Pediatric Pulmonary Hypertension on the World Stage: Do We Need Separate Neonatal Guidelines?

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In comparison with adult disease, pediatric pulmonary hypertension (PH) and related pulmonary vascular disease (PVD) remain relatively understudied and poorly understood.[1] Despite many advances over the past decades, PH continues to cause significant morbidity and mortality in diverse neonatal, pulmonary, cardiac, hematologic, and other systemic disorders of childhood.[2–6] Despite some similarities, many aspects of PH in children are distinct from adult PH.[1] Although new drug therapies are available for off-label use in pediatric PH, the long-term outcomes of children with severe PH often remain poor. Most clinical studies have emphasized the results of clinical trials in adult patients, yet PH in pediatrics can be devastating and often contributes to poor outcomes in diverse clinical settings in newborns, infants, and children.

Of several major challenges addressed in the recent 6th World Symposium on Pulmonary Hypertension (WSPH), one goal was to explore major issues regarding the pathobiology, diagnostic assessment, management, and outcomes of diverse childhood diseases associated with pediatric PH.[2] There are marked differences in the epidemiology of pediatric and adult PH, as well as very striking differences in function, structure, genetics,[7] and responsiveness to therapies between adults and children with PH.[8] Unfortunately, studies that address the safety and efficacy of PH therapies in children are rare, as most pharmaceutical studies have focused on the adult population and only in patients with a fairly limited range of associated conditions. Except for the use of inhaled nitric oxide therapy for neonates with persistent PH of the newborn (PPHN) as based on multicenter randomized trials,[9-11] nearly all of the current therapies for children remain almost exclusively based on results from adult clinical trials and small case series of the use of PH-targeted therapies.[8] Thus, pediatric PH has been understudied, and little is understood regarding the natural history, mechanisms of disease, and treatment of childhood PH, especially in the setting of neonatal and genetic developmental lung diseases.

DEVELOPMENTAL LUNG DISEASES

At the WSPH, the Pediatric Task Force summarized many unique features that distinguish pediatric and adult forms of PH, especially as related to classification, diagnosis, and treatment.[2] Most importantly, pediatric PH is intrinsically linked to issues of lung growth and development, including many prenatal and early postnatal influences.[7,8,12–16] Pediatric PH often presents in the immediate neonatal period, which led to its own specific disease classification in Group 1 disease as PPHN.[2] The Pediatric Task Force further emphasized that PPHN represents a syndrome that is composed of specific diseases, ranging from its most common form as a transient disease after birth of term or near-term infants to more severe forms that include diverse developmental lung diseases and specific genetic disorders (Tables 1 and 2). Some of the major recommendations of the Pediatric Task Force were to further expand the classification and characterization of developmental lung diseases within the Group 3 disease category. These diseases include genetic abnormalities of lung development, such as alveolar capillary dysplasia (due to genetic mutations of the *FOXF1* gene), surfactant protein gene mutations (such as surfactant protein C, *ABCA3*, and others), and more recently, abnormalities of the *TBX4* gene.[12]

These developmental lung diseases often present during the early postnatal period and are frequently associated with severe PH with marked growth abnormalities of the distal lung (Figure 1). These disorders commonly present clinically in infants who are born at term or near-term gestation, with the clinical presentation of hypoxemic respiratory failure and severe PPHN physiology that is characterized by profound hypoxemia and elevated pulmonary vascular resistance leading to extrapulmonary shunting of blood across the ductus arteriosus and/or foramen ovale. PH in these infants may be poorly or only partly responsive to inhaled nitric oxide and other PH-tar-

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Table 1. Developmental lung disease associated with pulmonary hypertension

Developmental Lung Diseases Associated with Pulmonary Hypertension
• Bronchopulmonary Dysplasia
• Congenital Diaphragmatic Hernia
• Down Syndrome
• Alveolar Capillary Dysplasia with Misalignment of Veins (e.g., FOXF1 gene)
• Lung Hypoplasia, Acinar Dysplasia
• Surfactant Protein Abnormalities
- SPB deficiency
- SPC deficiency
- ABCA3
• TTF-1/Nkx2
• TBX4
• Pulmonary Interstitial Glycogenosis
• Pulmonary Alveolar Proteinosis
• Pulmonary Lymphangiectasia

Table 2. Pulmonary vascular disease (PVD) in preterm infants: clinical phenotypes

Pulmonary Vascular Disease in Preterm Infants: Clinical Phenotypes
• **Early PH: (*Delayed Adaptation of the Lung Circulation at Birth)*:**
- ***Severe hypoxemic respiratory failure with extrapulmonary R-L shunt***
- ***Different patterns of delayed transition***
- ***Early echo findings of PH as a biomarker for worse late outcomes***
• **Late PH: (weeks to months)**
- ***High levels of respiratory support, supplemental O_2***
- ***Escalating respiratory care, recurrent cyanotic episodes***
- ***Echocardiogram findings of PH* at 36 weeks corrected age in stable infant**
- **Presentation after NICU discharge (with respiratory infection, PVS or progressive lung disease)**
• **Sustained PVD across the lifespan:**
- **PVD and cardiovascular disease in former preterms in older children and young adults**

geted drugs, or may respond to therapy but are unable to wean support during the newborn intensive care unit hospitalization. Histologically, these infants have marked parenchymal lung disease, as manifested by alveolar growth arrest with decreased surface area, variable degrees of hypercellularity and interstitial disease, reduced pulmonary vascular density, and signs of hypertensive remodeling of small pulmonary arteries (Figure 1). Current diagnostic approaches include genetic studies, chest computed tomography, and lung biopsy, with serial echocardiograms, measurements of N-terminal precursor of brain natriuretic peptide, and cardiac catheterization often included in the evaluation. Clinical course and outcomes are generally poor but can be highly variable, as case series for these rare disorders are somewhat limited. Some infants are candidates for early lung transplantation but experience is often limited to few centers with sufficient experience in treating young infants.

At the 6th WSPH, the Pediatric Task Force decided to include Down syndrome within the Group 3 classification as a developmental lung disease, except in Down syndrome subjects with anatomic congenital heart disease.[2] This decision was partly based on observations of the high rate of PPHN in Down syndrome subjects, and that abnormalities of lung development, including reduced alveolarization, decreased vessel density, persistence of the double-capillary network, prominent bronchial-pulmonary collateral shunt vessels, and hypertensive arterial remodeling, were often found in infants with PH.[13,14] In human fetal and neonatal lung specimens, Galambos et al. measured lung gene expression of anti-angiogenic factors, including *COL18A1* (endostatin), *COL4A3*, *TIMP3*, and *APP*, that are known to be expressed on Chromosome 21 (Figure 2).[15] They reported that these genes are overexpressed in Down syndrome lungs and that fetal lung vessel growth is decreased in subjects with Down syndrome. It appears that increased fetal lung anti-angiogenic factor expression due to trisomy 21 impairs lung vascular growth and signaling, which impairs alveolarization and contributes to high risk for pulmonary arterial hypertension during infancy.

PERSISTENT PH OF THE NEWBORN (PPHN)

The Pediatric Task Force further emphasized the need to recognize that PPHN, which has more traditionally been linked almost exclusively with term neonates in the past, can also occur in preterm infants (Table 2). In fact, recent studies suggest that the rate of PPHN is inversely related to gestational age at birth.[16] While PPHN typically resolves within the first months of life, the impact on later lung vascular growth and function remains unclear and warrants further study. Recent editorials and early reports have suggested that early disruption of vascular growth may increase the susceptibility of the adult pulmonary circulation for late onset of PH (e.g., "PVD across the lifespan").[17]

PVD IN BRONCHOPULMONARY DYSPLASIA (BPD)

Recent improvements in perinatal care have improved the survival of extremely premature infants, but nearly 45% of preterm infants develop bronchopulmonary dysplasia (BPD), the chronic lung disease of prematurity, which is often associated with PH.[18] Prospective cohort data suggest that roughly 25% of preterm infants less than 32 weeks of

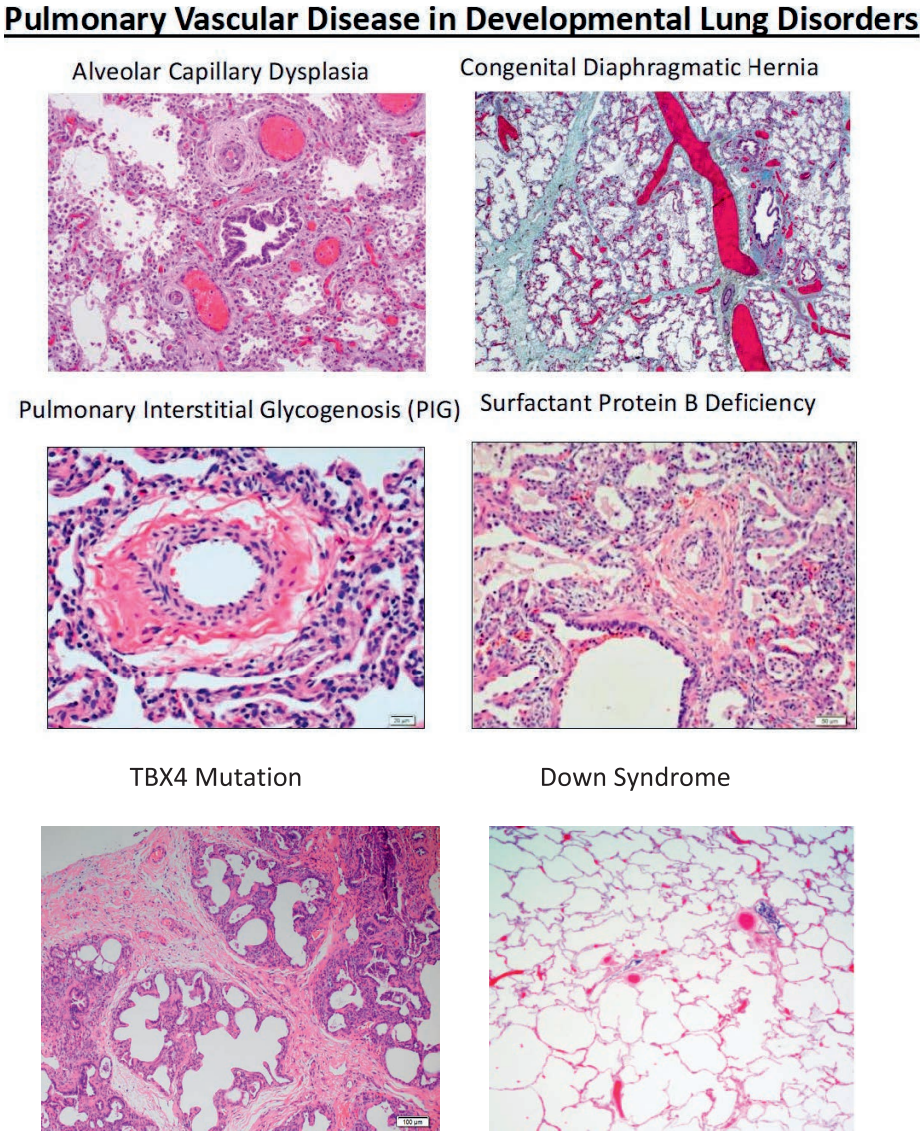

Figure 1: Histologic examples of diverse developmental lung disorders associated with severe pulmonary hypertension during early infancy.

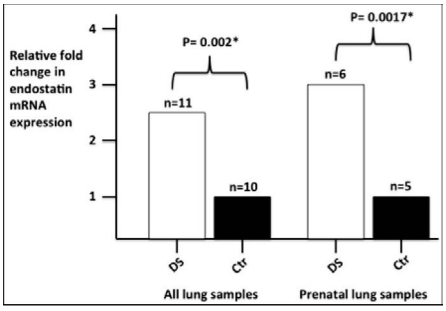

Figure 2: Increased lung endostatin gene expression in the human fetus and infant with Down syndrome. Comparisons between lungs from Down syndrome (DS) and non–Down syndrome (Ctr) subjects) are shown.

gestation at birth have echocardiographic evidence of PH at 36 weeks postmenstrual age and that PH is present in nearly 50% of preterm infants with severe BPD[18] (Figure 3). Despite the growing off-label use of PH-targeted therapies in preterm infants with PH, data are limited to best define clinical care strategies, and mortality remains high. Importantly, PH occurs most commonly in severe BPD, and the natural history and response to therapy is variable, reflecting the complex interaction of prenatal and postnatal factors that contribute to the pathobiology of BPD-associated PH.

In addition to postnatal lung injury, antenatal stress related to placental insufficiency with intrauterine growth restriction contributes to high risk of later PVD, highlighting the importance of early lung development.[19–23] Antenatal factors, such as chorioamnionitis, preeclampsia, and others, are strongly associated with an increased risk for BPD, especially when associated with intrauterine growth restriction as a biomarker for severe placental dysfunction and fetal stress. In addition to risk for PH, preclinical data suggest that disruption of angiogenesis impairs alveolarization in the developing lung.[24–26] Early changes in circulating angiogenic peptides, including decreased pro-angiogenic factors, increased anti-angiogenic factors (including sFlt-1, an endogenous vascular endothelial growth factor inhibitor that is markedly increased in blood and amniotic fluid of women with preeclampsia), and decreased endothelial progenitor cells, are associated with both abnormal placental vascular disease and high risk for BPD and PH. These data support the hypotheses that antenatal mechanisms that promote an anti-angiogenic fetal environment contribute to high risk for BPD and PH in preterm infants and suggest novel targets for disease prevention. Prospective clinical studies support these hypotheses, as early echocardiogram changes suggesting PVD at Day 7 of postnatal life is strongly associated with high risk for subsequently developing BPD or PH at 36 weeks corrected age, as well as late respiratory disease during childhood.[27–29]

LONGITUDINAL OUTCOMES OF EARLY PVD IN OLDER SUBJECTS

Postnatal growth of the pulmonary vascular bed during infancy and childhood is also important and may be the critical factor allowing for improvement of PH over time in a significant subset of children with BPD and PH. Long-term impact was highlighted recently in a study in which PH and pulmonary arterial stiffness were diagnosed by right-heart catheterization in a small cohort of young adults with a history of BPD during infancy.[30] These investigators identified that nearly half of their cohort had mean pulmonary artery (PA) pressures at rest that were above 20 mm Hg. This is especially important as the 6th WSPH recommended that the new

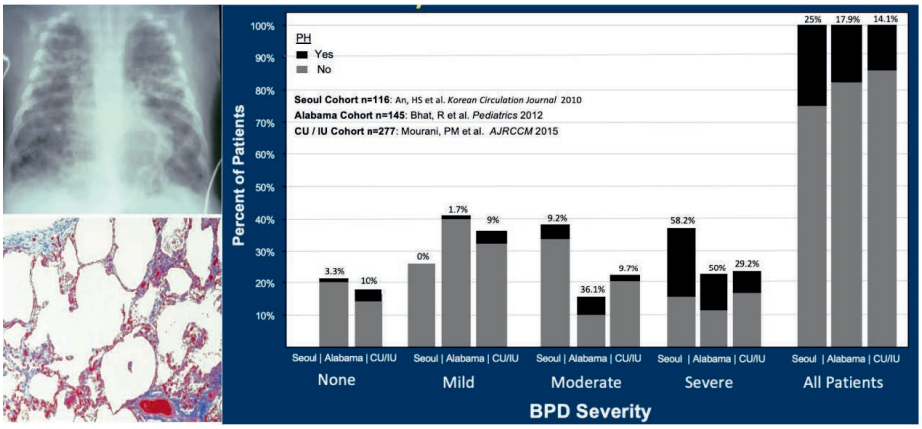

Figure 3: Bronchopulmonary dysplasia (BPD): radiologic and histologic features (left panel) and the incidence of BPD-associated pulmonary hypertension according to disease severity.

threshold value used to diagnose PH should be changed to measuring a mean PA pressure >20 mm Hg for children, with a continued emphasis on use of indexed pulmonary vascular resistance >3 WU*m^2. However, data are currently lacking regarding the impact of what was previously called "borderline" PH (mean PA pressure 21–24 mm Hg) in infants and children, especially in former preterm infants. Whether more aggressive monitoring and intervention of former preterm infants who meet this hemodynamic definition would improve cardiorespiratory function or obviate later PH is currently unknown. Further study will be necessary to determine any life-long consequences of early PVD as this population of infants and children enter adulthood.[17]

CONCLUSIONS

During the 6th WSPH, the Pediatric Task Force raised many questions regarding the growing importance of diverse developmental lung disorders associated with PH in the term and preterm newborn, including such diagnoses as PPHN, BPD, congenital diaphragmatic hernia, and several genetically based abnormalities of lung development. Critical gaps that limit our care for children with these diseases include the need for more extensive mechanistic preclinical work to better define developmental signaling pathways that regulate normal lung vascular growth and how disruption of these pathways leads to aberrant growth, function, and high risk for PH. In addition, there remains a need for better clinical characterization of the disease phenotypes that may set the stage for clinical trials that target infants with Group 3 disease. Current knowledge is limited for how to best intervene at early stages of disease that may lead to novel preventive strategies in preterm infants at risk for BPD, as well as better therapies beyond PH vasodilator drugs alone to improve outcomes of children with developmental lung disease.

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