The Left Heart, Systemic Circulation, and Bronchopulmonary Dysplasia: Relevance to Pathophysiology and Therapeutics

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Improved survival at extremes of gestational age (≤25 weeks) has led to an increase in the number of infants with bronchopulmonary dysplasia (BPD), the most common respiratory complication of preterm birth. The consensus definition of 'severe' BPD is requirement of ≥30% oxygen and/or positive pressure respiratory support.[1] BPD is a heterogeneous disease, with variable contributions from parenchymal, pulmonary arterial, and pulmonary venous components. In the post-surfactant era, the disease is mainly characterized histologically by fewer, larger, and simplified alveoli with heavily muscularized pulmonary arteries.[2] Insufficient vascular endothelial growth factor–C, which is important for lymphatic development, may contribute to abnormal lung fluid homeostasis and interstitial pulmonary edema, which negatively affects lung development.[3] Understanding disease pathophysiology and appraisal of the relative biological contribution of parenchymal vs vascular components to the clinical phenotype are likely to be important determinants of therapeutic intervention. Routine echocardiography (ECHO) screening for chronic pulmonary hypertension is now considered a standard of care in many perinatal centers,[4] however little attention is paid to the contributory role of abnormal left heart function to pulmonary vascular disease. The focus of this review is to discuss the relationship of prematurity to abnormalities in systemic vasculogenesis, abnormal left heart function, and appraise the relative contribution to ongoing pulmonary vascular disease. Contemporary opinions on postcapillary pulmonary hypertension, its transition to combined pre- and post-capillary pulmonary hypertension, and the roles of bedside ECHO and cardiac catheterization (CATH) in enhancing diagnostic/therapeutic precision are discussed.

ACE	Angiotensin Converting enzyme
BPD	Bronchopulmonary dysplasia
CATH	Catheterization
ECHO	Echocardiographic
EI	Eccentricity index
LA	Left atrial
LV	Left ventricular
NO	Nitric oxide
PDA	Patent ductus arteriosus
PVR	Pulmonary vascular resistance
PVS	Pulmonary vein stenosis
RAS	Renin-angiotensin system
RV	Right ventricular

Contemporary Appreciation of Chronic Pulmonary Hypertension and Evidence for Left Heart Disease

Pulmonary hypertension is a known complication of BPD, whose incidence increases with BPD severity, and is associated with increased morbidity and mortality.[5] A study of infants with 'severe' BPD reported the incidence to be ~39%.[6] Features of BPD-associated pulmonary hypertension include elevated pulmonary vascular resistance (PVR) with right ventricular (RV) hypertrophy and dysfunction. Clinically, this may manifest as greater respiratory support requirements or lability in oxygenation. Contemporary diagnostic and therapeutic opinions on BPD-associated pulmonary hypertension are based on ECHO assessment of RV performance and the responsiveness to pulmonary vasodilator therapy. Routine pulmonary vasodilators such as inhaled nitric oxide (NO) and sildenafil are used for chronic pulmonary hypertension, although neither has been approved by Food and Drug Administration for use in the population with BPD.

In the Panama Classification of Pediatric Pulmonary Hypertensive Vascular Disease, left ventricular (LV) diastolic dysfunction is included as an important component in this pathophysiology.[7] The European Society of Cardiology Guidelines also categorize patients with pulmonary hypertension into groups based on the underlying disease process and includes categories for chronic lung diseases and LV systolic/diastolic dysfunction.[8] Recently, investigators have focused on the relationship of left-sided cardiac and vascular changes to the pathogenesis, diagnosis, and treatment of a subset of infants with BPD. Scientific plausibility results from the fact that chronic systemic arterial stiffness may generate sufficient afterload to induce LV hypertrophy and/or dysfunction, high end-diastolic left atrial (LA) pressure and subsequent pulmonary venous hypertension and pulmonary edema.[9,10] This sequential contribution from the systemic circulation, termed as

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postcapillary pathophysiology, is less well appreciated as a modulator of BPD. In this subset of infants, current therapeutic strategies designed to lower PVR through use of pulmonary vasodilators may be counterproductive. Data from animal models corroborates this mechanism, as several anatomic and physiological features are common with humans.

Clinical data on the biological relevance of systemic (left-sided) pathology are limited to the impact of hypertension, which has been associated with LV hypertrophy or late unexpected sudden deaths in the setting of LV hypertrophy.[11,12] The incidence of systemic hypertension in infants with BPD was reported to be 43%,[11] which is comparable with the rate of pulmonary hypertension in infants with BPD. Our group also reported that infants with severe BPD had higher blood pressure compared with preterm infants, of comparable gestational age, without BPD.[13]

Neonatal Animal Models of Pulmonary Hypertension and LV Pathology

Given the complex, multifactorial nature of BPD and limited research options in a young and vulnerable population, animal models may provide valuable information to enhance the understanding of pathophysiology, disease progression, prognostic features, and possible therapeutic targets. Neonatal piglet and lamb experimental models allow measurement of pulmonary and systemic hemodynamics, as well as cardiac function and their correlation with circulating and tissue biomarkers of disease severity. N-terminal pro β-type natriuretic peptide is probably the most studied plasma protein biomarker and has prognostic value but may be nonspecific.[14,15] Different aspects of changes in pulmonary vascular structure and function are mimicked in young animals using specific triggers that mimic several characteristics of BPD with combined precapillary and postcapillary pulmonary hypertension. It is important to study such triggers in the context of the developing heart and pulmonary vasculature as present in infants with BPD. High pulmonary 'venous' pressure, whether because of LV dysfunction or pulmonary vein stenosis (PVS), adds an additional postcapillary component to BPD associated chronic pulmonary hypertension.[16,17] Mechanisms, which explain pulmonary hypertension and/or associated pulmonary vascular remodeling induced by LV dysfunction in BPD, may be further studied in a developing porcine model using nonrestrictive pulmonary vein banding at a young age, which becomes progressively restrictive as the animal matures.[18-20]

Prolonged, early postnatal exposure to a chronic hypoxic environment induces pulmonary hypertension with characteristic features of reduced number and increased muscularization of small pulmonary arteries, with increased PVR and reduced vascular compliance.[18,21–31] Unfortunately, few studies investigated alterations in the LV secondary to hypoxic exposure and/or as a cause of subsequent RV dysfunction. Chronic hypoxia in rats reduces the LV cross-sectional area,[32] which may in turn affect LV function and secondarily influence LA dynamics. BPD may also be accompanied by gradually evolving PVS, which impairs outflow from the stenosed lobes.[16,17] Some have suggested that PVS may not just be a congenital anomaly, but may develop secondary to premature birth when the immature heart is exposed to abnormal loading conditions or increased pulmonary venous return in conjunction with the inflammatory stimulus of mechanical ventilation.[33] This experimental paradigm represents a postcapillary insult to the developing pulmonary circulation, which initially results in postcapillary or 'passive' pulmonary hypertension, but ultimately leads to combined pre-and postcapillary or 'active' pulmonary hypertension as the disease progresses. The consequences of PVS include increased pulmonary arterial pressure, resistance, and vascular remodeling both at the site of the stenosis as well as further upstream in the pulmonary vasculature.[19,20]

Regulatory pathways in neonatal chronic pulmonary hypertension models are summarized in Table I (available at www.jpeds.com).[18,21-31] At a cellular and biochemical level, a healthy endothelium is important for the regulation of pulmonary vascular function by balancing vasodilators (NO and prostacyclin) and vasoconstrictors (endothelin-1 and angiotensin-II).[23,34] This balance is perturbed in pulmonary hypertension because of LV dysfunction secondary to enhanced endothelin-mediated constriction and reduced vasodilator influence of the NO-pathway, in part because of increased activity of cGMP-specific (type 5) phosphodiesterase.[20,23,35] Similarly, swine exposed to chronic neonatal hypoxia, which mimics arrested pulmonary development (as occurs in BPD), present with endothelial dysfunction and vascular remodeling that persist after re-exposure to normoxia. NO-pathway activation and/or inhibition of endothelin-mediated constriction lower PVR, induce pulmonary vasodilation, and attenuate pulmonary vascular remodeling (Table I). Altered function and expression of Ca-channels in vascular smooth muscle accompanies neonatal hypoxia-induced vascular remodeling and favors vasoconstriction (Table I).

The renin-angiotensin system (RAS) because of an imbalance between angiotensin converting enzyme (ACE) 1 and 2 (ACE/ACE-2), plays a role in pulmonary vascular remodeling. ACE-2, a homolog of ACE, converts angiotensin I into angiotensin,[1–7] which then activates the Mas receptor resulting in attenuation of pulmonary microvascular remodeling and prevention of RV remodeling in rats.[36] Hence, ACE-2 is thought to be the counter-regulatory enzyme of ACE. During chronic hypoxia, ACE is upregulated and ACE-2 is downregulated, tipping the balance toward the proinflammatory and pro-fibrotic AT1 mediated effects of angiotensin, thereby promoting pulmonary vascular remodeling.[37,38] Therefore, an ACE/ACE-2 imbalance might be important in BPD associated pulmonary hypertension and have therapeutic relevance.[39] Forced interference with this imbalance using diminazine, a veterinary anti-protozoan chemotherapeutic that activates ACE-2 as an off-target effect, leads to attenuated development of

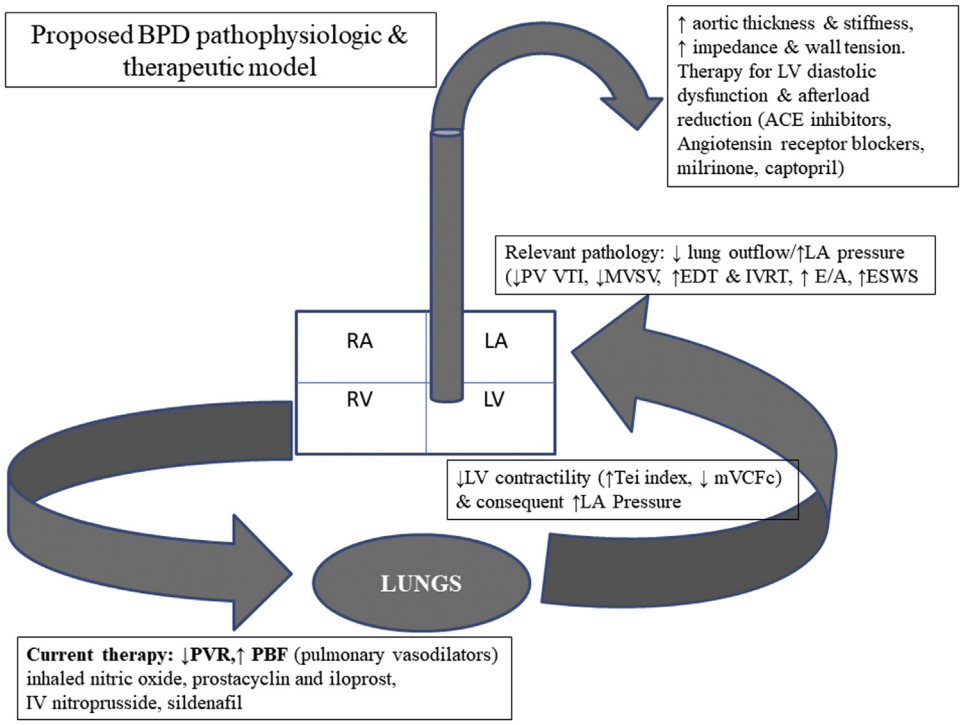

Figure 2. Flow diagram noting the assessment of aortic stiffness and consequent cardiac function. (With permission from SAGE journals. Sehgal et al, A new look at bronchopulmonary dysplasia: postcapillary pathophysiology and cardiac dysfunction. Pulm Circ 2016;6:508-15). *EDT-E*, wave deceleration time; *ESWS*, end systolic wall stress; *IVRT*, isovolumic relaxation time; *mVCFc*, mean velocity of circumferential fibre shortening; *MVSV*, mitral valve stroke volume; *PBF*, pulmonary blood flow; *PV*, pulmonary vein; *RA*, right atria; *VTI*, velocity time integral.

pulmonary hypertension in hypoxia-induced pulmonary hypertension.[40,41] The timing of such intervention is crucial as exposure to hypoxia and/or hyperoxia during critical phases of lung development could result in both up-and downregulation of ACE and ACE2. Experimental RAS data are summarized in **Table 1** and clinical studies are described later in the review. Taken together, these findings imply a role of RAS in the regulation of vascular tone and/or remodeling, possibly mediated by ACE/ACE-2 imbalance and could, therefore, provide potential therapeutic targets in infants with BPD.

Arterial Properties: Assessments and Therapeutic Relevance

Systemic hypertension complicates a subset of infants with BPD and has been associated with longer duration of respiratory support requirements and hospital stay, as well as higher mortality.[11,42] The contributory mechanisms and clinical/therapeutic importance of systemic hypertension or hemodynamics has received little attention in routine clinical practice or prospective investigation. Increased levels of proinflammatory cytokines, oxidative stress, and higher catecholamine levels (all implicated in BPD pathophysiology) could predispose to systemic arterial remodeling. Inflammation and oxygen toxicity are known to adversely affect vascular function through abnormal collagen deposition and endothelial dysfunction.[43] In addition, sympathetic over-activity could be both a key link and potential therapeutic target; specifically, instead of clearing 20%-40% of noradrenaline during single passage, infants with BPD produce catecholamines across the pulmonary circulation.[44] Increased catecholamines and systemic arterial stiffness may act in synergy to generate sufficient afterload to result in cardiac (morphologic/functional) and clinical effects.

One study examined systemic arterial structure and vasomotor function in a cohort of preterm infants with or without BPD at 36 weeks of postmenstrual age and compared them with healthy term infants.[13] The abdominal aorta was thicker with higher impedance, stiffness, and vascular resistance amongst the BPD group. The authors noted that measures of vasomotor function positively correlated with blood pressure. **Figure 1** (available at www.jpeds.com) shows the ventral wall of the aorta moving with each QRS complex on the accompanying electrocardiogram in an infant without BPD, and in infants with BPD, minimal or no ventral wall movement is seen with QRS complex, although the whole aorta moves with respiration. **Figure 2** depicts the sequential pathway of aortic stiffness, LV (diastolic) dysfunction, elevated end diastolic LA pressure, and its contribution to respiratory sequelae. These physiologic changes may contribute to pulmonary venous

congestion and edema, leading to reduced lung compliance. The clinical consequences include greater/prolonged need for respiratory support, inflicting further baro/volutrauma on the developing lung. Arterial stiffness may have important distal effects as well. The aorta is the conduit between the LV and distal vascular bed, which acts to dampen the intermittent pressure waveform from the LV and ensure the delivery of continuous and steady blood flow distally. Less cushioning exposes the distal vasculature to higher pulsatile stress, accelerating end-organ microvascular renal disease.[45,46] Attenuation of the microvascular arteriolar network secondary to systemic hypertension in turn adversely influences cardiac-vasculature coupling leading to cardiac dysfunction.[9] In patients with hypertension, the systemic vascular bed, as the source of LV afterload, has prognostic and therapeutic implications. This pattern is similar to patterns seen in adults with chronic obstructive pulmonary disease where systemic arterial stiffness plays a central role as a predictor of cardiovascular events.[47]

In adults, pulmonary hypertension is common among patients with left heart disease with a reported rate of >60% in patients with LV systolic dysfunction and >80% in patients with LV diastolic dysfunction.[48,49] Left-sided structural heart disease or other nonstructural conditions such as systemic hypertension and coarctation of the aorta may also lead to pulmonary hypertension via backpressure effects.[50] Postcapillary pulmonary hypertension, whether secondary to pulmonary venous occlusive disease/mitral or aortic valve disease or functional LV dysfunction, may contribute to the transudation of fluid across the pulmonary capillary beds leading to altered compliance and prolonged need for respiratory support.[48,49,51] In summary, the concept of postcapillary pulmonary hypertension pathophysiology has biological plausibility and clinical relevance.

Therapeutic Relevance

Standard pulmonary vasodilators may lead to acute pulmonary edema in patients with primary postcapillary pulmonary hypertension. Notably, patients with pulmonary hypertension secondary to mitral valve disease are excluded from the clinical trials evaluating pulmonary vasodilator therapies.[50] In adults, the cornerstone of therapy for patients with pulmonary hypertension and accompanying LV dysfunction is not pulmonary vasodilator therapy (such as NO) but includes systemic afterload reduction and diuretics designed to improve LV diastolic function and lower left atrial and pulmonary venous pressure. The experience of this approach in neonates and children is limited. Mourani et al described 2 infants, born at 28 and 24 weeks of gestational age, respectively, where pulmonary hypertension and ECHO features of LV diastolic dysfunction had not improved with diuretics and NO therapy.[10] Cardiac CATH data noted elevated pulmonary artery pressure (two-thirds of systemic pressure), and elevated pulmonary capillary wedge pressure which suggested LV diastolic dysfunction. Administration of captopril (systemic afterload reduction), preceded by milrinone in the first case, led to clinical improvement, normalization of ECHO measures and subsequent discharge home. This case report did not evaluate the properties of proximal or distal large arterial vessels. Further hemodynamic detail in similar cohorts of infants with severe BPD noted thickened/stiffer systemic arteries and affected left heart morphology and function.[9,13]

Clinical and ECHO improvement, after the initiation of ACE inhibitors, was recently demonstrated in 6 consecutive infants with severe BPD unresponsive to conventional therapy[52] with postnatal steroids, diuretics, and sildenafil. Captopril was administered primarily for systemic hypertension and ECHO and vascular ultrasounds were repeated after 5 weeks of therapy. Systolic blood pressure decreased from >99th percentile (>100 mm Hg in all cases) to levels between 50th and 95th percentile after 5 weeks. Importantly, a reduction in oxygen (55 ± 25% to 29 ± 3%, $P = .03$) and ventilator requirements was noted, which coincided with improved ECHO indices (a reduction in aortic intimal media thickness [840 ± 94 to 740 ± 83 μm, $P = .07$], increased aortic pulsatile diameter [36 ± 14 to 63 ± 25 μm, $P = .04$], and improved LV function). It is important to highlight that, although no pulmonary vasodilator therapy was provided, ECHO indices of RV function and elevated PVR improved. These data suggest that modification of systemic vascular hemodynamic may positively influence pulmonary hypertension in some patients. Figure 3 depicts the central role of ACE inhibition; specifically, it acts by resetting the balance between vasoconstriction/proliferation (angiotensin II, reactive oxygen species, endothelin-I) and vasodilatation/antiproliferation (bradykinin, NO). A recent study of adult patients compared calcium antagonists, β-blockers, diuretics, and ACE inhibitors. The investigators demonstrated that, although all agents were equally effective in reducing blood pressure, only ACE inhibitors improved endothelial function.[53] In addition, ACE inhibition affects arterial structure and function independent of blood pressure[54]; once again, this effect was seen by ACE inhibitors but not β-blockers.[55]

In summary, postcapillary pulmonary hypertension is a relevant consideration in patients with the clinical phenotype of BPD with presumed chronic pulmonary hypertension and warrants assessment in infants unresponsive to conventional therapy. ACE inhibition should be considered in selected cases, unresponsive to conventional pulmonary vasodilator, or diuretic therapy.

Evaluation of LV Dysfunction in Infants with BPD: Role of ECHO vs Cardiac CATH

Comprehensive ECHO is the optimum initial investigation of choice to delineate which ventricle is impacted most. Infants with pulmonary hypertension (including those with LV dysfunction), benefit from serial ECHOs to assess response to therapy and study natural history of disease.

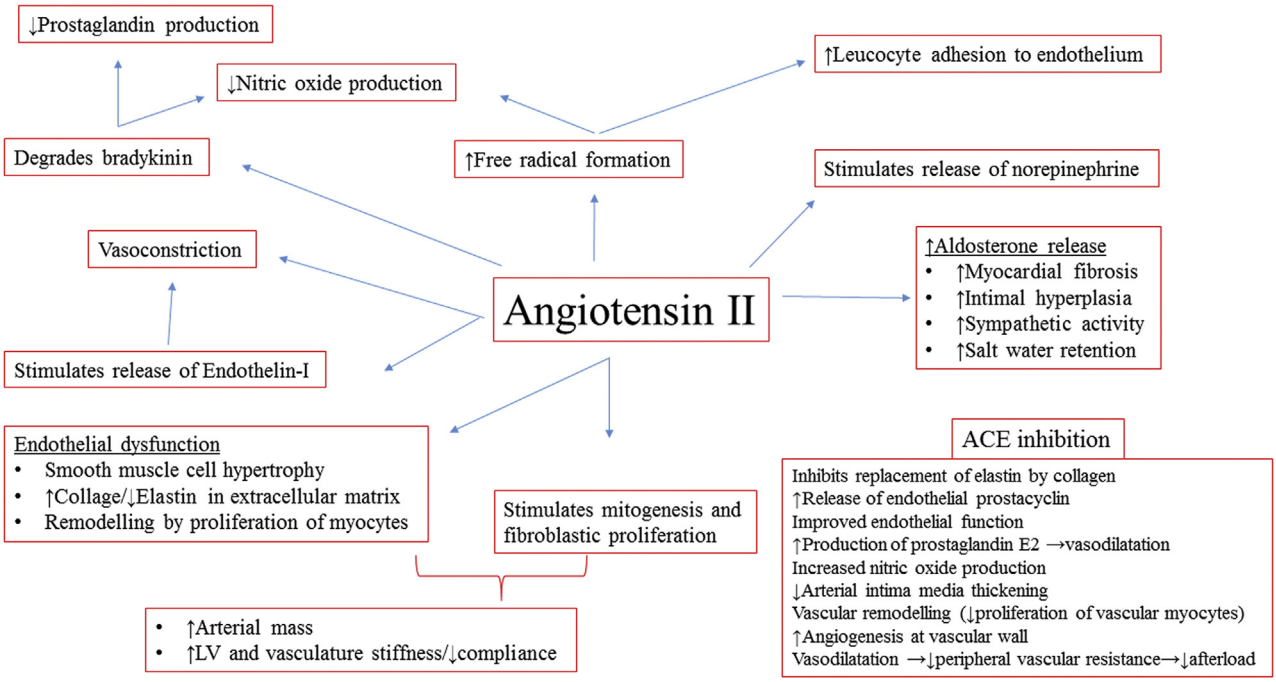

Figure 3. Central role of angiotensin II (and consequently ACE inhibition). (With permissions. Sehgal A, et al. ACE inhibition for severe bronchopulmonary dysplasia-An approach based on physiology. Physiol Rep 2018;6:e13821.).

ECHO Assessments

Growing recognition of chronic pulmonary hypertension in infants with BPD relates to easy access to bedside ECHO and screening at 36 weeks of corrected gestational age.[56] The impact of BPD on RV function is well understood. Tissue Doppler imaging assessments noted higher tricuspid E/E' ratio and RV myocardial performance index in infants with BPD compared with controls.[57] Appreciation of the diagnostic and therapeutic importance of assessment of LV measures in infants with BPD is, however, recent. Mourani et al described 2 infants with an unremittent course of severe BPD with both ECHO and CATH evidence of LV diastolic dysfunction.[10] Higher LV myocardial performance index in infants with severe BPD, compared with infants with no/mild BPD, has been reported.[58] Mitral E/A and tissue Doppler E/E′ ratios may be sensitive indicators of impaired LV diastolic function in infants with BPD.[59] These indices assess compliance of the ventricle by quantifying passive vs active filling. Our group prospectively studied a cohort of 20 infants with severe BPD and compared them with equally immature preterm infants with no BPD and healthy term infants.[9] Impaired ECHO indices of LV diastolic function (increased mitral E wave deceleration time and E/A ratio, end-systolic wall stress, and LV myocardial performance index) were noted.[9] However, even though ECHO is a readily available tool, which provides novel insights regarding LV diastolic dysfunction and its relative contribution to adverse cardiopulmonary health, data remain limited and the test may not be sufficiently sensitive.

The clinical and physiological effects of abnormal LV function may overlap with those of PVS, although there are likely to be major differences in end-diastolic LA pressure and inter-atrial shunting. Comprehensive ECHO may aid diagnosis of PVS using color Doppler interrogation from the 'crab-view' (modified short axis). Although there is no standard definition, increased pulmonary vein peak flow velocity >1.1 m/s and continuous nonphasic flow (loss of the typical biphasic Doppler pattern) are suggestive of PVS.[60,61] Drossner et al identified PVS in 26 subjects by ECHO, which demonstrated continuous, turbulent flow with a calculated mean gradient of >5 mm Hg. The median age at diagnosis was 7.4 months, and 11 (42%) infants had BPD.[33] A multicenter retrospective epidemiologic study identified PVS in 39 ex-premature infants of whom 29 (74%) had BPD. Once again, the postnatal age at diagnosis was late (>6 months).[17] A recent natural history study of chronic pulmonary hypertension noted that all preterm infants had BPD (of whom 89% was classified as severe) and a concurrent diagnosis of PVS was made in 26% of patients.[16] A Spanish study of premature infants identified PVS in 26% of infants with BPD associated pulmonary hypertension who underwent CATH.[62] An unremitting clinical course, lack of response to diuretics and no improvement (or deterioration) with pulmonary vasodilators such as NO or sildenafil should raise suspicion of PVS and/or LV functional disease. Of concern, interrogation of pulmonary vein flow may not always be performed as part of a routine chronic pulmonary hypertension evaluation.

ECHO assessment of shunts is based on the use of Doppler velocities as surrogate indices for differential resistance between the systemic and pulmonary circulations.[6] It is important to recognize, however, that peak velocity is also influenced by shunt volume, nonuniform vessel calibre (eg, patent ductus arteriosus [PDA]) or cardiac function itself. Chronic ductal shunting may remodel the LV but whether it directly causes diastolic dysfunction has not been well studied.[63,64] LV diastolic dysfunction has been identified after PDA ligation by multiple investigators.[65,66] Prematurity and pulmonary overcirculation (eg, PDA) have been associated with PVS.[33] In preclinical trials in baboons, pharmacologic PDA closure led to improved alveolarization and minimized the impairment in postnatal alveolar development.[67] The impact of prolonged PDA exposure on pulmonary vascular and cardiac remodeling requires prospective evaluation.

The role of LV dysfunction and interventricular interactions is important in chronic pulmonary hypertension pathophysiology. Increased RV pressure affects LV function by inducing septal displacement, which both limits LV inflow and further exacerbates pulmonary hemodynamics through elevated LA end diastolic pressures.[68,69] In human hearts, epicardial myofibers in the RV are circumferentially oriented and are contiguous with LV epicardial myofibres. In addition, RV subendocardial myofibers are longitudinally oriented and are contiguous with septal myofibers.[70,71] Interventricular septal configuration and motion are largely determined by LV/RV pressure differential. Increased mean pulmonary pressure leads to deviation of the septum during systole, giving the LV a characteristic D shape ("septal flattening"). The reliability of subjective assessment of septal flattening on ECHO assessment has recently been questioned.[72] The magnitude of the effect may be quantified using LV eccentricity index (EI), which provides an objective quantitative measurement of interventricular septal wall flattening/bowing. In infants born preterm, an EI ratio of >1.3 is suggestive of estimated RV systolic pressure >1/2 systemic.[73] **Figure 4** (available at www.jpeds.com) shows calculation of EI by dividing D1 (measurement parallel to the septum) by D2 (measurement perpendicular to the septum). Other investigators have demonstrated its utility in chronic pulmonary hypertension, where an independent association between end-systolic EI and BPD severity was noted.[74]

Although ECHO remains the initial modality of choice, CATH does add value and influence management and outcomes (**Table II**; available at www.jpeds.com). A positive acute vasoreactivity response in ex-premature infants with BPD predicted better long-term outcomes.[75] Khemani et al performed CATH in 13 ex-preterm infants with severe pulmonary hypertension on ECHO and evaluated the effects of 100% oxygen and 80 ppm NO.[76] A net increase in wedge pressure was noted in 7 of 12 (58%) infants after NO (in 6 of 12 [50%] with oxygen), which may relate to altered pulmonary capacitance, left heart compliance (diastolic dysfunction), or both. Long-term administration of pulmonary vasodilators such as NO or sildenafil (not approved for such use in the first place), is not physiologically justifiable in the presence of significant postcapillary pathology, and might cause clinical deterioration. Although cardiac CATH is considered the gold standard for the definitive diagnosis of chronic pulmonary hypertension,[75,77] it requires consideration of its risk/benefit ratio, including the likelihood of need for intervention during CATH (eg, PDA or atrial septal defect closure), expertise of the center performing the procedure, and need for transport of critically ill patients. A CATH Risk for Pediatrics score allows for the prediction of the risk of significant adverse events based on 8 identified risk factors and is used as a preprocedure screening tool.[78] CATH enables calculation of pulmonary blood flow (Qp), the difference in pulmonary vs systemic blood flow (QP:QS), and PVR (**Table II**). Change in pressures and pulmonary blood flow are used for calculation of PVR.[79,80] Diagnosis of pulmonary hypertension is made if mean pulmonary arterial pressure is >20 mm Hg or PVR index is >3 woodsunits.m^2. Additional measures include pulmonary artery to systemic pressure ratio ≥0.5, Pulmonary vascular resistance: Systemic vascular resistance ≥0.5, and normal wedge or left ventricle end diastolic pressure without evidence of significant PVS.[81] Recently, the global definition for chronic pulmonary hypertension has been lowered from 25 mm Hg to 20 mm Hg.[77,82]

Factors Affecting LV Remodeling and Dyssynchrony

Because the incidence of severe BPD is highest among extremely preterm infants (≤25 weeks of gestational age), the effect of prematurity on myocardial development is an important consideration. Recent observational studies in adults born at preterm gestation demonstrate increased risk of hypertension, exercise induced heart dysfunction, ischemic heart disease >40 years, and cardiac remodeling.[83-85] Despite the increased risk of adverse adult health outcomes, prematurity is not listed as an indication for screening by either the American Heart Association or European guidelines. In addition, data from animal experimental models suggest that preterm birth results in LV remodeling[86,87]; specifically, cardiomyocytes switch from a pattern of hyperplasia dominance to hypertrophy dominance at the time of preterm delivery with increased interstitial myocardial collagen deposition.[86-88] The normal pace and trajectory of maturation during fetal life is disrupted by premature birth when the immature myocardium is subjected to high LV afterload, prior to maturational adaptation.[89-91] Mikkola et al demonstrated that at 5 years of age, preterm born children have increased septal thickness and smaller LV cavity diameters, compared with children born at term.[92] In young adults (20-39 years of age), increased LV mass, quantified on cardiovascular magnetic resonance, was noted in 102 ex-preterm

infants compared with 132 term infants. Although ejection fraction was preserved, longitudinal LV systolic, diastolic, and rotational strain were abnormal and affected diastolic relaxation.[93] Increased levels of antiangiogenic factors and smaller kidney volume suggest that vascular dysfunction and renal factors responsible for elevated blood pressure in adults born preterm are additional risk factors.[94,95] The association between both myocardial hypertrophy and hypertension with higher doses and/or longer duration of steroid therapy is also relevant for a proportion of infants with severe BPD.[96] There is also evidence of adverse cardiac development in patients at comparatively lower doses (0.4-0.6 mg/kg/day, weaning over a period of 2-3 weeks).[97] The physiologic consequences of a hypertrophied/stiff LV myocardium include abnormal LV diastolic function.

ECHO assessment of LV dyssynchrony has been studied in adults using speckle-tracking methodology.[98] These imaging techniques are particularly useful in assessing cardiac loading conditions.[99] Practical applications of speckle tracking ECHO have been noted in infants with BPD and pulmonary hypertension.[100] Khoo et al noted that RV strain/strain rate, and contraction synchrony measured by speckle tracking ECHO correlated with ventricular function, indicating it might be useful for monitoring ventricular function in infants with hypoplastic left heart syndrome.[101] A recent study noted that RV dysfunction, measured by fractional area change, was associated with mechanical dyssynchrony measured by increased RV dyssynchrony index in these infants.[102] This may have potential implications for cardiac resynchronization therapy in univentricular patients. The impact of prematurity and BPD on LV: RV synchrony is currently a knowledge gap.

Additional Imaging Modalities

Other advanced quantitative modalities may aid evaluation of infants with BPD. Cardiac magnetic resonance provides information on heart development, presence or absence of remodeling, and biventricular systolic and diastolic function. Although its utility is limited by lack of wide availability, this noninvasive modality may be useful in infants not suitable for CATH. Normative data are required for ex-preterm infants. Computed tomography may aid evaluation of parenchymal lung disease, especially tracheobronchomalacia, pulmonary artery size (compressing airways), further identify PVS, which was suspected on ECHO,[103] and characterize the presence, size, and significance of collaterals. Some investigators propose this as the initial procedure of choice for the above indications.[62] Noori et al found an acceptable agreement between cardiac output measured by electrical cardiometry and ECHO in healthy term neonates.[104] A recent meta-analysis of 11 pediatric studies (603 patients [including 1 neonatal study; 20 subjects]) noted a high mean percentage error, indicating need for further research before its clinical use.[105]

Conclusions

Infants with severe BPD represent a medically complex and vulnerable patient population. Many have prolonged neonatal intensive care unit stays, ongoing respiratory morbidity postdischarge, and repeated hospital readmissions. As scientific knowledge advances, there is increased recognition that the pathophysiologic contributors are diverse and this may not be a single disease. The natural history of LV diastolic dysfunction in premature infants with BPD, particularly those with an unremitting clinical course unresponsive to standard therapy with diuretics and pulmonary vasodilators, is needed. Identification of postcapillary pulmonary hypertension in a subset of these infants can dramatically alter the course of illness. Multimodal assessments (ECHO, CATH, magnetic resonance) in such patients may allow intermodality correlation and delineate measures most specific to LV diastolic dysfunction, especially those that guide therapeutic decision-making. Whether cardiac magnetic resonance-augmented CATH provides further detail about systemic afterload, needs prospective analysis. Future research should focus on disease stratification in terms of biologic contributors, disease-specific mechanisms, and putative therapeutic strategies. ■

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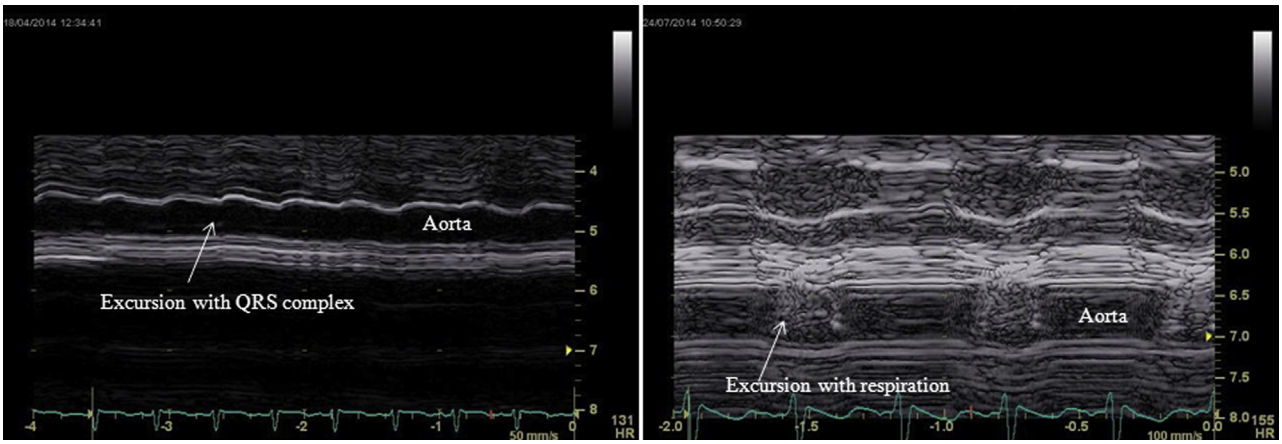

Figure 1. M-mode images of aorta: **A,** term infant-pulsatile with each QRS complex; **B,** infant with bronchopulmonary dysplasia. (With permission from Springer Nature. Sehgal et al, Systemic arterial stiffness in infants with bronchopulmonary dysplasia: potential cause of systemic hypertension. J Perinatol 2016;36:564-9).

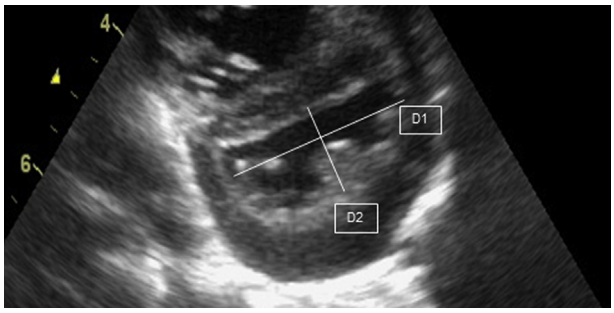

Figure 4. Calculation of eccentricity index (D1,measurement parallel to the septum) and (D2, measurement perpendicular to the septum).

Table I. Regulatory mechanisms in the pathophysiology of experimental neonatal pulmonary hypertension

Pathway/ mechanism	Vascular function and dominant vascular bed in healthy subjects	Model	Animal	Cellular/molecular findings	Intervention	Effect invention
NO	Vasodilatation (P >S)	CNH	Swine	↓NOS[21-23] eNOS uncoupling↑[22] ↓Exhaled NO[18] =PDE-V[25]	L-citrulline (eNOS recoupling) (chronic) PDE- V inhibition (acute) PDE- V inhibition (chronic)	↑NO ↓PAP ↓PVR[22] ↓PVR[26,27] =SVR[26] =PVR =SVR[26]
		PVS	Swine	↑eNOS expression ↑PDE-V activity[28]	eNOS-inhibition PDE-V inhibition (acute)	↑PVR[28] ↓PVR[28]
Endothelin	Vasoconstriction (S >P)	CNH	Swine	↑Circulating ET[24]	ET_A blockade (chronic)	↓PVR (P = .18) ↓PA remodeling ↓RV afterload ↑Exhaled NO ↓SVR[24]
		PVS	Swine	↑Circulating ET ↑PPET, ↑ECE, ↓ET_B mRNA expression[18]	ET_{AB} blockade (acute)	↓PVR ↓SVR[18]
RAS	Vasoconstriction (S >P)	CNH	Swine	↑AT1 (endothelium, macrophages) ↑AT2 (macrophages) ↓AT1 (total lung)[23]	AT-1 blockade (chronic)	↓ PAP, ↓ PVR =SVR[23]
		PVS	Swine		AT-1 blockade (chronic)	↓PAP, ↓PVR ↓PV remodeling ↓RV hypertrophy = SVR[29]
Ion channels	Vasoconstriction (P >S)	High altitude	Lamb	↑SOC (TRPC4 and STIM1)[30]	SOC blockade (acute)	↓PAP ↓PVR[30]
		CNH	Swine	↑L-type Ca channel[31]	L-type Ca channel blockade (acute)	↓PVR[31]

AT-1, angiotensin receptor 1; *CNH*, chronic neonatal hypoxia; *ECE*, endothelin converting enzyme; *eNOS*, endothelial nitric oxide synthase; *ET*, endothelin; ET_A, endothelin receptor A; ET_B, endothelin receptor B; *mRNA*, messenger RNA; *P*, pulmonary circulation; *PAP*, pulmonary arterial pressure; *PPET*, preproendothelin; *PV*, pulmonary vein; *S*, systemic circulation; *SOC*, store operated Ca channels.

Table II. Calculation of pulmonary blood flow (QP) and indications for catheterization

Formula to calculate QP

Qp = oxygen consumption/(pulmonary vein oxygen content−pulmonary artery oxygen content):
Oxygen content = Hb (g/dL) × 10dL/L × 1:36mL/g × %saturation:
Therefore, QP = VO2/(Hb x 1.36 × 10 × (PV sat – PA sat)

$$QP: QS = \frac{AOsat - MVsat}{PVsat - PAsat}$$

Formula to calculate PVR

$$PVRi = \frac{PAm - LAm}{Qp} = \text{Woods Units.M2}$$

Indications for cardiac catheterization

- When echocardiography is unable to accurately delineate PH severity
- In setting of poor responsiveness or adverse effects of PH-targeted therapy
- Estimating the haemodynamic contributions of other cardiovascular co-diagnoses (PDA, intra-cardiac shunts) and collateral vessels (by aortogram)
- Temporarily occlude shunts to determine whether the dominant physiologic determinant is high PVR or increased blood flow owing to shunt
- More accurate assessment of LV diastolic function (systemic afterload)
- Exclusion of pulmonary vein stenosis/obstruction by pulmonary venogram
- Assessment of pulmonary capillary wedge pressure (assess capillary bed morphometry/pathology)
- Enable acute vasoreactivity testing
- Calculation of pulmonary blood flow (Qp), the difference in pulmonary vs systemic blood flow (QP:QS)

AO, aorta; *Hb*, hemoglobin; *LAm*, mean left atrial pressure; *MV*, mitral valve; *PA*, pulmonary artery; *PAm*, mean pulmonary arterial pressure; *PH*, pulmonary hypertension; *PVRi*, pulmonary vascular resistance index; VO_2, peak oxygen consumption on the test day.