational age at birth <34 weeks and birthweights between 500–1250g were screened with echocardiograms at 7 days of age and 36 weeks PMA.[17] All echocardiograms were interpreted by a single cardiologist, but this this study employed 3 different a priori criteria for PH to determine which was most closely associated with outcome. The most liberal criteria which were met by any of the following findings: an estimated right ventricular systolic pressure (RVSP) > 40 mm Hg, RVSP/systemic systolic blood pressure (sBP) > 0.5, any cardiac shunt with bidirectional or right-to-left flow, or any degree of ventricular septal wall flattening were most similar to the two studies described above. According to these criteria, the incidence of PH was 14% at 36 weeks PMA, with the highest incidence of PH (29%) occurring in infants with severe BPD, but relatively consistent rate of PH (about 10%) in infants with none, mild, and moderate BPD. PH diagnosed by these criteria was associated with greater mortality and increased duration of respiratory support after adjustment for gestational age at birth, BPD status, and other clinical factors. Applying alternate, more strict criteria for PH, dramatically reduced the incidence of PH (3.3% for criteria only using TRJV based threshold or reversal of cardiac shunt, and 4.7% for criteria that included, TRJV, reversal of shunt, or moderate to severe septal flattening).

A fourth prospectively conducted study at Women & Infants Hospital of Rhode Island (USA) enrolled 120 infants born <28 weeks PMA who underwent echocardiogram screening at 10–14 days of age and 36 weeks PMA.[66] They employed more strict criteria for PH (estimated systolic pulmonary artery pressure to systemic systolic artery pressure ratio > 0.5 or moderate or severe interventricular septal flattening). Using these criteria, they found an incidence of PH of 8% at 36 weeks PMA which is comparable the incidence of 4.7% found in the study by Mourani et al. using the similar criteria.[17]

Aligning similar criteria for PH, these studies reveal comparable rates of PH in patients diagnosed with BPD, with the majority of PH patients having severe BPD. It should be noted that PH can be identified as a "late" finding, with 65% of BPD infants with PH being diagnosed after having a "normal" echocardiogram between 4 to 6 weeks of age.[16] With the exception of the study by Mirza,[66] these studies employed liberal criteria for PH, only

requiring any evidence of septal flattening, and one only requiring the presence of a TRJ without applying threshold for pressure estimates.[16] Yet, using liberal criteria for PH, these studies and others have reported higher death rates and increased morbidities in preterm infants with BPD and PH compared to those without PH.[15–17,61,63,67] These data suggest that routine screening of preterm infants near term, especially those with more severe BPD will result in identification of substantial number of infants with PH who are at risk for increased morbidity and mortality. These data may further provide useful prognostic information for parents and caregivers and may allow the opportunity for early intervention.

Despite its usefulness for diagnostic screening, echocardiograms still have limitations that may preclude diagnosis of PH, fail to accurately diagnose the severity of PH[14] in those identified by echocardiogram, or fail to identify additional cardiovascular abnormalities that contribute to PH. Thus, we recommend cardiac catheterization (Table 1) for preterm infants with the following: 1) persistent signs of severe cardiorespiratory disease or clinical deterioration not directly explained by other diagnostic evaluations; 2) suspected of having significant PH despite optimal management of their lung disease and associated morbidities; 3) chronic vasodilator therapy is being considered; 4) unexplained, recurrent pulmonary edema. The goals of cardiac catheterization are to: assess the severity of PH, exclude or document the severity of associated anatomic cardiac and vascular lesions that may be amenable to intervention during catheterization, and to assess pulmonary vascular reactivity in patients who fail to respond to oxygen therapy alone.

Risk factors for PVD and PH in Preterm Infants

Past clinical studies have suggested that sustained elevations of pulmonary artery pressure as assessed by serial echocardiograms may be associated with increased risk for BPD,[64,68] supporting the hypothesis that PH in premature newborns may be an early clinical marker for predicting BPD. Early echocardiographic signs of pulmonary vascular disease in preterm infants have now been associated with increased risk for both BPD and late PH as well as with prolonged oxygen treatment.[17,66] Sustained evidence of elevated right ventricular pressure through the first week after birth may reflect early pulmonary vascular injury that increases risk for BPD. Whether these changes are secondary to delayed transition to extrauterine life, injury due to excessive hemodynamic stress from PDA or other shunts as has been previously reported,[69–71] or other forms of vascular injury remains to be determined. Understanding the drivers behind these early vascular changes will be crucial to developing novel intervention strategies to prevent both BPD and PH in these infants.

In addition to early hemodynamic indicators of PVD, clinical factors associated with late PH in most studies include lower gestational age, birth weight, and longer periods of respiratory support. Patent ductus arteriosus,[15] infection,[15] oligohydramnios,[72] small for gestational age[16,47] and low birth weight z-score[17] have also been identified as risk factors for PH in infants born preterm. Further examination of clinical factors associated with PH, including prenatal risks, along with translational investigations and rigorous screening of infants will help elucidate how these clinical factors impair normal pulmonary vascular development and lead to BPD and PVD.

Other Pulmonary Vascular and Cardiac Abnormalities Associated with BPD

While pulmonary hypertension is an extreme form of PVD in preterm infants, other cardiac and pulmonary vascular abnormalities may contribute to increased PVR and exacerbate PH in these infants (Table 2). Several of these abnormalities may be detected by echocardiogram and others may require alternate imaging such CT, MRI, and/or cardiac catheterization to detect. Echocardiographic assessment of anatomic cardiac disease, especially shunt lesions, is an important aspect of cardiovascular evaluation of BPD infants. Excessive left-to-right flow through cardiac level shunts can lead to pulmonary artery remodeling and increased PVR. Unfortunately, the degree of shunt flow cannot always be accurately estimated by echocardiogram and may require cardiac catheterization to quantify the degree of shunt. Other pulmonary vascular abnormalities such as systemic to pulmonary collaterals or pulmonary venous stenosis can occasionally be detected with echocardiogram, but often require cardiac catheterization to identify. However, these abnormalities may be amenable to treatment intervention during the catheterization, such as coiling or balloon dilation, respectively.[73] Impaired cardiac function may result from pulmonary hypertension (right sided dysfunction) or may contribute to it (left sided dysfunction). Preterm birth has been associated with alterations in RV structure and reduced function in young adults, suggesting that the heart in addition to the vasculature may be susceptible to perinatal events.[74] Decreased shortening fraction, left ventricular ejection fraction, or signs of left ventricular hypertrophy may be signs of left ventricular dysfunction, which may require catheterization for confirmation.[14,75,76] Diastolic function may also lead to elevated PVR, but is difficult to ascertain by echocardiogram, and often requires catheterization for diagnosis as well.[75] In one study, the combined modality of CT scans (21 patients) and catheterizations (14 patients) identified cardiovascular anomalies in 19 of 29 BPD infants with PH, including systemic to pulmonary collaterals (n = 9), pulmonary vein stenosis (n = 7), atrial septal defects (n = 5), and PDA (n = 9).[77] MRI of the chest may provide an additional modality for evaluating pulmonary vascular function and hemodynamics. Phase-contrast flow measurements via MRI could estimate pulmonary artery velocities and pulmonary arterial pressure. These techniques have been applied in other forms of PH, detecting changes of PVD prior to symptoms.[78–82]

BPD lung disease can also increase PVR exacerbating PVD and contribute to PH. Air trapping and hyperinflation from airways disease can over stretch small pulmonary arteries increasing PVR. Conversely, atelectasis constrains pulmonary vessels also increasing PVR. Acute episodes of hypoxia and hypercarbia can induce pulmonary artery vasoconstriction, especially within remodeled/dysmorphic vessels.

Treatment of Pulmonary Hypertension in BPD

Despite recent evidence that PH is more common in preterm infants than previously thought and is associated with increased morbidity and mortality, proven strategies to improve outcomes are lacking. Several studies have shown improvement in the severity of PH with various strategies,[13,15,83] but controlled trials of PH treatment in BPD have not been performed. As pointed out earlier, animal and clinical data suggest that contributions from impaired pulmonary vascular development, cardiac abnormalities and dysfunction, and

parenchymal lung disease all contribute to elevated PVR and PH in preterm infants with BPD and may contribute to evolving PVD or time. Therefore, targeted strategies to optimize these areas form the approach to PH therapy in BPD infants (Table 1, Figure 3).

Since a higher rate of PH has been found in those with more severe lung disease, it seems reasonable to aggressively target factors contributing to lung disease, including episodes of hypoxia, ventilatory insufficiency, bronchoconstriction, chronic reflux and aspiration, and upper and lower airway obstruction.[40] Immuno-prophylaxis against respiratory infections including respiratory syncytial virus is also an important strategy.

The goal to wean severe BPD infants from respiratory support in preparation for discharge from the NICU should be carefully weighed against the risks for intermittent hypoxia and hypercarbia which can trigger vasoconstriction and further vascular remodeling. Assessments of oxygenation during feeding and sleep should be performed before weaning infants completely from supplemental oxygen. Targeting oxygen saturations to 92–95% should be sufficient to prevent the adverse effects of hypoxia in most infants without increasing the risk of additional lung injury or other systemic effects of hyperoxia. Chronic mechanical ventilation support should be considered for infants who are failing to wean from noninvasive positive pressure support or for infants with frequent episodes of hypoxia and/or impaired ventilation or with inadequate growth velocity despite supplemental oxygen.

As noted above, identifying anatomic cardiovascular abnormalities (Table 2) which contribute to increased PVR and PH and could benefit from specific targeted interventions are important to rule out before considering chronic vasodilator therapy because vasodilators could result in adverse clinical effects in the presence of these lesions. Although the use of vasodilators targeted at pulmonary arterial structural remodeling and vasoreactivity is a rational approach, none of the medications approved for adult use are approved for children in the United States. Given the complex maturational influences related to lung vascular development in preterm infants,[84,85] special consideration should be given to use of these medications in infants and children relative to adults (Figure 3). Additionally, use of systemic vasodilators (delivered via the bloodstream) may worsen ventilation/perfusion mismatch and oxygenation in BPD infants.

Inhaled nitric oxide (iNO) is approved for treatment of persistent pulmonary hypertension of the newborn and is the drug with the most safety data available in preterm infants, having been used in several clinical trials for the prevention of BPD.[86–88] While the studies performed do date do not justify routine use of iNO for BPD, prolonged iNO therapy for PH may be considered for hospitalized infants who are ventilated or by nasal cannula delivery.[89,90] In such patients, dose response studies performed during cardiac catheterization may help to optimize the level of iNO therapy. The acute hemodynamic response to iNO in patients with BPD and PH has been shown to be greater than to calcium channel blockers[91] with doses as low as 2 ppm demonstrating improvements of pulmonary pressure. iNO is easiest to deliver via mechanical ventilation and available data suggests that it can be safely administered for prolonged periods. If PH improves in response to iNO, it can gradually be weaned off over days to weeks with careful monitoring prior to discontinuation of mechanical ventilation. For infants in whom iNO fails to sufficiently improve PH as the sole

agent, or for those whose clinical setting and needs (upon extubation from mechanical ventilation) may benefit from alternate vasodilator therapy due to limitations with iNO administration, a second-line agent such as sildenafil may be added.

Sildenafil, a selective type 5 phosphodiesterase inhibitor, is approved by the federal drug administration (FDA) for the treatment of PH in adults, but has had large appeal for use in infants and children due the ease of administration in comparison to other PH medications. It has been used extensively off-label for the treatment of PH in BPD based on several case reports and a couple of retrospective studies suggesting safety with potential efficacy.[13,83] A recent pilot trial of sildenafil did not improve short-term respiratory outcomes (development of BPD) of extremely preterm infants, but further studies are warranted to determine whether treatment could mitigate development of severe PVD. In 2012, the FDA issued a recommendation against the use of sildenafil in children ages 1–17 (http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm317743.htm). The decision was based on reports of increasing mortality with increasing sildenafil doses in a long-term clinical trial in pediatric patients with PH secondary to idiopathic pulmonary arterial hypertension and congenital heart disease.[92] In 2014, the FDA issued a clarification of the statement (http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm391152.htm) stating there may be situations in which the benefit-risk profile of sildenafil may be acceptable in individual children, where treatment options are limited and close monitoring can be provided. Thus, careful consideration and extreme caution should be exercised when contemplating sildenafil treatment for infants and children. Other vasodilators including prostacyclin analogs, endothelin receptor antagonists, and soluble guanylate cyclase modulators could be considered for use in BPD infants with PH, but there are very limited data available examining the effectiveness and safety of these medications for this population.

Currently, there is limited evidence on how long to continue these therapies if initiated. Often, many infants are discharged from the neonatal intensive care unit on these medications and followed-up by pediatric pulmonologists, cardiologists, or centers focusing on pulmonary hypertension. If pulmonary hypertension gradually resolves with lung growth as expected, the medications may be either gradually tapered off, or the infant allowed to outgrow the dose before discontinuation of the drugs one by one (usually the most "invasive" or least effective medication is weaned off first).

BPD infants treated with PH medication require close monitoring of pulmonary and hemodynamic status. Objective assessments of oxygenation should be performed when weaning infants from oxygen therapy or when infants develop respiratory infection. Serial echocardiograms, which should be obtained at least every 2–4 weeks with the acute initiation of therapy and at 4–6 month intervals with stable disease is recommended. Brain natriuretic peptide (BNP) may augment monitoring,[93] but evidence does not support its use in the absence of echocardiography and other monitoring modalities. Acute worsening of PH or failure to respond to therapy may reflect several factors, including late pulmonary vascular anatomic abnormalities. Repeat diagnostic procedures, including cardiac catheterization may be indicated for these patients (Figure 3). We recommend weaning

medications with serial normal or near-normal echocardiogram findings over weeks with careful monitoring of pulmonary function and growth velocities.

Conclusion

PVD in preterm infants with BPD is characterized by altered lung vascular development, growth, structure, or function, which precedes the onset of measureable PH. PVD due to disruption of normal pulmonary vascular development in association with preterm birth is an important determinant of the pathobiology of BPD and contributes significantly to morbidity and mortality. Exposure to adverse stimuli during the antenatal and/or early postnatal periods impair normal pulmonary vascular development and creates and imbalance between risk and resiliency factors. Recent studies have revealed the magnitude of PH in preterm infants, but many aspects of PVD remain understudied, and ongoing investigations continue to explore risk factors, mechanisms of disease, and long term outcomes. Prospective studies are needed to definitively establish standardized clinical criteria for PVD and PH in BPD, and to determine the best methods for early diagnosis, risk stratification, and disease monitoring. Larger collaborative studies and improved clinical infrastructure to conduct these important investigations will provide answers to these critical questions.

Acknowledgments

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Key points

- Pulmonary vascular disease (PVD) and cardiovascular abnormalities are an increasingly recognized component of bronchopulmonary dysplasia (BPD) and contributes significantly to morbidity and mortality.

- Complex interactions between antenatal and postnatal factors contribute to impair normal pulmonary vascular signaling pathways, leading to altered growth, structure, and function of the developing pulmonary circulation after preterm birth.

- The impairments of the developing pulmonary vasculature may result prolonged oxygen requirements, exaggerated effects of anatomical shunt lesions, exercise intolerance, altered pulmonary blood flow distribution in response to acute respiratory infections, and ultimately PH.

- Several studies utilizing echocardiogram to screen preterm infants have determined the incidence of PH in BPD to be 16–25%, yet some cardiovascular abnormalities may be missed with echocardiogram and require cardiac catheterization.

- Further studies are needed to determine the risk factors, mechanisms of disease, and long term outcomes, and to better define the clinical approach and treatment of PVD in BPD.
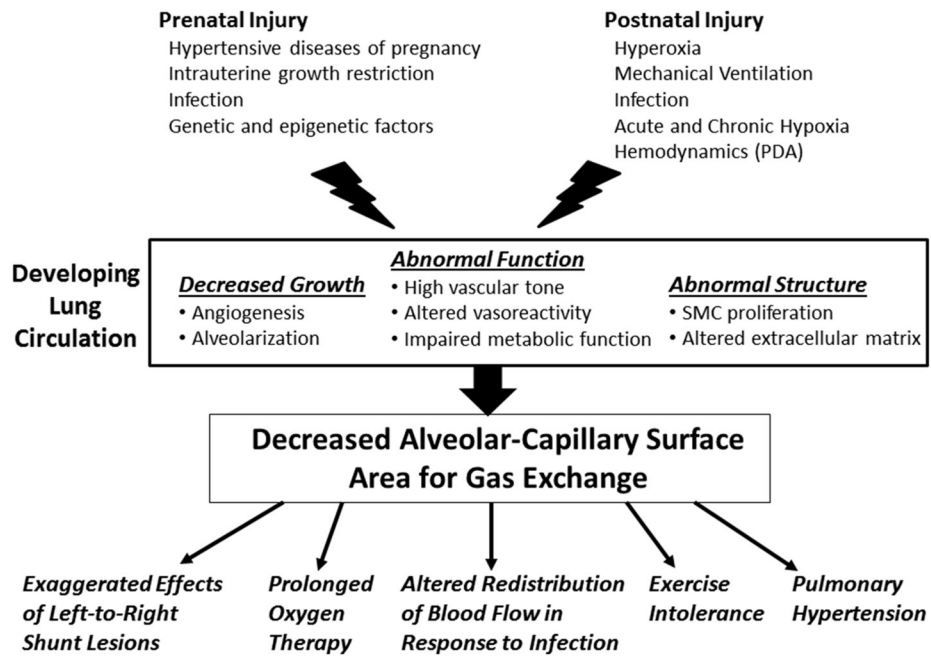
Figure 1.
Schematic illustrating the components contributing to pulmonary vascular disease in bronchopulmonary dysplasia and the clinical manifestations that result. PDA: patent ductus arteriosis, SMC: smooth muscle cells.
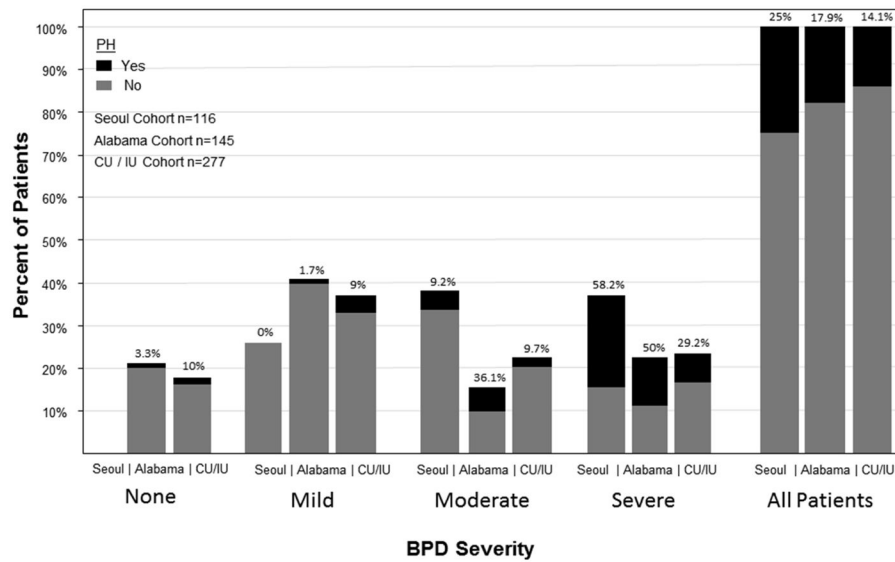
Figure 2.
The incidence of PH according to the degree of BPD severity. Incidence of PH among preterm infants from three studies, Seoul,[15] Alabama,[16] and Colorado/Indiana.[17] The percentage of patients listed on the Y-axis represents the proportion of patients in each study in whom BPD status was ascertained. Please see text for inclusion criteria of each of the studies. BPD severity was based on NIH criteria.[38] Physiologic assessment of oxygenation to determine BPD status[94] was applied in the Alabama and CU/IU cohorts. The Seoul cohort did not include preterm infants without BPD. Numbers above the bars indicate the percentage of patients with PH.
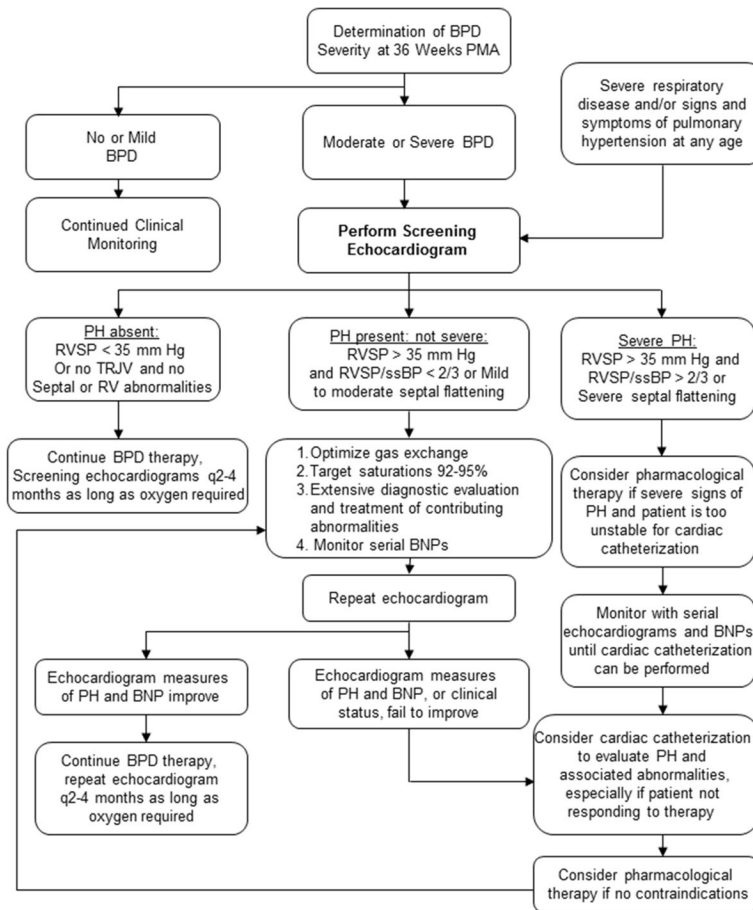
Figure 3.
Proposed clinical approach to screening, evaluation, and monitoring of pulmonary hypertension in bronchopulmonary dysplasia. Adapted from Mourani PM, Abman SH. Pulmonary vascular disease in bronchopulmonary dysplasia: physiology, diagnosis, and treatment. In: Abman SH, ed. *Bronchopulmonary Dysplasia*. New York: Informa; 2010:347–363; with permission.
[95] BNP: brain natriuretic protein; BPD: bronchopulmonary dysplasia; PMA: postmenstrual age; PH: pulmonary hypertension; RVSP: right ventricular systolic pressure; TRJV: tricuspid regurgitant jet velocity; ssBP: systemic systolic blood pressure; RV: right ventricle.

Table 1

Approach to Pulmonary Hypertension in BPD

Screening echocardiograms for:

Severe BPD at 36 weeks

Infants with prolonged ventilator and/or oxygen requirements

Cyanotic episodes

Marked hypercarbia

Persistent pulmonary edema, diuretic dependence

Poor growth, IUGR, oligohydramnios

General evaluation and treatment for factors contributing to persistent respiratory disease and PH

Ensure adequate oxygenation (awake, asleep, feeds)

Assess the adequacy of ventilation

Chronic aspiration (barium swallow, swallowing study, pH probe, impedance study)

Structural airway disease: malacia, subglottic stenosis

Optimal treatment of reactive airways disease

Neurological abnormalities: hydrocephalus

Ensure optimal nutrition

Consider cardiac catheterization when work-up fails to reveal a clear etiology for poor clinical status or when optimal management of these factors fail to achieve clinical improvement

Assess severity of PH

Anatomic heart disease/shunt lesions

Structural vascular abnormalities (eg, arterial stenosis, pulmonary venous obstruction, systemic to pulmonary collateral vessels, others)

Catheter-based interventions

Assess cardiac function (LV diastolic dysfunction)

Acute vasoreactivity/hypoxia testing for selection of chronic therapy

BPD: bronchopulmonary dysplasia, IUGR: intrautuerine growth restrcition, PH: pulmonary hypertension, LV left ventricular

Table 2

Factors Contributing to Increased PVR in PH

Pulmonary Vascular Disease	Cardiac Disease	Lung Disease
High tone and reactivity	RV dysfunction	Hypoxemia
Hypertensive vascular remodeling	Impaired LV contractility	Hyperinflation
Decreased vascular growth	LV diastolic dysfunction	Atelectasis
Systemic-to-pulmonary collateral vessels	left-to right-shunt lesions	Hypercarbia
Pulmonary vein stenosis		

RV: right ventricular; LV: left ventricular