Pulmonary Hypertension in Established Bronchopulmonary Dysplasia

Physiologic Approaches to Clinical Care

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KEYWORDS

- Oxygen • Hypoxia • Cardiopulmonary interaction
- Hypoxic pulmonary vasoconstriction

KEY POINTS

- Strong laboratory and clinical data suggest that antenatal factors, such as preeclampsia, chorioamnionitis, oligohydramnios, and placental dysfunction leading to fetal growth restriction, increase susceptibility for bronchopulmonary dysplasia (BPD)-associated pulmonary hypertension (PH) after premature birth.
- Early echocardiogram findings of pulmonary vascular disease during the first postnatal week are strongly associated with short-term and long-term complications of prematurity, including high risk for developing BPD, late PH, and a more severe respiratory course with worse long-term outcomes.
- Mechanisms contributing to PH in infants with BPD include high pulmonary vascular tone and vasoreactivity in response to acute or intermittent hypoxia, abnormal lung vascular growth, and vascular structural remodeling.
- In addition to pulmonary vascular disease, abnormalities in lung mechanics and gas exchange, right and left ventricular dysfunction, and shunts across the ductus arteriosus and atrial septum contribute substantially to the development and progression of PH in infants with BPD.
- Echocardiogram metrics and serial assessments of NT-proBNP provide useful tools to diagnose and monitor clinical course during the management of BPD-associated PH, as well as monitoring for such complicating conditions as left ventricular diastolic dysfunction, shunt lesions, and pulmonary vein stenosis.
- Therapeutic strategies should include careful assessment and management of underlying airways and lung disease, cardiac performance, and systemic hemodynamics, prior to initiation of PH-targeted drug therapies.

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INTRODUCTION

Major advances in perinatal and *neonatal intensive care* unit (NICU) care have dramatically improved survival of extremely premature infants in the modern post-surfactant era. Despite striking improvements in diagnostics, therapeutics, and bedside care, however, preterm newborns remain at high risk for significant mortality and morbidities, which include the development of bronchopulmonary dysplasia (BPD), the chronic lung disease of prematurity.[1–4] BPD is perhaps the most common sequelae of premature birth, with the incidence remaining at nearly 45% for infants born prior to 29 weeks gestational age, and this rate has not improved over the past decades.[4–7] Importantly, there has been a growing proportion of infants developing more severe forms of BPD, which is most likely due to the increase in survival of extremely premature newborns at 22 to 24 weeks gestation, who are particularly associated with high risk for BPD due to greater fragility of the developing lung at such an early period of lung development.[7]

There has also been a growing recognition of the clinical importance of pulmonary vascular disease (PVD) and the impact of pulmonary hypertension (PH) on the clinical course and outcomes of preterm infants with BPD.[8–11] Even in their original description of BPD in 1967, Northway and colleagues state that "...(of infants with late deaths) all patients had striking cardiomegaly and right ventricular hypertrophy (and that) the pathogenesis of cor pulmonale is puzzling..."[1] PH has long been associated with poor survival in preterm infants with BPD even beyond the severity of underlying lung disease. A diagnosis of PH that persists beyond the first few months of life was linked with mortality rates as high as 40% to 50%, in 1980,[11] which is identical to rates that have been reported in very recent studies as well.[11–17] Importantly, prospective cohort studies show the presence of echocardiographic evidence of PH in 14% to 25% of preterm infants at 36 weeks' post menstrual age (PMA), with especially high rates of PH identified in infants with severe BPD (range: 29%–58%).[11,13,14,16] Finally, as highlighted in a report from the registry of the multicenter Pediatric Pulmonary Hypertension Network, BPD-PH has been recognized as a major public health issue as one of the most common causes of pediatric PH, accounting for nearly 25% of cases in the Registry.[18]

Thus, despite major advances in perinatal and NICU care that have led to improved survival and changes in the nature of BPD over the decades, the diagnosis of PH and its management continue to be a major challenge in infants with established BPD. With evolving or established BPD, PH is often clinically manifested by persistent respiratory distress, the sustained need for high levels of respiratory support, recurrent cyanotic episodes, and other signs. In some infants, the presence of PH with milder lung disease at the time of NICU discharge is associated with high risk for progressive PH, late respiratory problems, the need for hospital readmissions, exercise intolerance, and other morbidities. Although recent recommendations from American Heart Association (AHA) and American Thoracic Society (ATS) guidelines,[19] the Pediatric Pulmonary Hypertension Network[20] and others have outlined current consensus strategies for the monitoring, evaluation, and care of BPD-associated PH, there remains clear acknowledgment that the lack of physiologic, pharmacologic, and randomized clinical trial data limit our current care, and that there is a striking need for further research to better enhance short-term and long-term outcomes. This review provides a brief overview of current understanding of BPD-associated PH, with particular focus on disease pathogenesis and the important role of defining underlying physiologic phenotypes that include cardiac, lung, and lung vascular interactions, which lead to targeted strategies that optimize clinical care.

PATHOGENESIS OF PULMONARY VASCULAR DISEASE IN BRONCHOPULMONARY DYSPLASIA

In addition to central and small airways disease, BPD is characterized by an arrest of vascular and alveolar growth, which contributes to increased susceptibility for the development of PH. However, mechanisms underlying the pathogenesis of PH in BPD are likely multifactorial, and reflect the impact of the interplay between antenatal and postnatal injuries on lung vascular growth, pulmonary arterial remodeling, and vasoreactivity, and contribute to the "vasculopathy" of BPD, which includes the development of early and late PH (**Fig. 1**).

Laboratory and clinical studies demonstrate that early disruption of angiogenesis during the critical period of active lung vascular development during late gestation and after premature birth impairs growth of the distal airspace, leading to high risk for PH as well as BPD (the "vascular hypothesis" of BPD) (**Figs. 2** and **3**).[21–25] Previous studies demonstrate that early disruption of lung vascular growth due to hemodynamic stress *in utero* or by treatment with anti-angiogenesis agents during the early postnatal period cause PH and also impair alveolarization.[21,26,27] For example, partial occlusion of the ductus arteriosus in late gestation fetal sheep reduces vessel density and induces pulmonary artery smooth muscle thickening but also reduces septation and alveolar growth.[28] These changes are associated with severe PH at birth with poor vasodilator responsiveness to mechanical ventilation and oxygen therapy.[28–30]

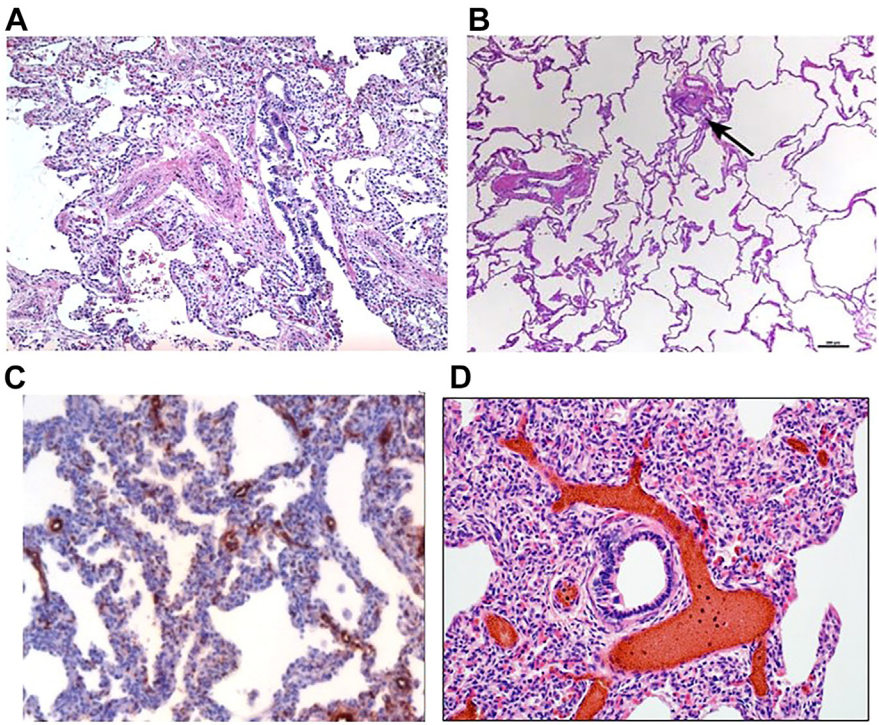

Fig. 1. Diverse histopathologic features of the lung circulation in BPD-associated PH. Pulmonary vascular pathology includes thickening of the vascular media with adventitial thickening (*A*), reduced vascular density with decreased alveolar surface area (*B*), dysmorphic growth of distal lung microvasculature. *Arrow* indicates small pulmonary artery (*C*), and prominent intrapulmonary bronchopulmonary anastomotic vessels (*D*).

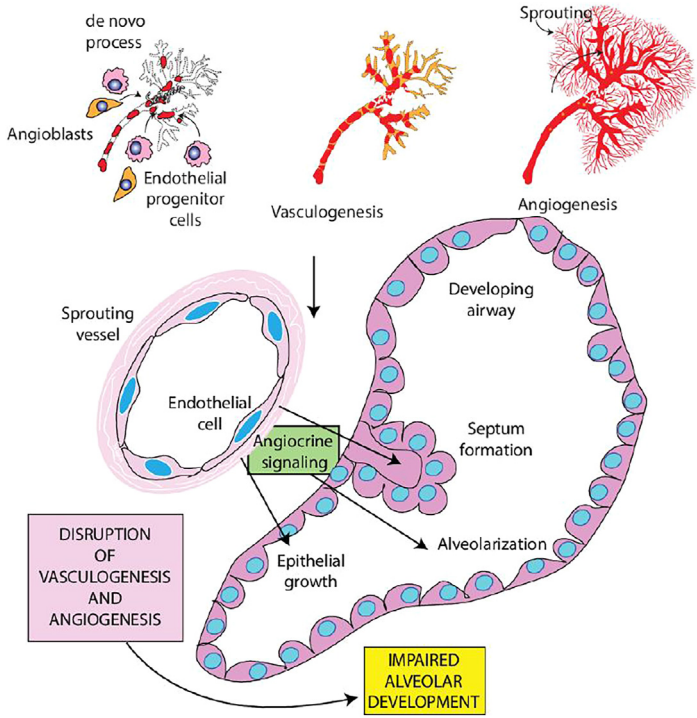

Fig. 2. Schematic illustration of the role of disruption of endothelial and epithelial cell interactions during lung development in the pathogenesis of BPD. The top panel shows normal progression of vessel formation through vasculogenesis and angiogenesis. The bottom panel shows the "angiocrine" signaling between endothelium from a developing vessel and airway. (Image Courtesy of Dr. Satyan Lakshminrusimha.)

Brief treatment with angiogenesis inhibitors shortly after birth, including drugs that specifically target vascular endothelial growth factor-A (VEGF-A) signaling, were shown to cause severe PH.[21,27] Thus, in addition to causing PH, early disruption of lung angiogenesis impairs alveolarization, suggesting an important role of vascular

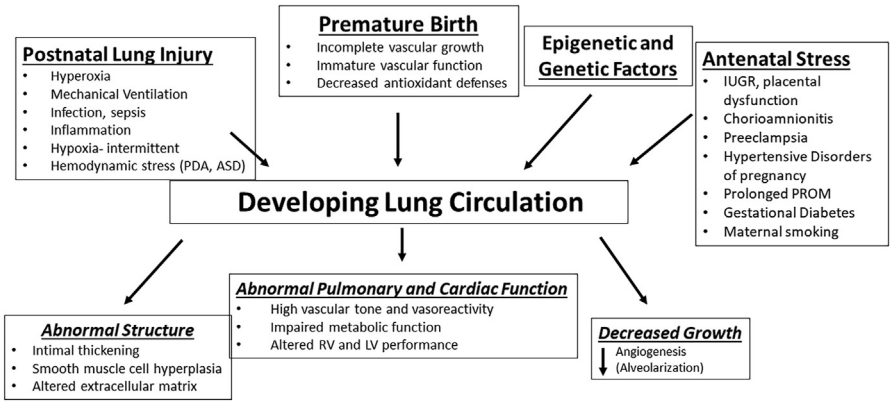

Fig. 3. Multifactorial mechanisms contributing to the pathogenesis of pulmonary vascular disease in BPD.

growth and "angiocrine" signaling for normal development of the distal airspace.[26,31] (see Fig. 2; Fig. 4).

Clinically, these laboratory-based findings were reflected from human autopsy findings which demonstrate decreased lung VEGF expression and striking evidence of lung simplification and a dysmorphic vasculature from preterm infants dying with BPD, providing clinical evidence supporting the important role for angiogenesis in the pathobiology of BPD.[24] Laboratory studies further show that endothelial-derived products promote alveolar epithelial growth and septation, highlighting the important role of "angiocrine signaling" during normal lung development, and support the hypothesis that early therapeutic strategies that preserve lung endothelial survival and function in at risk infants may decrease the incidence or severity of BPD and BPD-PH.

Such factors as the severity of prematurity, low birthweight, the diagnosis of small for gestational age, oligohydramnios, and other markers reflecting antenatal stress have been strongly associated with high risk for BPD-associated PH.[32–42] Abnormal placental vascular structure with evidence of placental hypoperfusion is strongly associated with neonatal outcomes of intrauterine growth restriction (IUGR) and increased risk for the development of BPD and BPD- PH.[33–37] Animal models of antenatal stress that mimic chorioamnionitis (inflammation), preeclampsia, and severe IUGR have been shown as sufficient to impair vascular growth and induce long-standing postnatal PH independent of exposure to well-established postnatal stresses, including hyperoxia and ventilator-induced lung injury.[43–45] Clinical studies have further shown that antenatal factors identified at birth,[42,46] cord blood biomarkers of impaired angiogenesis,[47,48] and early echocardiography findings of PH in the days after birth are strongly linked to high risk of BPD, PH, prolonged NICU days, and even late respiratory outcomes during early childhood.[49–56] Thus, antenatal determinants not only cause acute PH and hypoxemic respiratory disease that often contributes to the need for prolonged invasive ventilation and a severe NICU course, but also injury *in utero* can cause sustained disruption of lung and vascular structure throughout infancy, reflecting the sustained impact of fetal programming on the late clinical course. Antenatal stresses, including chorioamnionitis and preeclampsia, in preterm neonates contribute to BPD risk.[38,39] Multiple molecular mechanisms linking antenatal stress to BPD pathogenesis have been identified as potential therapeutic targets for disease

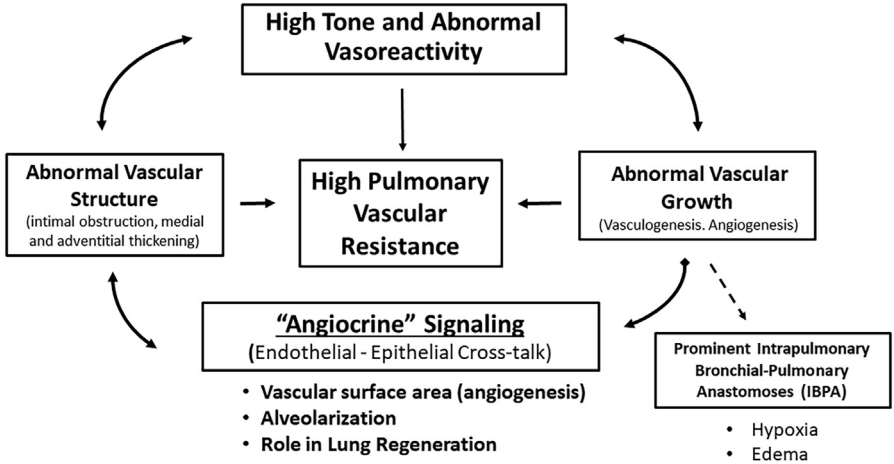

Fig. 4. Physiologic mechanisms contributing to pulmonary vascular disease and the development of PH in BPD.

prevention, including the potential role for augmentation of hypoxia-inducible factor (HIF), insulin-like growth-1 factor (IGF-1), and VEGF signaling pathways.[57–60] Overall, these findings suggest that angiogenesis is necessary for alveolarization during normal lung development, and that injury to the developing pulmonary circulation during a critical period of lung growth can contribute to reduced lung surface area.

Clinically, echocardiography-confirmed signs of early PH and delayed vascular transition are strongly associated with a higher risk for the subsequent development of BPD, late PH, and increased mortality.[49–57,61,62] A prospective study demonstrated that early echocardiographic evidence of increased pulmonary artery pressure even without evidence of severe PH, RV dysfunction, or severe hypoxemia at day 7 is associated with high risk for the subsequent development of BPD and its severity, the presence of PH at 36 weeks' PMA, and late respiratory outcomes during early childhood.[16,49] The combination of the need for invasive ventilation and PH by echocardiogram at postnatal day 7 is especially strongly associated with late morbidities.[49] Thus, early PVD as demonstrated by echocardiographic signs of PH at day 7 of life may provide a useful "biomarker" for identifying preterm infants at high risk for developing severe BPD, late PH, and chronic respiratory disease during early childhood.

In a landmark study, Dr Arjaans and colleagues further examined the idea of whether early PH in preterm infants born at less than 30 weeks gestion during the first week of life is associated with high risk for BPD and other outcomes.[53] This team performed echocardiograms to examine the incidence and nature of early PH, and to then characterize subsequent outcomes. The diagnosis of early PH was made according to standard echocardiographic metrics during the first 3–10 days of postnatal life. Early PH, which was diagnosed in 55% of subjects, was further characterized by 3 phenotypes: 1) Persistent pulmonary hypertension of the newborn (PPHN), as defined by the presence of high pulmonary vascular resistance (PVR) with right-to-left extrapulmonary shunting; 2) PH due high flow as reflected by large left-to-right ductal shunts; and 3) PH without PPHN physiology or high flow. They report that early PH within each of these physiologic groups was associated with severe BPD and/or death before 36 weeks' postmenstrual age, and that the PPHN group had the worst outcomes. Whether specific therapies to match these distinct physiologies in preterm infants with early PH can reduce BPD or BPD-PH remains unknown, but their findings lead to the speculation that selective strategies that limit injury to the pulmonary vasculature during acute hypoxemic respiratory failure may attenuate the subsequent development of BPD or BPD-PH.

Postnatal lung injury due to inflammation and oxidative stress due to hyperoxia and ventilator-induced lung injury further impairs growth, structure, and function of the developing lung circulation after premature birth.[63] Endothelial cells are particularly susceptible to oxidant injury caused by hyperoxia and inflammation, leading to cellular dysfunction. Small pulmonary arteries rapidly undergo striking changes, with smooth muscle cell proliferation, maturation of immature pericytes into mature smooth muscle cells, and increased vascular matrix production from activated fibroblasts.[64,65] In addition to reduced vascular surface area, structural changes in the lung vasculature due to narrowing of the vessel diameter and decreased vascular compliance contribute further to high PVR.[66,67] (see **Fig. 4**).

The adverse effects of chronic hypoxia on the progression of PH in diverse settings, including BPD-PH, are well-established; however, several recent studies now suggest a strong association of even mild or intermittent hypoxia (IH) in its pathogenesis early in the postnatal course after birth. In comparison with historic controls, simply increasing oxygen saturation targets to a slightly higher range (90%–95% vs 88%–92%) during the first weeks of life was associated with a striking reduction in PH in

preterm infants.[68] Recent studies have further shown that IH beginning in the first week after birth was associated with an increased risk of developing severe BPD in a large and multi-center cohort of extremely preterm infants.[69] Longer duration of intermittent hypoxemic events was associated both with a diagnosis of BPD-PH and with death among infants with BPD-PH. Gentle and co-workers confirmed these findings in a retrospective case-control single-center study,[70] further suggesting that minimizing the frequency of even brief episodes of hypoxia early in the clinical course may reduce the risk for BPD-PH and improve long-term respiratory outcomes among extremely preterm infants.

Similarly, hemodynamic stress is very well-established as a major cause of PH, especially in the setting of congenital heart disease, but whether high flow through the patent ductus arteriosus (PDA) increases the risk for BPD or BPD-PH in extremely low gestational age newborns has been uncertain. Recent studies suggest that early PH due to high left to right shunt across the PDA is strongly associated with subsequent BPD.[53] A retrospective case-control study showed that in the setting of extremely preterm infants on respiratory support on postnatal day 28, both the presence and a longer duration of a PDA was associated with the development of BPD-PH at NICU discharge.[71] This association of prolonged exposure to a hemodynamically significant PDA being linked with a greater risk for BPD-PH was demonstrated in data from a meta-analysis by using a Bayesian approach to data analysis.[72] These studies suggest that early closure of the PDA, especially in the setting of a reduced pulmonary vascular bed, may be a targetable strategy for attenuating BPD-PH in at-risk infants.

In addition to the potential adverse pulmonary vascular impact due to high flow through the PDA, Vyas-Read and colleagues have shown that increased left-to-right flow through a persistent atrial septal defect (ASD) was more common in preterm infants who developed BPD-PH than matched subjects without an ASD.[73] Observational studies suggest that ASD closures in preterm infants with severe BPD can lead to improvements in cardiopulmonary course.[74,75] Thus, based on data from these studies and others, the preterm lung circulation as characterized by a reduced surface area, with increased vascular tone and an enhanced myogenic response, may increase susceptibility for additional vascular injury due to the hemodynamic stress of prolonged exposure to a PDA or ASD, suggesting that early interventions may potentially prevent the presence or severity of BPD-PH in susceptible preterm infants.

SELECTED PHYSIOLOGIC ASPECTS OF BRONCHOPULMONARY DYSPLASIA-PULMONARY HYPERTENSION

Although it is plausible that PH is simply a marker of more advanced lung disease, high pulmonary artery pressure clearly contributes to the disease severity in many infants with severe BPD, causing poor right ventricular function, impaired cardiac output, limited oxygen delivery, worsened pulmonary edema, and perhaps a higher risk of sudden death. Physiologic abnormalities of the pulmonary circulation in BPD include elevated PVR and abnormal vasoreactivity, as evidenced by the exaggerated vasoconstrictor response to acute hypoxia (**Fig. 5**). As studied during cardiac catheterization, acute exposure to hypoxia causes large elevations in pulmonary artery pressure, even in infants with modest basal levels of PH.[76] This study further showed that the degree of hypoxia that increases PH can be fairly modest in many patients, and that achieving oxygen saturations above 92% to 94% was effective in lowering pulmonary artery pressure. The current recommendation for treatment of patients with BPD and PH is to avoid oxygen saturations below 92%, and to maintain levels of 94% to 96%.

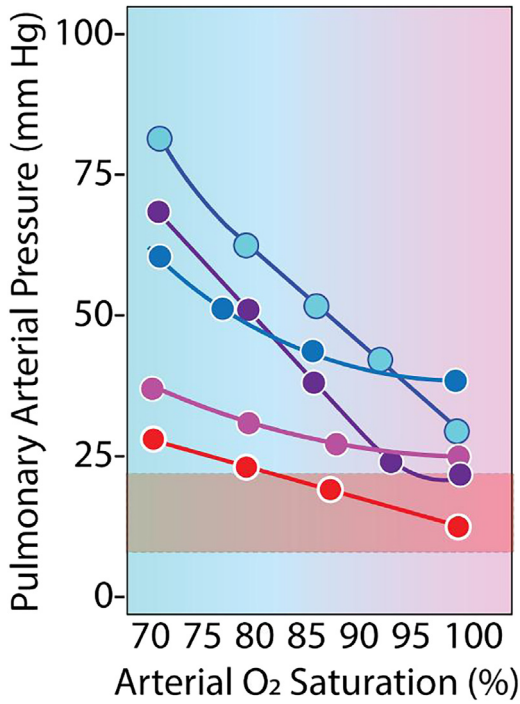

Fig. 5. Schematic diagram showing acute pulmonary vasoreactivity during brief exposure to hypoxia in patients with BPD-PH demonstrating variability in baseline pulmonary arterial pressure and response to hypoxemia.[76]

Whether the risk of attaining higher oxygen saturations is to induce more lung injury remains unconfirmed, but the adverse effects of hypoxemia are clear. Strategies that maintain lower pulmonary artery pressure or limit injury to the pulmonary vasculature during the treatment of acute hypoxemic respiratory failure may attenuate the subsequent development or contribution of PH to BPD.

In addition to PH, clinical studies have also shown that metabolic function of the lung circulation is impaired in BPD-PH, as reflected by the lack of pulmonary clearance of circulating norepinephrine across the lung.[77] The lung circulation normally clears 20% to 40% of circulating norepinephrine during a single passage through the lung, but transpulmonary measurements of circulating norepinephrine levels in infants with severe BPD performed during cardiac catheterization had negligible clearance and a net production of norepinephrine across the pulmonary circulation. Whether impaired metabolic function of the lung contributes to the pathophysiology of BPD by increasing circulating catecholamine levels, or if it is simply a marker of endothelial dysfunction due to pulmonary vascular disease, remains unknown. It has been speculated that high catecholamine levels may lead to LV diastolic dysfunction or hypertrophy (LVH) or systemic hypertension, which are known complications of BPD.

DIAGNOSTIC STRATEGIES FOR BRONCHOPULMONARY DYSPLASIA-PULMONARY HYPERTENSION

Due its non-invasive nature, well-standardized approaches and verified metrics, and the ease of its bedside use, the echocardiogram provides a useful approach for

diagnosing PH and defining the severity of disease, identifying anatomic defects, characterizing the presence and nature of shunt lesions and pulmonary vein stenosis (PVS), and assessing left ventricular size and performance. The striking growth of world-wide programs in targeted neonatal echocardiography has provided remarkable opportunities for providing precise and serial physiologic hemodynamic assessments which better define physiologic phenotypes, responses to therapeutic interventions, and long-term outcomes. Specific echocardiographic parameters and their relative utility remain under study as discussed in recent review publications.[78–84] Recommendations of the PPHNet regarding the timing of obtaining diagnostic or screening echocardiograms are summarized in **Fig. 8** below.

Cardiac catheterization is considered the "gold standard" for more precise characterization of PH and cardiac performance by direct measurements of pulmonary hemodynamic to better determine disease severity, assess acute vasoreactivity testing (AVT), and identify associated cardiovascular co-morbidities, such as anatomic cardiac lesions, systemic-pulmonary collateral vessels, pulmonary venous obstruction, and left heart dysfunction. Although in experienced centers, the complication rates of catheterization are relatively low,[85] careful consideration must be given due to its invasive nature and potential risks in sick premature infants and patient selection must be considered carefully. As a result, PH-specific therapy in the BPD-PH population is most often initiated as based on clinical and echocardiogram-based findings of PH without cardiac catheterization. In the setting of BPD-PH, the procedure is generally reserved to enhance clinical decision-making in the following settings: 1) clinical and echocardiogram findings of sustained PH despite optimized respiratory and cardiac care; 2) considerations of adding another agent in patients already under treatment with a single initial PH-targeted drug with or without inhaled NO; 3) clinical suspicions of associated cardiovascular problems, including left ventricular dysfunction, pulmonary venous obstruction, the need to better define the contributions of high flow due to left-to-right shunts due to PDA, ASD, arterio-venous malformations, or other vascular lesions; 4) worsening pulmonary edema and increased diuretic need after the initiation of PH drug therapy, suggesting left ventricular diastolic dysfunction and/or pulmonary PVS; and 5) considerations of the need for chronic use of systemic prostanoid therapy.[20]

Functional studies such as AVT can help guide the selection of drug therapy, as older subjects with positive AVT are often preferentially treated with calcium channel blockade, but experience with AVT is exclusively based on studies in the setting of World Symposium of Pulmonary Hypertension (WSPH) Group 1 disease. In a recent study of BPD-PH, positive AVT was more strongly associated with better late outcomes than baseline pulmonary hemodynamics.[86] Cardiovascular MRI has been used to assess cardiac performance in PH as well, often in conjunction with cardiac catheterization, and is particularly useful as a non-invasive approach to diagnosing PVS.[87–90]

In addition to the use of serial echocardiograms and clinical assessments of cardiovascular and pulmonary disease, circulating changes in brain-type natriuretic peptide (BNP) or N-terminal cleavage product (NT-pro-BNP) levels are useful in monitoring disease course and the response to clinical therapies over time. In some centers, serum BNP or NT-pro-BNP levels are used to screen preterm infants for PH, and if elevated, an echocardiogram is subsequently performed. Most clinicians use changes in these biomarkers to supplement echocardiogram findings to better enable clinical decision-making to fine-tune cardiorespiratory and drug interventions. BNP and NT-pro-BNP are not specific for right ventricular disease alone, however, and may be elevated in the setting of high-flow shunts or with LV stress.

SELECTED ASPECTS OF CARE

The management of BPD-associated PH includes defining the relative contributions of airway, lung, cardiac, and pulmonary vascular disease to the pathophysiology of PH (**Figs. 6** and **7**).

Respiratory

An overall approach for screening and managing BPD-PH as developed by the Pediatric Pulmonary Hypertension Network (PPHNet) is outlined in **Fig. 8** and is related to consensus recommendations from joint AHA and ATS guidelines (see **Fig. 8**).[20] The initial clinical strategy for the management of PH in infants with BPD begins with treating the underlying lung disease, including 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 bronchial reactivity, improving lung edema, airway function, lung mechanics and lung volumes, assessing the need for non-invasive or invasive support, and any other intervening factors. Periods of acute hypoxemia, whether intermittent or prolonged, can often contribute to late PH in BPD. A sleep study may be necessary to determine the presence of noteworthy episodes of hypoxemia and whether hypoxemia has predominantly obstructive, central, or mixed causes. Additional studies that may be required include flexible bronchoscopy for the diagnosis of anatomic and dynamic airway lesions (such as tracheomalacia) that can contribute to hypoxemia and poor clinical responses to oxygen therapy. Upper gastrointestinal series, pH or impedance probe, and swallow studies may be indicated to evaluate for gastro-esophageal 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 fraction of inspired oxygen (FiO_2) despite conservative treatment, strong consideration should be given to chronic mechanical ventilatory support to halt progression of PH.

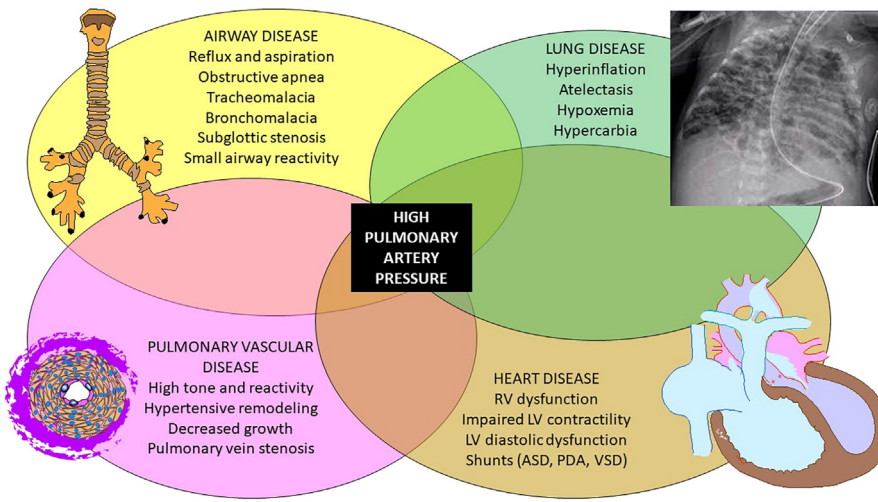

Fig. 6. Pathophysiologic mechanisms underlying BPD-associated PH: potential effects of heart, lung, and vascular interactions on elevated pulmonary artery pressure. (Image Courtesy of Dr. Satyan Lakshminrusimha.)

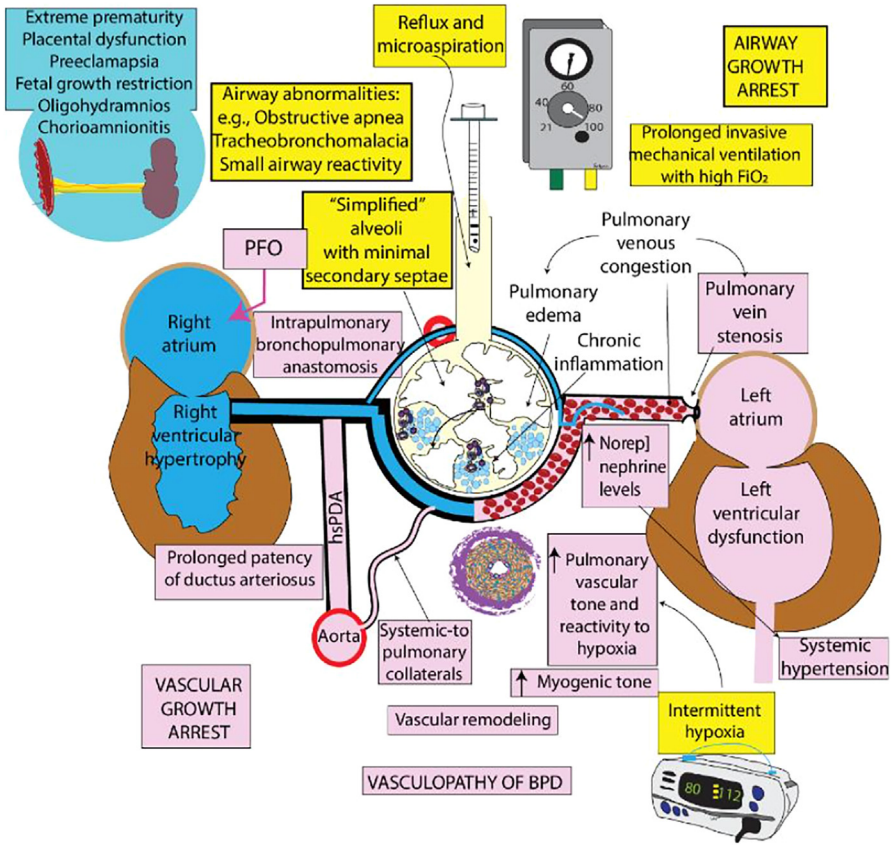

Fig. 7. Schematic illustrating diverse interactive mechanisms that can contribute to the pathophysiology of BPD-PH. Vascular lesions are shown in pink boxes and airway lesions are shown in yellow boxes. (Image courtesy of Dr. Satyan Lakshminrusimha.)

ASSOCIATED CARDIOVASCULAR ABNORMALITIES IN BRONCHOPULMONARY DYSPLASIA-PULMONARY HYPERTENSION

Cardiovascular abnormalities associated with BPD include (LVH, systemic hypertension, and the development of prominent systemic to pulmonary collateral vessels (see Fig. 7). An early report described infants with severe BPD and LVH in the absence of right ventricular hypertrophy and suggested that left ventricular dysfunction may contribute to recurrent edema in BPD.[91] Systemic steroid treatment can cause LVH, and in this setting, LVH tends to be transient, resolves with cessation of steroid treatment, and is of uncertain clinical importance. A high incidence of systemic hypertension has also been recognized as a cardiovascular complication of BPD, but its cause remains obscure.[92] Systemic hypertension may be mild, transient, and respond readily to pharmacologic treatment; however, the rise in blood pressure can be striking in some cases. On occasion, further evaluation of such infants shows considerable renal vascular or urinary tract disease. Whether the high incidence of systemic hypertension in BPD reflects altered neurohumoral regulation or increased catecholamines, angiotensin, or antidiuretic hormone levels is not known. Prominent bronchial or other systemic to pulmonary collateral vessels were noted in early morphometric studies of

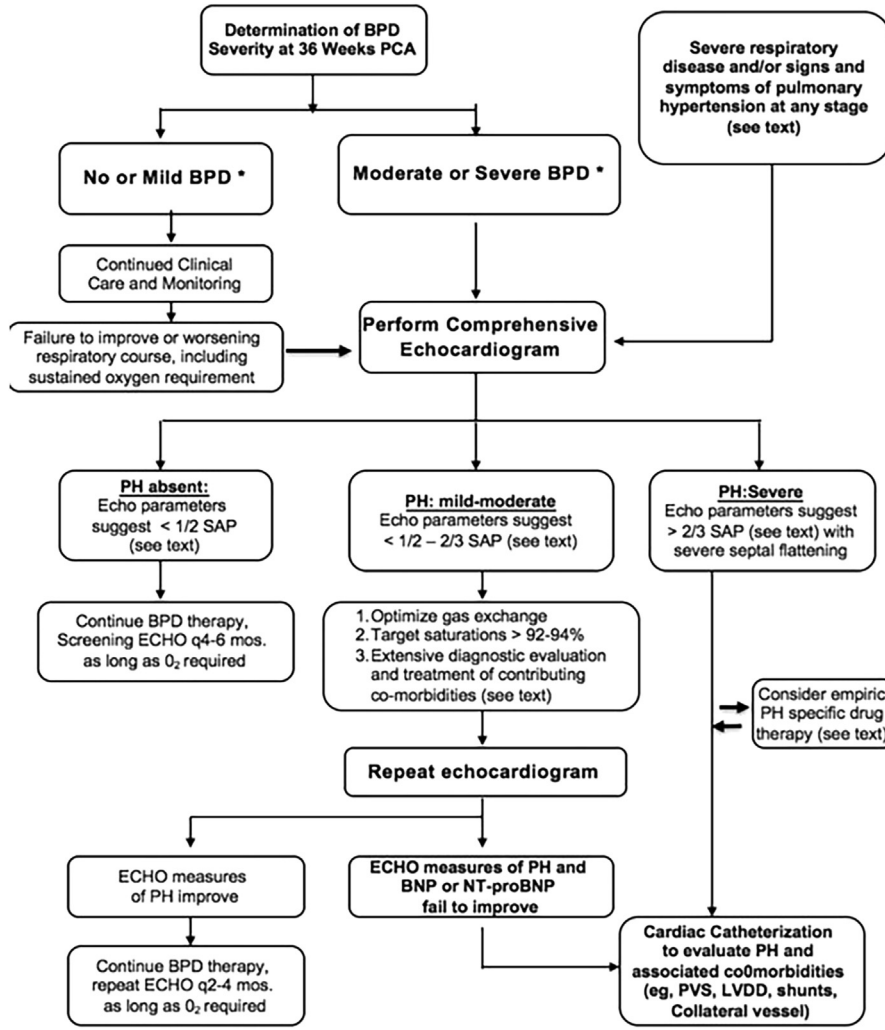

Fig. 8. Approach to the diagnosis and management of BPD-associated PH.[20]

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 appreciable shunting of blood flow to the lung, causing edema and the need for higher FiO_2. Some infants have improved after embolization of large collateral vessels, as reflected by a reduced need for supplemental oxygen, ventilator support, or diuretics, but the actual contribution of collateral vessels to the pathophysiology of BPD is poorly understood.

Although causality cannot be assumed, available data show that prolonged exposure to a post-tricuspid valve high-volume and high-pressure shunt, such as a hemodynamically significant moderate to large left-to-right PDA, ventricular septal defect (VSD), or ASD, increases the likelihood of the development of PH related to high pulmonary flow, over-circulation, and pulmonary vascular remodeling. In these patients, decreasing the PVR by using pulmonary vasodilators can further increase left-to-right

shunting and induce systemic hypotension with reduced RV perfusion, which can worsen RV performance. This emphasizes the need for monitoring PH in high-risk preterm infants with prolonged exposure to post-tricuspid valve shunts and incorporating the risk of developing or worsening PH into the clinical decisions regarding the definitive closure by catheter occlusion or surgery.

ASDs are characterized by high-volume and low-pressure pre-tricuspid valve shunts, and may contribute to late PH.[93–95] Some studies have demonstrated improvement in PH and respiratory signs after ASD closure, suggesting that earlier closure of ASDs or PDAs may hasten recovery from BPD-PH and reduce the need for late PH-targeted drug therapies. PVS is an additional cause of late PH in BPD (**Fig. 9**), usually presenting beyond term corrected age in premature infants beyond term corrected age.[96,97]) PVS can present with the onset or worsening of PH by echocardiogram, which may or may not be initially accompanied by progressive pulmonary edema with an increasing need for higher FiO_2 or diuretic requirement, especially in

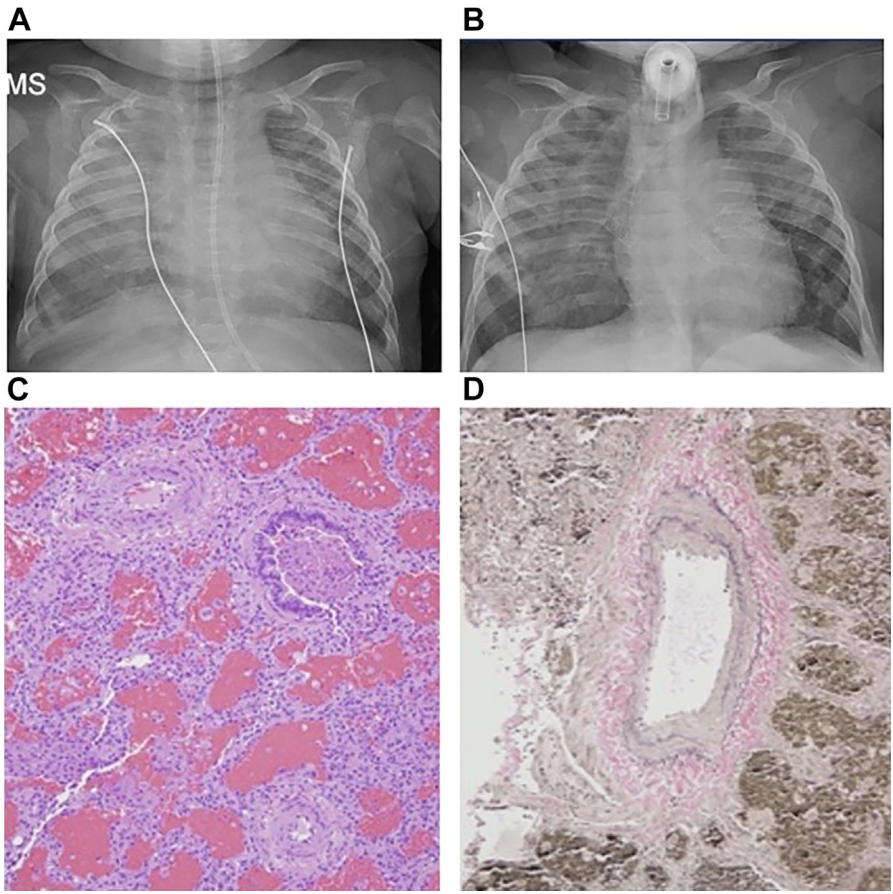

Fig. 9. Radiologic and histopathologic features of pulmonary vein stenosis (PVS) in BPD-associated PH. The upper panel represents CXR signs of pulmonary edema before (*A*) and after (*B*) stent placement. The lower panel shows lung histopathology from an infant with PVS that demonstrates striking pulmonary arterial remodeling with acute hemorrhage (*C*) and muscularization of pulmonary veins (*D*).

response to PH vasodilator therapy (Fig. 10). Diagnosis can be suggested by echocardiogram, followed by cardiac MRI or catheterization, and PH drugs should be used very cautiously due to the risk of worsening respiratory distress. Multiple PVS sites are associated with worse outcomes than single vein involvement.[97] Current treatment approaches include PVS dilation and stenting with close monitoring with serial echocardiograms, imaging scans, and cardiac catheterization to assess disease course. In some centers, sirolimus therapy has been used to abate progressive pulmonary venous obstruction after anatomic interventions.

In addition, there has been a growing recognition regarding the role of left ventricular diastolic dysfunction (LVDD) as a contributor to PH, usually in combination with precapillary disease. LVDD is often clinically suspected in subjects who have persistent or progressive pulmonary edema requiring increasing amounts of diuretic therapy, which is worsened with the addition of PH-targeted drug therapy (see Fig. 10). LVDD can also be associated with a more prolonged ventilator course than patients with BPD-PH who do not have a poorly compliant LV. Mechanisms contributing to LVDD in preterm infants are uncertain, but may be related to early myocardial injury, altered LV development systemic hypertension.[98–100] When diagnosed, afterload reduction of the LV with milrinone followed by chronic angiotensin-converting enzyme inhibitors (ACEi) are often used.[101] Close monitoring of renal function is important to avoid acute kidney injury, especially in the setting of aggressive diuretic use with ACEi therapy.

Ambulatory Care Post-Neonatal Intensive Care Unit Discharge

Most patients with "resolving" BPD show progressive increases in growth parameters and follow their growth curves for body weight and length. Patients who show evidence of poor growth, lack of respiratory improvement, intermittent tachypnea or cyanosis, or additional signs of PH by echocardiogram may require more extensive studies. First, prolonged, or intermittent periods of acute hypoxia are often important causes of late PH in BPD. Clinical evaluations of such patients should include prolonged measurements of oxygen saturation by pulse oximeter while awake, asleep, and during feeds. Brief assessments of oxygenation ("spot checks") are not sufficient for decisions on the level of supplemental oxygen needed. As described earlier, targeting oxygen saturations to 92% to 94% should be sufficient to prevent the adverse

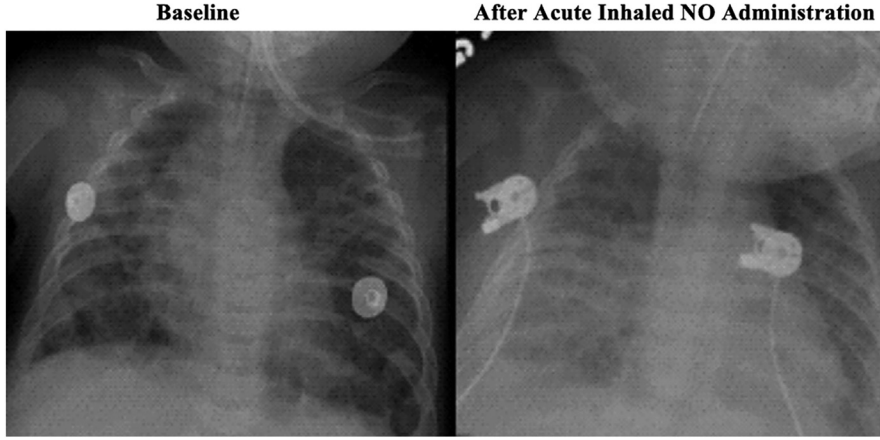

Fig. 10. Inhaled NO increases pulmonary edema in a BPD patient with LV diastolic dysfunction.

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 hypoxemia and whether apnea has predominantly obstructive, central, or mixed causes. It is not uncommon to uncover unsuspected causes of airway obstruction in patients with BPD and persistent PH, such as tonsillar and adenoidal hypertrophy, vocal cord paralysis, subglottic stenosis, tracheomalacia, and others. Additional studies that may be required include flexible bronchoscopy for the diagnosis of anatomic and dynamic airway lesions (such as tracheomalacia) that may contribute to hypoxemia and poor clinical responses to oxygen therapy. Growth failure during home oxygen therapy may be the result of poor parental compliance or premature discontinuation of supplemental oxygen, as previously reported.[27] In this study, nearly one-third of families in a home oxygen program had prematurely discontinued oxygen therapy. Assessments of PH should generally include serial echocardiograms in infants with the diagnosis of BPD, even if stable or rapidly improving, to enable safe discontinuation of PH medications.

The authors recommend serial echocardiograms in patients with moderate or severe BPD, or with past echocardiograms showing the presence of PH. Previous work suggests that with adequate oxygen therapy and related interventions, PH should progressively improve and resolve in most children by 8 to 12 months of age. Cardiac catheterization is reserved for patients with the most severe disease which has not responded to oxygen therapy. The purpose of cardiac catheterization is to rule out anatomic cardiac lesions, especially associated with high flow due to left to right shunts.

Experience suggests that infants with BPD do not tolerate even relatively small atrial or ventricular level shunting and are at high risk of developing more severe PH than other patients. This may be because of the decrease in vascular surface area relative to body size and cardiac output in BPD, and the fact that even mild increases in pulmonary blood flow may represent relatively high shunt. As a result, the authors advise earlier closure of shunt lesions in patients with BPD, especially with the growing development of non-invasive approaches. In addition, cardiac catheterization is useful for the following: to ensure the absence of pulmonary vein stenosis or veno-occlusion; to define the level and severity of PH; to assess vasoreactivity to increased oxygen tension or to assess the response to vasodilator treatment; and to determine whether large systemic to pulmonary collateral vessels are present. Studies of vasoreactivity are helpful to determine the relative safety—that is, lack of systemic hypotension and impaired cardiac contractility—and potential efficacy of PH-targeted drugs, which would be initiated in patients with exceptional PH despite adequate oxygen therapy. Clearly, cardiac catheterization is invasive and reserved for the most severely ill infants who develop PH despite optimal medical management.

Late Pulmonary Hypertension in Adults Born Prematurely

In addition to the need for close follow-up and monitoring throughout infancy and early childhood, multiple investigators have noted late echocardiographic markers of PH that persist into early adulthood.[102] There is growing evidence for PVD in older children and young adults, or "PVD across the lifespan," in which there has been growing evidence for high risk of development of "borderline" PH and abnormal cardiac structure and function in young adults who were born preterm. In addition, cardiac imaging studies of adults born prematurely have shown small LV and RV chamber size with thickened ventricular walls, along with elevated systemic vascular resistance, and a high proportion of adults who develop congestive heart failure at a younger age[103] Clearly, there is a need for close cardiovascular as well as pulmonary function

monitoring throughout the life course. Identification of early risk factors for late cardiorespiratory outcomes is required to design and install personalized preventive treatment strategies.

SUMMARY

In addition to persistent respiratory disease, survivors of premature birth with BPD are at risk of cardiovascular sequelae, including PH, as well as cardiac dysfunction, systemic hypertension, exercise intolerance, and related clinical problems. Early monitoring with serial echocardiograms aids the selection of infants with BPD who are at high risk of cardiovascular morbidity and allows for earlier initiation of treatment after a rigorous diagnostic evaluation. The major treatment of PH in BPD is supplemental oxygen with appropriate levels of respiratory support, but infants with late PH despite adequate treatment require pharmacologic treatment in addition to careful management of underlying respiratory disease. Despite increasing experience with PH-targeted drugs for chronic PH management, strong evidence for selecting specific agents or combinations of agents at diagnosis and for long-term therapy remains limited. Exciting new data suggest that insights into physiologic phenotypes of early PH may provide unique opportunities for clinical trials to address novel interventions to reduce the incidence and severity of BPD and BPD-PH. Finally, better designed and appropriately powered multicenter randomized controlled trials are needed to improve our understanding of disease natural history, response to therapeutic interventions, and optimal endpoints for studies of BPD-PH over the lifespan.

Best Practice Box

- Extremely preterm infants with lung disease requiring late or sustained levels of high respiratory support should be screened early with echocardiograms to detect PH.
- Evaluating airway abnormalities, such as tracheobronchiomalacia, vocal cord paralysis, subglottic stenosis, and small airway hyperreactivity, as well gastroesophageal reflux and aspiration is part of workup for severe BPD with PH.
- Infants with BPD-PH can have intermittent hypoxemia, which may lead to spikes or sustained PH due to increased hypoxic pulmonary vascular reactivity. Targeting SpO_2 in the 92% to 94% with continuous or frequent monitoring to minimize hypoxemia may reduce the risk of PH.
- In addition to strategies that optimize oxygenation, respirator support, and systemic cardiovascular performance, PH-targeted drug therapy, including PDE5 inhibitors and endothelin antagonists, is the mainstay of BPD-PH management. Exacerbations are treated with inhaled nitric oxide and severe and poorly responsive PH despite optimal management may improve with systemic prostanoid therapy.
- Infants with BPD-PH not responding to initial PH-specific drug therapy may require cardiac catheterization to assess severity and phenotype of PH and to evaluate shunts, LVDD, and PVS.
- Preterm infants with BPD-PH have pulmonary vascular disease that persists into adulthood and requires serial pulmonary function testing and cardiovascular monitoring with serial echocardiograms.

DISCLOSURE

The authors report no conflicts of interest related to this chapter.

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