Pulmonary Vascular Disease in Bronchopulmonary Dysplasia

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Pulmonary vascular disease and pulmonary hypertension (PH) contributes significantly to the pathogenesis, pathophysiology, and clinical course of infants with bronchopulmonary dysplasia (BPD). This article briefly reviews the impact of premature birth on the developing lung circulation, mechanisms that contribute to the development of PH in premature newborns, and the diagnostic evaluation and management of severe PH in infants with BPD.

Despite advances in our understanding of its pathobiology and the growing availability of drug therapies, pulmonary hypertension (PH) and related pulmonary vascular diseases (PVDs) continue to cause significant morbidity and mortality in children.[1-3] Whereas similarities exist regarding the etiology and disease pathogenesis of some forms of pediatric and adult PH, many cardiopulmonary diseases associated with PH are unique to neonates, infants, and children.[2,3,5] Specifically, aspects of the developmental biology of the growing lung are key determinants of PVD, as vascular injury during susceptible periods of growth and adaptation can have long-standing impact on vascular growth throughout childhood and may impact growth of the distal lung airspace as well.[4-6]

The most common clinical setting for PH related to the disruption of normal developmental vascular pathways include the important impact of PVD associated with premature birth, most specifically in the setting of the chronic lung disease known as bronchopulmonary dysplasia (BPD) (**Figure 1**).[5] BPD is the chronic lung disease of infancy that occurs in premature infants after oxygen and ventilator therapy for acute respiratory disease at birth. As first characterized nearly 5 decades ago, BPD was originally described as severe chronic respiratory morbidity and high mortality in relatively late-gestation preterm infants, as infants below 28 weeks gestation rarely survived in that era.[7] With surfactant therapy, improved ventilator care, more aggressive nutrition, and other interventions, the increases in survival of even the most immature newborns at gestational ages between 23 and 28 weeks has been remarkable.[8,9] However, these successes have not led to a reduction in persistence of BPD: a major problem, occurring in an estimated 10,000 to 15,000 infants per year in the United States alone now. This has important implications, as infants with BPD require prolonged neonatal intensive care unit (NICU) courses; have frequent readmissions during the first 2 years after NICU discharge for respiratory infections, asthma, and related problems; and have persistent lung function abnormalities and exercise intolerance as adolescents and young adults.[10]

Despite striking changes in the nature and epidemiology of BPD over time, PH continues to contribute significantly to high morbidity and mortality in BPD, and is present early in the course of disease.[11-13] Even the original descriptions of BPD noted striking pulmonary hypertensive vascular remodeling in severe cases, and that the presence of PH beyond 3 months of age was associated with high mortality (40%).[13] Now in the "post-surfactant era" or the "new BPD," late PH continues to be strongly linked with poor survival, with a recent report suggesting mortality rates of nearly 70% for infants with severe PH.[14] This article briefly discusses our current understanding and approach for preterm infants with BPD and PH, including recent guidelines from the joint American Heart Association/American Thoracic Society report on the care of children with PH.[3]

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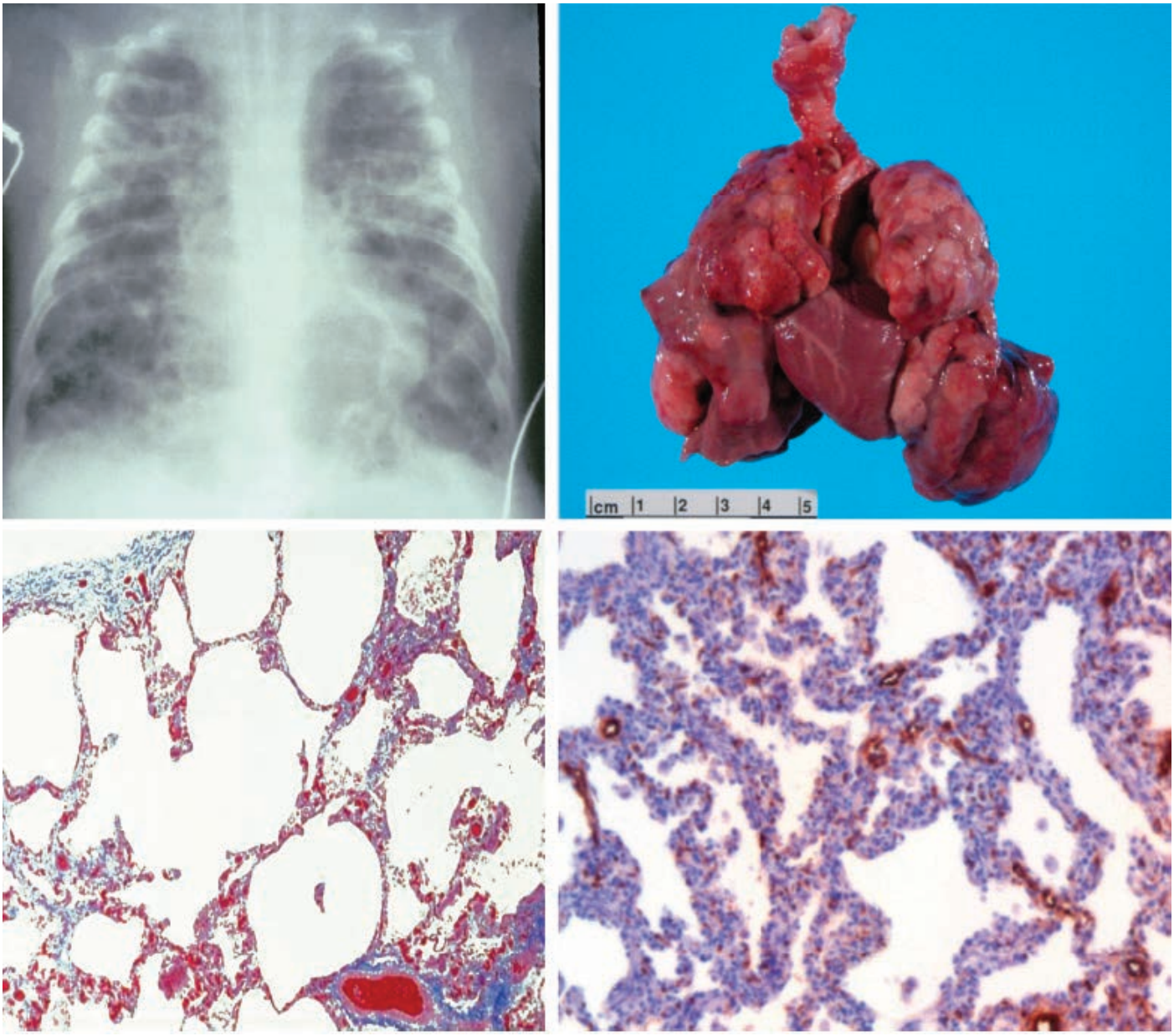

Figure 1: Radiologic, anatomic, and histologic abnormalities of severe BPD with associated PH. Reproduced with permission of Annual Review of Physiology, Volume 67, by Annual Reviews. Stenmark KR, Abman SH. Lung vascular development: implications for the pathogenesis of bronchopulmonary dysplasia. *Annu Rev Physiol*. 2005;67:623-661.

PULMONARY VASCULATURE IN BPD

In addition to the adverse effects of PH on the clinical course of infants with BPD, the lung circulation is further characterized by abnormal growth of the pulmonary circulation, including a reduction of small pulmonary arteries and an altered pattern of distribution within the lung interstitium.[15-18] This reduction of alveolar-capillary surface area impairs gas exchange, which increases the need for prolonged oxygen and ventilator therapy, causes marked hypoxemia with acute respiratory infections and exercise, and increases the risk for developing severe PH (**Figure 2**).

Experimental studies have shown that early injury to the developing lung can impair angiogenesis, which further contributes to decreased alveolarization and simplification of distal lung airspace (the "vascular hypothesis").[19] Angiogenic signaling pathways, including those involving vascular endothelial growth factor (VEGF) and nitric oxide are important mediators of normal pulmonary vascular development.[20-22] Disruption of vascular growth and signaling may contribute to impaired lung structure,[4-6] leading to a marked reduction in alveolar-capillary surface area and to the symptoms of BPD and PH. Placental overproduction of soluble VEGF receptor-1, which inhibits VEGF signaling, mainly causes maternal endothelial dysfunction and plays a central role in the pathogenesis of pre-eclampsia,[23-26] and may impair pulmonary vascular growth in fetus. Intrauterine growth restriction (IUGR) is another condition that has been associated with disruption of VEGF signal-

Pulmonary Vascular Disease in BPD

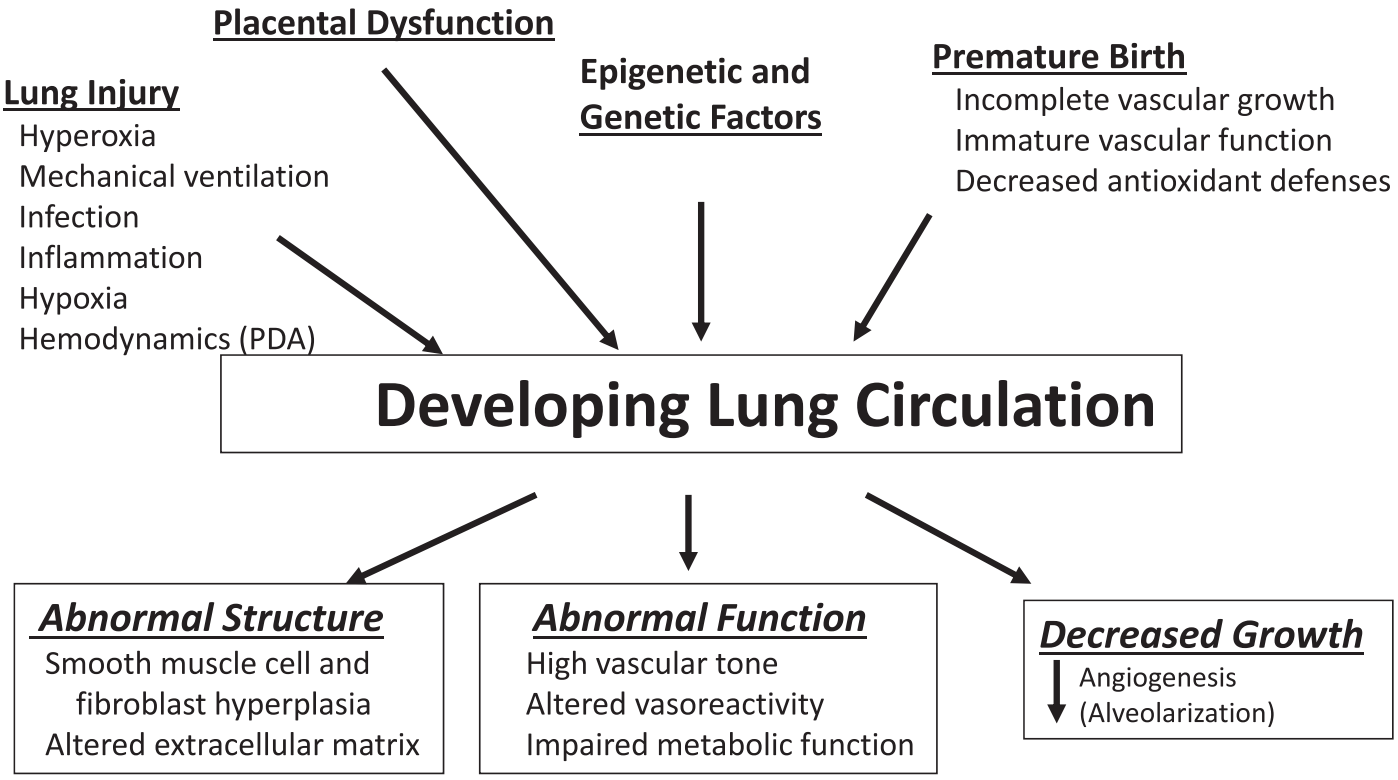

Figure 2: Schematic illustrations of PVD in BPD.

ing[27] and an increased risk for BPD and PH in preterm infants.[28] Thus, abnormalities of the lung circulation in BPD are not only related to the presence or absence of PH, but more broadly, PVD after premature birth as manifested by decreased vascular growth and structure also contributes to the pathogenesis and abnormal cardiopulmonary physiology of BPD.

These laboratory concepts have recently been demonstrated in a prospective clinical study in which early echocardiogram findings of PVD at Day 7 of life was strongly associated with the subsequent diagnosis of BPD and poor respiratory outcomes.[29] 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,[30,31] supporting the hypothesis that PH in premature newborns may be an early clinical marker for predicting BPD. Early echocardiographic signs of PVD in preterm infants have now been associated with increased risk for both BPD and late PH, as well as with prolonged oxygen treatment.[29,32] 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 patent ductus arteriosus (PDA) or other shunts as has been previously reported, 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. PDA, infection, oligohydramnios, small for gestational age, and low birth weight z-score 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 PH.

From the earliest descriptions of BPD, PH has long been recognized as being associated with high mortality in BPD.[13,14] Early injury to the lung circulation leads to the rapid development of PH after premature birth. Abnormalities of the pulmonary circulation in BPD include increased vascular tone and vasoreactivity, hypertensive remodeling, and decreased growth.[20] Physiologic abnormalities of the pulmonary circulation in BPD include elevated pul-

monary vascular resistance (PVR) and abnormal vasoreactivity, as evidenced by the marked vasoconstrictor response to acute hypoxia.[33] Cardiac catheterization studies have shown that even mild hypoxia can cause marked elevations in pulmonary artery pressure in some infants with BPD, including infants with only modest basal elevations of PH. Increased pulmonary vascular tone contributes to high PVR even in older children with BPD without hypoxia, suggesting that abnormal vascular function persists even late in the course. Reduced vascular growth (angiogenesis) also limits vascular surface area, causing further elevations of PVR, especially in response to high cardiac output with exercise or stress. The ability of the lung to achieve normal gas exchange requires ongoing growth and maintenance of an intricate system of airways and vessels, including the establishment of a thin yet vast blood-gas interface.

Clinically, reduced vascular surface area implies that even relatively minor increases in left-to-right shunting of blood flow through a patent foramen ovale, atrial septal defect (ASD), or PDA may induce a far greater hemodynamic injury in infants with BPD than in infants with normal lung vascular growth. Prominent bronchial and other systemic-to-pulmonary collateral vessels are also found in morphometric studies of infants with BPD, and can be readily identified in many infants during cardiac catheterization. Although these collateral vessels are generally small, large collaterals may contribute to significant shunting of blood flow to the lung, causing edema and need for higher FiO_2.

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 increasingly symptomatic later in life.[34,35] BPD infants have demonstrated decreased pulmonary diffusing capacity compared to age-matched term controls, suggesting that BPD infants have decreased alveolar surface area available for gas exchange.[35] These differences were also found in children at 11 years of age who had been born extremely preterm and in adult survivors of BPD.[34] Thus, reduced arterial number, structural abnormalities of the vessel wall, and abnormal vascular function together with impairments in respiratory mechanics and cardiac function, can contribute to increased PVR and PVD in BPD, leading to significant morbidity and mortality. Future work is needed to better define basic mechanisms of lung vascular growth and development, which will likely lead to novel therapeutic approaches to diseases associated with impaired vascular growth and PVD.

DIAGNOSTIC APPROACH

Although the exact incidence of PH in BPD is uncertain, marked PH beyond the first few months of life has been recently associated with a 47% mortality within 2 years after diagnosis.[14] PH is not only a marker of more advanced BPD, but high PVR also causes poor right ventricular function, impaired cardiac output, limited oxygen delivery, increased pulmonary edema, and possibly a higher risk for sudden death. PH in BPD is increasingly recognized in preterm infants with lower mortality risk, and retrospective studies have noted PH in roughly 25% to 37% of infants with BPD. Based on strong correlations between PH and survival in BPD, early detection of PH may provide helpful prognostic information and lead to the earlier application of more aggressive respiratory support, cardiac medications, vasodilators, and surgical or interventional cardiac catheterization procedures to improve late outcomes. Prospective data regarding the precise incidence and natural history of PH in BPD are lacking, and most information on diagnostic and therapeutic strategies are based on clinical observations, rather than rigorous, randomized clinical trials.

In general, we recommend early echocardiograms for the diagnosis of PH in preterm infants with severe respiratory distress syndrome who require high levels of ventilator support and supplemental oxygen, especially in the setting of oligohydramnios and IUGR. Infants with more severe prematurity (<26 weeks) are at highest risk for late PH. Similarly, infants with a particularly slow rate of clinical improvement, as manifested by persistent or progressively increased need for high levels of respiratory support, should be assessed for PH. In the setting of established BPD, preterm infants who at 36 weeks post conceptual age still require positive pressure ventilation support are not weaning consistently from oxygen, have oxygen needs at levels disproportionate to their degree of lung disease, or have recurrent cyanotic episodes warrant screening for PH or related cardiovascular sequelae. Other clinical markers often associated with more severe disease include feeding dysfunction and poor growth, recurrent hospitalizations, and elevated $PaCO_2$. High $PaCO_2$ is a marker of disease severity and reflects significant airways obstruction, abnormal lung compliance with heterogeneous parenchymal disease, or reduced surface area, and is an indication for PH screening. Another strategy would be to use echocardiograms to screen every patient at 36 weeks of age who is diagnosed with moderate or severe BPD, but how often PH would be missed in patients with milder BPD is uncertain.

Serial electrocardiograms have inadequate sensitivity and positive predictive value for identification of right ventricular hypertrophy (RVH) as a marker of PH. Some patients can have significant RVH and PH despite minimal or normal electrocardiogram findings. As a result, we recommend serial echocardiograms for screening for PH in patients with BPD. Estimated systolic pulmonary artery pressure (sPAP) derived from the tricuspid regurgitant jet (TRJV) measured by echocardiogram has become one of the most utilized findings for evaluating PH. Past studies have shown excellent correlation coefficients (r values between 0.93 and 0.97) when compared with cardiac catheterization measurements in children less than 2 years old with congenital heart disease.[36] However, these studies evaluated echocardiogram and cardiac catheterization performed simultaneously under the same hemodynamic conditions, and the utility of echocardiograms in predicting disease severity as applied in the clinical setting is less clear.

The utility of echocardiogram assessments of PH in infants with BPD has been compared with subsequent cardiac catheterization measurements of pul-

monary artery pressure.[37] sPAP could be estimated in only 61% of studies, and there was poor correlation between echocardiogram and cardiac catheterization measures of sPAP in these infants. Echocardiogram estimates of sPAP correctly identified the presence or absence of PH in 79% of these studies, but the severity of PH was correctly assessed in only 47% of those studies. Seven of 12 children (58%) without PH by echocardiogram had PH during subsequent cardiac catheterization. In the absence of a measurable TRJV, qualitative echocardiogram findings of PH, including right atrial enlargement, RVH, right ventricular dilation, pulmonary artery dilation, and septal flattening, either alone or in combination have relatively poor predictive value. Factors associated with chronic lung disease, specifically marked pulmonary hyperinflation, expansion of the thoracic cage, and alteration of the position of the heart, adversely affect the ability to detect and measure TRJV. As used in clinical practice, echocardiography often identifies PH in infants with BPD, but estimates of sPAP were not obtained consistently and were often not reliable for determining disease severity. Other measures of right ventricular strain and PH, including acceleration time (AT)/ejection time (ET) ratio and the Tei index could be helpful in the absence of a measurable TRJV, but have not been fully evaluated in infants with BPD. Despite its limitations, echocardiography remains the best available screening tool for PH in BPD patients.

In patients with PH by echocardiogram, we generally recommend cardiac catheterization for patients with BPD who:

1. Have persistent signs of severe cardiorespiratory disease or clinical deterioration not directly related to airways disease
2. Are suspected of having significant PH despite optimal management of their lung disease and associated morbidities
3. Are candidates for chronic PH drug therapy
4. Have unexplained, recurrent pulmonary edema, and other questions

The goals of cardiac catheterization are to: assess the severity of PH; exclude or document the severity of associated anatomic cardiac lesions; define the presence of systemic-pulmonary collateral vessels, pulmonary venous obstruction, or left heart dysfunction; and to assess pulmonary vascular reactivity in patients who fail to respond to oxygen therapy alone. Other critical information can be acquired during cardiac catheterization that may significantly aid in the management of infants with BPD. In particular, assessment of shunt lesions, especially ASDs; the presence, size, and significance of bronchial or systemic collateral arteries; determining the presence of pulmonary artery stenosis; and structural assessments of the pulmonary arterial and venous circulation by angiography are among several key factors that may affect cardiopulmonary function. A recent report highlighted the importance of pulmonary vein stenosis or veno-occlusive disease in premature infants.[38]

Most importantly, elevated pulmonary capillary wedge pressure (PCWP) or left atrial pressure (LAP) may signify left-sided systolic or diastolic dysfunction. Left ventricular diastolic dysfunction (LVDD) can contribute to PH, recurrent pulmonary edema, or poor inhaled nitric oxide (iNO) responsiveness in infants with BPD, and measuring changes in PCWP and LAP during acute vasoreactivity testing may help with this assessment. In addition to high pulmonary vascular tone, abnormal vasoreactivity, hypertensive vascular remodeling, and decreased surface area, LVDD can also contribute to high pulmonary artery pressure in infants with BPD.[39] Up to 25% of BPD infants with PH who were evaluated by cardiac catheterization had hemodynamic signs of LVDD in one retrospective study. Some infants with LVDD present with persistent requirements for frequent diuretic therapy to treat recurrent pulmonary edema, even in the presence of only mild PH.

TREATMENT OF PH IN BPD

The initial clinical strategy for the management of PH in infants with BPD begins with treating the underlying lung disease. This includes an extensive evaluation for chronic reflux and aspiration, structural airway abnormalities (such as tonsillar and adenoidal hypertrophy, vocal cord paralysis, subglottic stenosis, tracheomalacia, and other lesions), assessments of bronchoreactivity, improving lung edema and airway function, and others. Periods of acute hypoxia, whether intermittent or prolonged, are common causes of persistent PH in BPD (**Table 1, Table 2**). Brief assessments of oxygenation ("spot checks") are not sufficient for decisions on the level of supplemental oxygen needed. Targeting oxygen saturations to 92% to 94% should be sufficient to prevent the adverse effects of hypoxia in most infants, without increasing the risk of additional lung inflammation and injury. A sleep study may be necessary to determine the presence of noteworthy episodes of hypoxia and whether hypoxemia has predominantly obstructive, central, or mixed causes.

Additional studies that may be required include flexible bronchoscopy for the diagnosis of anatomical and dynamic airway lesions (such as tracheomalacia) that may contribute to hypoxemia and poor clinical responses to oxygen thera-

Table 1. Diagnostic Approach to Infants With PH in BPD.

- Evaluation of Underlying Lung Disease
  - Prolonged monitoring of O_2 (awake, asleep, feeds)
  - $PaCO_2$ – contribution to PH or marker of disease severity, need for chronic (effective) ventilation?
    - Chronic aspiration (barium swallow, swallowing study, pH probe, impedance study)
    - Sleep study
  - Structural airway disease: flexible bronchoscopy
  - Reactive airways disease
  - Chest CT scan
- Cardiac Catheterization

Table 2. Guidelines for PH Management in BPD.[3]

- Screening for PH by echocardiogram is recommended in infants with ***established BPD*** (class I, Level B)
- ***Evaluation and treatment of lung disease***, including assessments for hypoxemia, aspiration, structural airways disease, and the need for changes in respiratory support, is recommended in infants with BPD and PH ***before initiation*** of PAH-targeted therapy (class I, Level B)
- Evaluation for chronic therapy for PH in infants with BPD should follow recommendations for all children with PH and include ***cardiac catheterization*** to diagnose disease severity and potential contributing factors such as LVDD, anatomic shunts, pulmonary vein stenosis, and systemic collaterals (class I, Level B)
- Supplemental oxygen therapy is reasonable to avoid episodic or sustained hypoxemia and with the goal of maintaining O_2 saturations between ***92% and 95%*** in patients with established BPD and PH (class IIa, Level C)
- PAH-targeted therapy can be useful for infants with BPD and PH on optimal treatment of underlying respiratory and cardiac disease (class IIa, Level C)

py. Upper gastrointestinal series, pH or impedance probe, and swallow studies may be indicated to evaluate for gastroesophageal reflux and aspiration that can contribute to ongoing lung injury. For patients with BPD and severe PH who fail to maintain near normal ventilation or require high levels of FiO_2 despite conservative treatment, consideration should be given to chronic mechanical ventilatory support. Despite the growing use of pulmonary vasodilator therapy for the treatment of PH in BPD, data demonstrating efficacy are extremely limited, and the use of these agents should only follow thorough diagnostic evaluations and aggressive management of the underlying lung disease. Current therapies used for PH treatment in infants with BPD generally include iNO, sildenafil, endothelin-receptor antagonists, and calcium channel blockers (CCBs).

Inhaled nitric oxide causes selective pulmonary vasodilation and improves oxygenation in infants with established BPD (**Table 3**).[39] Although long-term iNO therapy has been used in BPD infants, especially for those who require continued mechanical ventilator support, efficacy data are not available. Although iNO for PH therapy is often initiated at doses of 10-20 ppm, most patients subsequently tolerate weaning of the iNO dose to a range of 2-10 ppm. The lower dose may further enhance ventilation/perfusion matching, allowing for better oxygenation at lower FiO_2.

Sildenafil, a highly selective phosphodiesterase type 5 (PDE-5) inhibitor, augments cyclic guanosine monophosphate (cGMP) content in vascular smooth muscle, and has been approved for adults with PH alone and in combination with standard treatment regimens. Studies of sildenafil therapy in children with PH have been limited, but include a demonstration of its efficacy in the treatment of persistent PH of the newborn,[40] and its safety and possible efficacy during long-term therapy in older children with PH.[41] By prolonging cGMP levels during iNO-induced vasodilation, PDE-5 inhibitors may be useful to augment the response to iNO therapy or to prevent rebound PH after abrupt withdrawal of iNO. In a study of 25 infants with chronic lung disease and PH (18 with BPD), prolonged sildenafil therapy as part of an aggressive program to treat PH was associated with improvement in PH by echocardiogram in most (88%) patients without significant rates of adverse events.[38] Although the time to improvement was variable, many patients were able to wean off mechanical ventilator support and other PH therapies, especially iNO, during the course of sildenafil treatment without worsening of PH. The recommended starting dose for sildenafil is 0.5 mg/kg/dose every 8 hours, and systemic blood pressure should be closely monitored. If there is no evidence of systemic hypotension, this dose can be gradually increased over 2 weeks to achieve desired pulmonary hemodynamic effect or a maximum of 2 mg/kg/dose every 6 hours.

Bosentan, a nonselective endothelin receptor antagonist, is commonly used in older patients with PH. A retrospective study suggested that bosentan may be safe and effective for the treatment of PH in children as young as 9 months,[42] but data are limited to case reports regarding its use in BPD infants. Monthly liver function testing is required to monitor for hepatotoxicity. CCBs benefit some patients with PH, and short-term effects of CCBs in infants with BPD have been reported.[43,44] Nifedipine can acutely lower pulmonary artery pressure and PVR in children with BPD; however, some patients were acutely hypoxemic during this study, and the effects of nifedipine on pulmonary artery pressure were not different from the effects of supplemental oxygen alone. In comparison with an acute study of iNO reactivity in infants with BPD, the acute response to CCBs was poor and some infants developed systemic hypotension. We generally use sildenafil or bosentan for chronic therapy of PH in infants with BPD.

Table 3. PH Drugs in BPD.

- Inhaled NO (5-20 ppm)
- Sildenafil (0.5-2 mg/kg/dose q 6-8 hours)
- Bosentan (1/4 tab daily initially, then BID)
- Prostacyclin analogues:
  - Epoprostenol (Flolan; IV)
  - Inhaled iloprost
  - Remodulin (treprostinil; IV, SQ, inhaled)
- Milrinone

Intravenous prostacyclin analogues (PGI_2; epoprostenol, treprostinil) therapy has been used extensively in older patients with severe PH, and has been shown to improve survival of patients with advanced disease. PgI_2 has been used in some infants with BPD and late PH, but concerns regarding its potential to worsen gas exchange due to increased ventilation/perfusion mismatching in the setting of chronic lung disease and systemic hypotension have limited its use in this setting. Ongoing work with

subcutaneous infusions of treprostinil suggests that this may be a safe and effective strategy for severe disease. Although another stable PgI_2 analogue, iloprost, is available for inhalational use, the need for frequent treatments (6 to 8 times daily) and occasional bronchospasm may be significant factors restricting its use in the setting of BPD.

Currently, there is limited evidence on how long these therapies need to be continued. Often, many infants are discharged from the NICU on these medications and followed up by pediatric pulmonologists or centers focusing on PH. If PH gradually resolves with lung growth as expected, the medications may be either 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 first to be halted. In addition to close monitoring of pulmonary status, infants with BPD and PH should be followed by serial echocardiograms, which should be obtained at least every 2 to 4 weeks with the acute initiation of therapy, and at 4- to 6-month intervals with stable disease. Abrupt worsening of PH may reflect several factors, including the lack of compliance with oxygen therapy or medication use, but can be related to the progressive development of pulmonary vein stenosis or veno-occlusive disease. Repeat cardiac catheterization may be indicated for patients being treated for PH with vasodilator therapy who experience clinical deterioration, worsening PH by echocardiogram, or when echocardiogram measurements fail to provide adequate hemodynamic assessment of sicker patients. We recommend weaning medications with serial normal or near-normal echocardiogram findings, and that the addition of biomarkers such as pro-NT brain natriuretic peptide levels may be useful for long-term follow-up.

CONCLUSION

In summary, PVD and PH contribute to the pathophysiology and cardiorespiratory outcomes of infants with BPD. Data are extremely limited regarding many aspects of the care of PH in BPD, including the need to learn more about its natural history and prevalence, mechanisms that cause PH or contribute to progressive disease, and the relative risks and benefits of current therapeutic strategies. Although new therapies are now available for the treatment of PH, their role in the clinical care of severe BPD and improving long-term outcomes requires more thorough investigation.

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