Review Article

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Addressing the challenges of phenotyping pediatric pulmonary vascular disease

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Abstract

Pediatric pulmonary vascular disease (PVD) and pulmonary hypertension (PH) represent phenotypically and pathophysiologically diverse disease categories, contributing substantial morbidity and mortality to a complex array of pediatric conditions. Here, we review the multifactorial nature of pediatric PVD, with an emphasis on improved recognition, phenotyping, and endotyping strategies for pediatric PH. Novel tailored approaches to diagnosis and treatment in pediatric PVD, as well as the implications for long-term outcomes, are highlighted.

Keywords

childhood, pulmonary hypertension, registry studies, long-term outcomes

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Pulmonary vascular disease (PVD) and pulmonary hypertension (PH) add significant morbidity and mortality in a diverse mix of pulmonary, cardiac, and systemic disorders in children. Despite recent advances in our understanding of its pathobiology and the growing availability of drug therapies, pediatric PVD remains understudied and still relatively little is known about basic disease mechanisms, natural history, age-appropriate clinical endpoints, optimal therapeutic strategies, and long-term outcomes for children with PH.[1–3] Clinical care decisions are often limited by the relative lack of studies based on multicenter randomized trials in children, the marked heterogeneity of conditions and co-morbidities associated with pediatric PVD, the relatively small number of patients at individual centers, or a dependence on anecdotal experience or adult-based studies.[3,4] Here, we review the multifactorial nature of pediatric PVD, with an emphasis on the need for improving the recognition and phenotyping of pediatric PH, developing tailored approaches to diagnosis and treatment, and implications for long-term outcomes in pediatric PVD.

Defining pediatric pulmonary vascular disease: The importance of comprehensive phenotyping and patient registries

While similarities exist regarding the etiology and disease pathogenesis of some forms of pediatric and adult PH, many cardiopulmonary and systemic diseases associated with PH are unique to neonates, infants, and children.[2–4] First, multiple aspects of the developmental biology of the

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growing lung are key determinants of disease pathobiology. Lung vascular injury during susceptible periods of lung growth and adaptation can have a long-standing impact on childhood PVD and may impact growth of the distal lung airspace as well (Fig. 1). Examples include the increased recognition of the importance of PVD after premature birth, the contribution of PVD to poor outcomes in many developmental lung diseases (DLD), its association with genetic syndromes, particularly Down syndrome, and many other factors that reflect both prenatal and postnatal influences on pulmonary vascular development (Fig. 2). In addition, there are striking maturational differences in responsiveness to PH-specific drug therapies, pharmacodynamics and pharmacokinetics, and perhaps, the potential for late adverse effects.[5–8] Little is understood regarding critical co-morbidities that impact long-term outcomes in specific pediatric diseases with PH, how to best monitor disease progression or response to therapy, and whether early recognition or preventive therapeutic strategies can be applied in children to minimize disease severity during adulthood.

Current definitions and classifications of pediatric PH

The definition of PH in pediatrics is nearly identical to that applied to adults, though some important differences exist, especially during the early transitional period after birth.[2,4] Pulmonary arterial pressure (PAP) equals systemic arterial pressure in utero but rapidly falls after birth, generally achieving adult values by 2–3 months of postnatal age. After 3 months of age in term infants at sea level, PH is diagnosed when the mean PAP exceeds 25 mmHg. However, the lack of an elevated PAP does not exclude the presence of pulmonary hypertensive vascular disease (PHVD) in some settings. In particular, the pulmonary vascular resistance (PVR) index is important in the diagnosis and management of PHVD in children with congenital heart disease (CHD).

Pediatric PH is currently categorized in similar fashion as adult PH, which is based on the World Health Organization (WHO) classification that was most recently revised at the 5th World Symposium for Pulmonary Hypertension in Nice, France (Table 1).[9] Based on concerns regarding the applicability of an adult-focused system for the phenotypic heterogeneity of neonatal and childhood PH, the pediatric task force of the Pulmonary Vascular Research Institute (PVRI), an international collaborative group that was created to promote global research in PH, proposed a novel classification that may prove useful as a pediatric-specific system (Table 1).[10] The goals of the Panama Classification System are to highlight the phenotypic heterogeneity of PHVD from the fetus to the adolescent and the impact on diagnosis, treatment, and research, but whether this system has clinical utility remains unknown.[10] Currently, the PVRI pediatric diseases classification is bulky, contains overlapping features between categories, and needs further

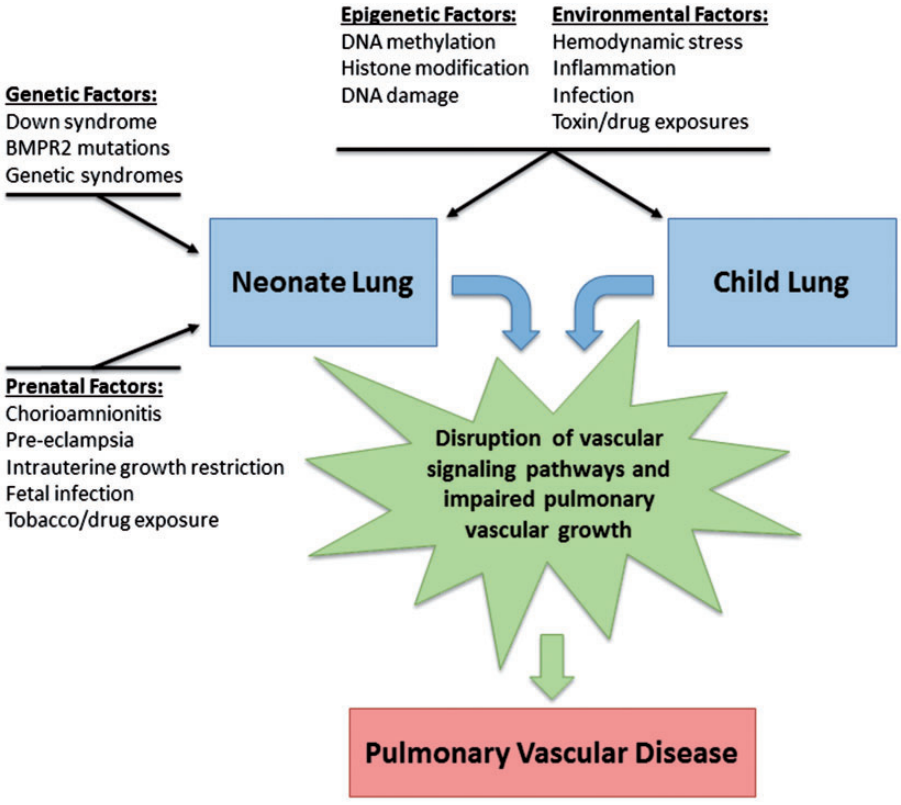

Fig. 1. Diverse and interactive factors contributing to pulmonary vascular disease in pediatrics.

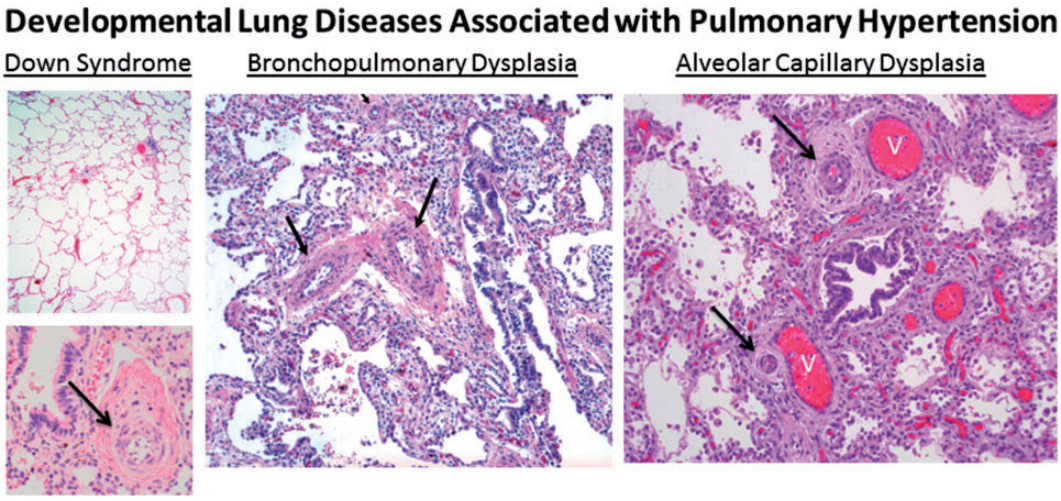

Fig. 2. Developmental lung diseases associated with neonatal pulmonary hypertension, including Down syndrome (left panel), bronchopulmonary dysplasia (middle panel), and alveolar capillary dysplasia (right panel). In addition to hypertensive remodeling of small pulmonary arteries (denoted by arrows in each panel), these disorders are further characterized by decreased alveolarization, abnormal lung vascular growth, and prominent intrapulmonary vessels (bronchopulmonary or venous, as noted by V in right panel, alveolar capillary dysplasia).

Table 1. Comparison of the Nice WHO classification of pulmonary hypertension versus the Panama Pediatric Pulmonary Hypertensive Vascular Disease Classification System. Diagnoses specific to pediatric pulmonary hypertensive vascular disease are underlined in the WHO classification.

WHO PH Classification		Pediatric PHVD Classification
1. Pulmonary arterial hypertension 1.1 Idiopathic 1.2 Heritable 1.2.1 BMPR2 1.2.2 ALK1, ENG, SMAD9, CAV1, KCNK3 1.2.3 Unknown 1.3 Drug and toxin induced 1.4 Associated with 1.4.1 Connective tissue disease 1.4.2 HIV infection 1.4.3 Portal hypertension 1.4.4 Congenital heart disease 1.4.5 Schistosomiasis 1'. PVOD and/or PCH 1.1" Persistent PH of the Newborn 2. PH due to left heart disease 2.1 LV systolic dysfunction 2.2 LV diastolic dysfunction 2.3 Valvular disease 2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathy	3. PH due to lung disease or hypoxemia 3.1 Chronic obstructive pulmonary disease 3.2 Interstitial lung disease 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern 3.4 Sleep disordered breathing 3.5 Alveolar hypoventilation syndromes 3.6 Chronic exposure to high altitudes 3.7 Developmental lung diseases 4. Chronic thromboembolic disease (CTEPH) 5. PH with unclear or multifactorial mechanisms 5.1 Hematologic disorders: chronic hemolytic anemia, myeloproliferative disorders, splenectomy 5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis 5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders 5.4 Others: tumor obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH	1. Prenatal or developmental PHVD 2. Perinatal pulmonary vascular maladaptation 3. Pediatric cardiovascular disease 4. Bronchopulmonary dysplasia 5. Isolated pediatric PHVD (isolated pediatric PAH) 6. Multifactorial PHVD in congenital malformation syndromes 7. Pediatric lung disease 8. Pediatric thromboembolic disease 9. Pediatric hypobaric hypoxic exposure 10. Pediatric pulmonary vascular diseases associated with other system disorders

refinement. However, the promise that such a system will better characterize PH phenotypes, define co-morbidities, and enable practitioners to better care for children with PH remains a worthy goal, and the system will likely evolve due to practical modifications over time.

Insights into pediatric PVD gained from international registries

Recently, data from several registries have added to our knowledge on the incidence and prevalence of diverse forms of pediatric PH. Although the true incidence and prevalence of PH in the pediatric population remain uncertain, recent epidemiologic data from national or international registries estimated an annual incidence of 64 cases per million children.[11–15] The incidence of idiopathic pulmonary arterial hypertension (IPAH) was 0.7 cases per million, which is slightly less than adult reports, and PAH associated with CHD was 2.2 cases per million. Past reports from pediatric registries have primarily emphasized that IPAH, heritable PAH (HPAH), and PAH associated with CHD constitute the majority of cases (WHO Group 1 disease). For example, of the 362 patients included in the Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension (TOPP) registry, 88% had Group 1 disease, including 57% with IPAH or FPAH and 36% with PH associated with CHD.[14] Only 12% of enrolled patients had PH associated with respiratory diseases, with bronchopulmonary dysplasia (BPD) being the most frequent disorder, yet many single sites have far more patients with BPD and PH (WHO Group 3 disease) than suggested in the TOPP Registry data. Similarly, the National Pediatric PH Registry of the Netherlands reported that the most common causes of persistent or progressive PAH were persistent pulmonary hypertension of the newborn (PPHN), PAH associated with CHD, and IPAH/HPAH.[11] Yet PH associated with chronic lung diseases, such as BPD, cystic fibrosis (CF), and DLD, and systemic disorders such as metabolic or hematologic disease, were lacking in this registry as well. These patterns likely reflect practice or referral bias, the use of right heart catheterization as a requirement for enrollment into the registry, or a lack of active engagement of consultant services in more common forms of pediatric PH.

Survival in pediatric PAH has improved dramatically since the advent of targeted PAH therapies. In contrast with a 3-year survival rate of less than 50% in historic data, the Registry to EValuate Early and Long-Term PAH (REVEAL) reported 1-, 3-, and 5-year estimated survival rates in children of 96%, 84%, and 74%, respectively, with no significant difference between IPAH and CHD associated PAH.[12]

More recently, del Cerro et al. published data from the Spanish PH Registry, which has provided more extensive information on disease incidence, prevalence, and the impact of functional class, WHO Group, and other factors on survival in children (Fig. 3).[15] The Spanish Registry included many forms of PH and thereby provides a more accurate picture of the nature of pediatric PVD. In the Spanish Registry, 61% of the patients had PAH (WHO Group 1), 14% had PH with left heart disease (WHO Group 2), 18% had PH associated with respiratory disease (WHO Group 3), 1% had thromboembolic PH (WHO Group 4), and 4.5% had multifactorial factors (WHO Group 5), including metabolic diseases. Importantly, 31% of the patients had PH associated with multiple etiologies, suggesting the need for more accurate phenotyping beyond traditional classification schemes alone. This study further showed that independent risk factors for mortality included etiology, age at diagnosis younger than 2 years, advanced functional class, and high right atrial pressure as assessed by right heart catheterization.[15] Although limited by its retrospective nature, this report provides a more accurate landscape that better reflects diverse causes of PH commonly seen in pediatric practice. However, as with data from the other registries, there is likely some selection bias of referral patients, as the number of newborns, infants, and children with BPD, DLD, and CF are likely under-represented. Thus, this study further highlights the need to evaluate all causes of PH and to include collaborations with multidisciplinary teams (e.g. pulmonologists, cardiologists, neonatologists, intensivists, hematologists, and others) to more accurately reflect the full scope of pediatric PH.

The development of high quality patient registries represents only the beginning of the extensive work that must be done in order to more robustly phenotype and characterize the natural history, disease course, response to therapies, and late outcomes of pediatric PH. A major challenge towards improving outcomes in children with PVD is the extremely small number of patients at each medical center, highlighting the critical need for developing high quality national and international patient registries and related databases of children with diverse forms of PVD for supporting more extensive and high quality observational and interventional studies. As highlighted in a recent NHLBI Conference, improving outcomes for children with PVD will require the ability to establish the natural history and longitudinal course of at-risk pediatric patients through more extensive phenotyping; link clinical data with predictors of disease, such as proteomic, genetic, and epigenetic biomarkers; identify clinical features to better characterize patients through physiologic assessments with age-appropriate function; validate clinically useful endpoints and surrogates for performing clinical trials in young children with PAH; establish novel approaches to diagnose, monitor disease progression, and treat children with PH; and improve our ability to perform post-marketing surveillance of PH-specific therapies.[16]

Diagnosing pulmonary vascular disease in children

Delays of 1–2 years after the onset of disease are not uncommon in pediatric PH, which is likely due to the non-specific

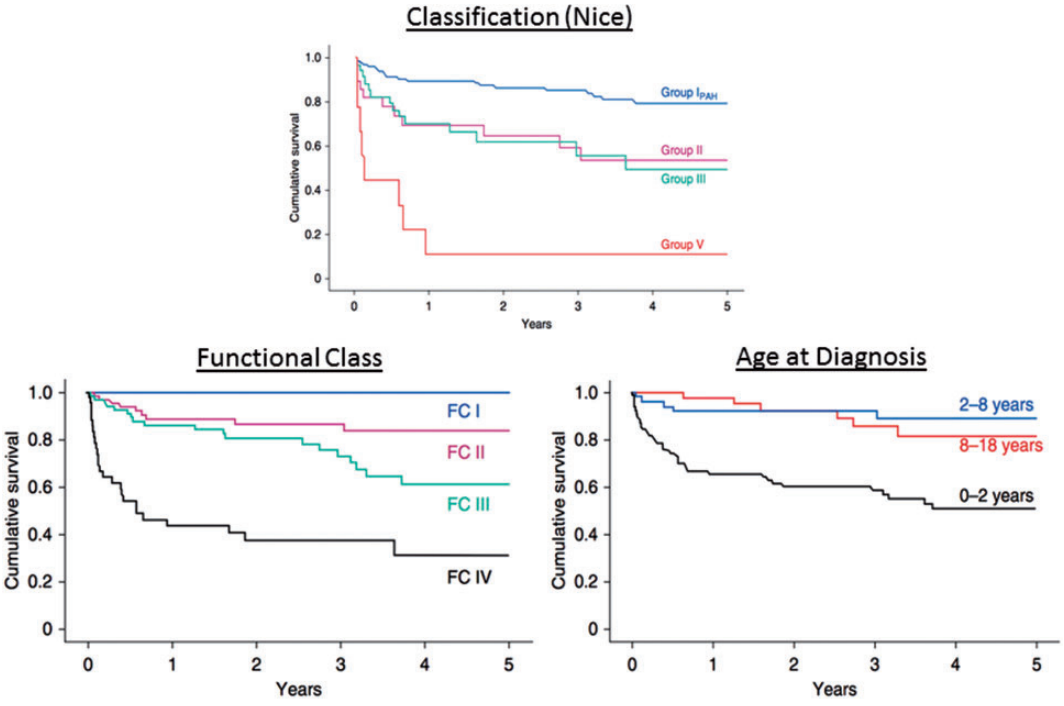

Fig. 3. Factors associated with survival in pediatric pulmonary hypertensive vascular disease from the Spanish Registry highlight the importance of large registry studies for uncommon diseases such as pediatric pulmonary hypertension. (Reprinted with permission of the American Thoracic Society. Copyright © 2016 American Thoracic Society. Del Cerro Marin MJ, Sabate Rotes A, Rodriguez Ogando A, et al. 2014. Assessing pulmonary hypertensive vascular disease in childhood. Data from the Spanish registry. *Am J Respir Crit Care Med* 190: 1421–1429. *The American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society.)

nature of early symptoms, such as dyspnea on exertion, fatigue, and syncope, as well as the diversity of etiologies of pediatric PHVD.[10,12,17] Children with PH are often misdiagnosed with more common childhood conditions, such as asthma, vasovagal syncope, or seizures, prior to making the correct diagnosis of PAH or PHVD. Due to disease complexity and heterogeneity, the relatively limited numbers of cases, and the importance of experience with specific diagnostic procedures and therapeutic strategies, the evaluation and care for pediatric PH patients should be provided or co-managed by specialty PH centers that include comprehensive, multidisciplinary medical subspecialists, nursing, and social work expertise.[4] Routine follow-up visits should be performed, at a minimum, every 3–6 months with more frequent visits for patients with advanced disease, or after initiation of or changes to therapy. Those co-managed should be seen at a minimum biannually by or in consultation with PH specialty centers.

At the time of initial PH diagnosis, a comprehensive history and physical examination in combination with diagnostic testing for assessment of PH WHO Group classification and formal assessment of cardiac function should be performed. Initial evaluation for suspected PH includes chest X-ray, electrocardiogram, and echocardiogram, with normal findings on all three demonstrating a sensitivity of 100% to rule out PH in the TOPP registry.[14] Additionally, computed tomography (CT) of the chest with and without contrast, 6-minute walk test, laboratory studies including NT-pro brain natriuretic peptide (BNP), and cardiac catheterization should be considered critical components of a thorough evaluation. Other tests such as a sleep study, cardiopulmonary exercise testing, laboratory work for systemic disorders, magnetic resonance imaging (MRI), and lung perfusion scans may have greater value in select populations. Recently, a joint committee from the American Heart Association and American Thoracic Society published the first guidelines document regarding the evaluation and therapy of children with PH, but this report strongly emphasized the current lack of research-based evidence supporting many clinical practices.[4]

Proteomic strategies for pediatric PVD: Endotyping and biomarker identification of disease risk, diagnosis, and progression

Unfortunately, clinical prediction models are at best only moderate predictors of PVD, responsiveness to therapy, or late outcomes.[18] This problem highlights current limitations of phenotyping alone and additional strategies are urgently needed to aid in risk stratification, diagnosis, and therapeutic monitoring for infants and children with PVD. Endotyping, or classifying by sub-groups based on common mechanisms that modulate the development or progression of disease, would improve current classification

schemes, aid in selecting therapeutic strategies that directly target the underlying pathophysiology, and improve patient selection for prospective studies. One way to improve these diagnostic capabilities is through the identification of biomarkers, potentially allowing for early prevention as well as directed treatment.

Although biomarkers are currently being investigated in adult PAH, translation to pediatric PVD is lagging.[19] Among pediatric diseases associated with PH, biomarkers in BPD remain the most extensively studied.[20,21] For example, angiogenic (VEGF, PIGF, endostatin, ANG-1),[22–27] inflammatory (IL-1b, IL-6, IL-8, IL-10, IL-17, interferon-γ, RANTES, and TNF-β),[28–31] and epithelial and fibrotic markers (MMP9, TIMP1)[32,33] have been identified as possible predictors of disease risk or severity in BPD. However, these markers have not been clearly correlated to development of BPD-associated PVD and rarely studied in validation cohorts. Circulating BNP and NT-pro-BNP have been used to follow infants at risk of PH, but BNP is difficult to use in neonates except for trends because of the significant developmental regulation and the broad difference in assay values between vendors.[34,35]

A multi-site, national effort through the development of a longitudinal registry and biobank, which utilizes broadly based, unbiased discovery platforms, and state-of-the-art proteomic techniques, may enhance pediatric PVD prediction and phenotyping. Such a resource would provide the biologic sample and clinical outcome measures such that discovery and validation could be systemically performed to develop biomarker panels, which could then be further validated in clinical trials. Validated biomarker panels could potentially serve as surrogate outcomes for developing rapid cycle, clinical intervention trials to accelerate improved outcomes.

Addressing the challenges of pediatric diagnostic assessment with tailored imaging approaches: A look at BPD-associated PH

PH and cor pulmonale, resulting from extreme forms of PVD, are recognized factors associated with high mortality in children with chronic lung disease.[36–38] In the past decade, patients with BPD and PH had reported survival rates of 52% 2 years after the diagnosis of PH.[38] However, the absence of a data-derived definition of PH in this population and lack of non-invasive, reliable, and quantifiable diagnostic assessments to diagnose PH has impeded studies of this disease.

Non-invasive assessment via echocardiography, despite its limitations, has become the most frequent modality for screening and diagnosis of PH in pediatric patients.[39] The most objective measure of PH by echocardiogram is the estimated right ventricular systolic pressure (RVSP) derived from the tricuspid regurgitant jet velocity (TRJV).[40–43] Applied from adult criteria, a threshold of RVSP $>$ 35 mmHg (TRJV $>$ 3 m/s) to define PH has been used. Due to relatively low blood pressures in preterm infants, estimated pulmonary pressure $>$50% of the systemic pressure has also been used to define PH and appears to correlate better with measurements performed during cardiac catheterization.[39,44] Studies of high-risk BPD infants with known or suspected PH reveal a measurable TRJV in 31–61% of these infants.[39,45–47] However, prospective studies in broad populations of preterm infants have found that a measurable TRJV is more rare (6–10%)[47,48] and was the determining factor to diagnose PH in a very small proportion of infants. Thus, qualitative echocardiogram findings are often utilized to diagnose PH, including right atrial enlargement, right ventricular (RV) hypertrophy, RV dilation, pulmonary artery dilation, and interventricular septal flattening. Septal flattening appears to be among the more sensitive of these measures, but could be vulnerable to poor inter-observer reliability and is not quantitative.

Additionally, impaired global cardiac function may result directly from PH in the setting of right heart dysfunction or may contribute to it in the setting of diastolic or left heart dysfunction. Preterm birth has been associated with alterations in RV structure and reduced function in young adults, suggesting that the developing heart in addition to the vasculature may be susceptible to perinatal events.[49] The RV myocardial performance index (MPI; also known as the Tei index) has been used as a surrogate for increased PVR in BPD and has been shown to remain elevated in infants with BPD compared to preterm infants without BPD.[50] Newer echocardiographic techniques such as tricuspid annular plane systolic excursion (TAPSE), RV speckle-tracking, and Doppler tissue imaging may provide additional information.[51]

Despite the usefulness for diagnostic screening, echocardiograms still have limitations that may preclude diagnosis of PH, fail to accurately diagnose the severity of PH in those identified by echocardiogram,[39] or fail to identify additional cardiovascular abnormalities that contribute to PH, including the degree of shunt flow, making cardiac catheterization the gold standard for diagnosis of PH. Cardiac catheterization provides accurate measurements of RV and PAP as well as the ability to detect anatomic lesions that contribute to elevated pulmonary pressure, such as pulmonary vein stenosis and systemic to pulmonary artery collateral vessels. These lesions have been reported in BPD but are not easy to diagnose or evaluate using echocardiography. In addition, the relative role of shunt lesions in PH, such as an atrial septal defect, ventricular septal defect, or patent ductus arteriosus, can be best assessed during cardiac catheterizations, which can have important therapeutic implications for discerning the effects of high flow from PVD in a given subject with BPD and PH. Finally, cardiac catheterization provides an opportunity to diagnose the relative contribution of left ventricular diastolic dysfunction to PH, which is difficult to assess non-invasively.

Unfortunately, the risks of cardiac catheterization are not insignificant, especially in critically ill preterm infants on

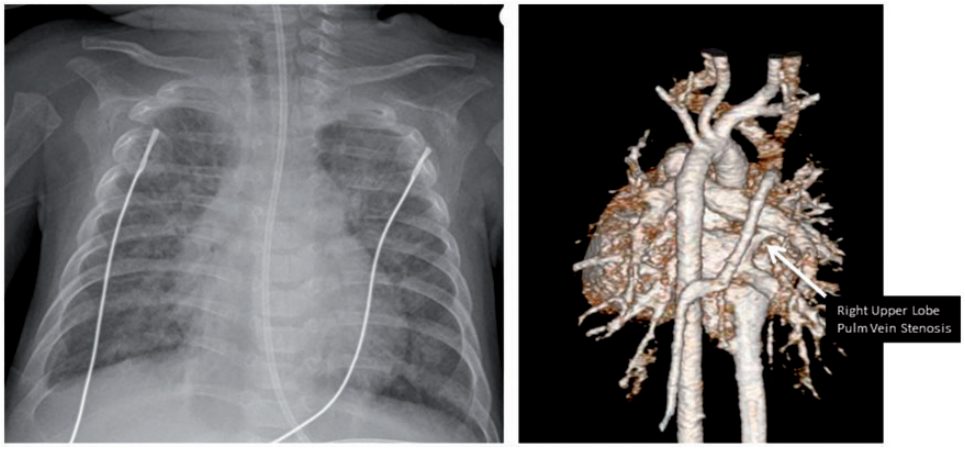

Fig. 4. Chest X-ray (left panel) and CT angiography demonstrating pulmonary vein stenosis in an infant with severe bronchopulmonary dysplasia and pulmonary hypertension.

high ventilator settings. As a result, many providers reserve cardiac catheterization for children with suspected or confirmed PH who fail to improve despite optimal respiratory support and are being considered for PH-specific drug therapies as well as those in whom there is high suspicion of anatomic cardiac lesions or systemic-pulmonary collaterals, pulmonary venous obstruction, or myocardial dysfunction which would be amenable to catheter based interventions.

High resolution CT scanning may be helpful as an adjunct investigation in some infants to evaluate both the lung parenchyma and the vasculature (Fig. 4). For example, del Cerro et al. evaluated 29 patients with PH and BPD without major congenital heart disease, in whom CT scanning was done in 21 and cardiac catheterization in 14 patients. Cardiovascular anomalies were noted in approximately two-thirds of patients, notably aortopulmonary collaterals (n = 9), pulmonary vein stenosis (n = 7), atrial septal defects (n = 4), and patent ductus arteriosus (n = 9).[52]

MRI of the chest may provide an additional modality for evaluating pulmonary vascular function and hemodynamics. Phase-contrast flow measurements via MRI could estimate pulmonary artery velocities and PAP. Newer functionality to provide electrocardiographic gating and respiratory motion suppression enhances measures of RV wall structure and function. In addition, ongoing work is currently assessing the ability of cardiac MRI to perform acute vasoreactivity testing, which has normally been predominantly performed during cardiac catheterization. These techniques have been applied in other forms of PH, detecting changes of PVD prior to the onset of symptoms.[53–57]

Treatment of pulmonary vascular disease in children

Treatment of PVD in children must begin with understanding the underlying etiology and clinical physiology. For example, for children with PVD secondary to chronic lung disease, as in BPD, respiratory support and management of underlying lung disease should be targeted and optimized before consideration of PH-specific drug therapies.[58] Impaired gas exchange may cause hypoxic vasoconstriction, elevated PAP, and eventually, structural remodeling of the pulmonary arteries. An initial step for the management of PH in BPD infants is to target higher oxygen saturations, generally above 92–95%. To improve gas exchange, a full respiratory evaluation is critical, which may lead to impactful interventions. Factors contributing to hypoxemia, including bronchospasm and airway obstruction, should be diagnosed and treated appropriately. Tracheobronchomalacia, diagnosed by flexible fiberoptic bronchoscopy, may result in further airway obstruction. Recurrent infection, gastroesophageal reflux, and aspiration cause airway inflammation and further impair ventilation. In cases of severe chronic respiratory failure, long-term mechanical ventilation via tracheostomy may help improve gas exchange and sustain better lung volumes to optimize mechanical effects on PVR, and may benefit the child's neurodevelopmental potential.

After maximizing respiratory support, PAH-targeted drug therapy may be considered. Although randomized controlled trials in children are lacking for many of these medications, adult studies, expert consensus, and recent guidelines support their use.[4,59,60] In most cases, cardiac catheterization is indicated prior to initiation of therapies to exclude conditions that may be worsened by pulmonary vasodilator therapy such as left ventricular dysfunction, intra-cardiac shunts, collateral vessels, and pulmonary veno-occlusive disease.[61,62]

Pharmacological therapies for PVD target three important vasoactive signaling mechanisms: the nitric oxide, endothelin, and prostacyclin pathways.[59] First, inhaled nitric oxide, as well as soluble guanylate cyclase (sGC) stimulators and activators, cause vasodilation by increasing cyclic guanosine monophosphate (cGMP) production in the pulmonary arterial smooth muscle cell.[63–65] Phosphodiesterase-5 (PDE-5) inhibitors prevent cGMP degradation to also cause vasodilation. Second, the potent vasoconstrictive effect of endothelin-1 can be prevented by endothelin receptor antagonists (ETRA).[66]

Finally, prostacyclin analogues cause vasodilation by activating cyclic adenosine monophosphate (cAMP).[67] Current guidelines for the sequential or combined use of these therapies have been published,[4] but largely reflect limitations of data from small case series reports or studies in adult patients and personal experience. More information is needed to compare the relative efficacy of current PAH drugs as initial therapy in specific diseases, as well as optimal combinations of agents. More recently, there has been growing enthusiasm for the initial use of combination therapy at the time of PH diagnosis in adult PH; whether or not this will improve long-term outcomes in pediatric PVD has not yet been studied.

Limitation of current therapies for pulmonary vascular disease in children

Although the aforementioned therapies have demonstrated varying degrees of clinical utility, they possess a number of general and specific limitations. Inhaled nitric oxide is one of the most selective pulmonary vasodilators and has been FDA-approved for the management of neonatal respiratory failure and PPHN, but must be inhaled continuously. At higher doses, there may be a loss of the ''microselective'' effect on ventilation-perfusion matching or a potentiation of oxidative stress and inflammation, particularly in the setting of parenchymal lung disease.[68] Although PDE-5 inhibitors are both clinically effective and easily administered, sildenafil was associated with an apparent dose-related increase in mortality for children with IPAH.[5,69,70] Despite the FDA black box warning, however, mortality in children likely reflects problems with study design and other factors in the STARTS trial.[6] Most series describing clinical experience with sildenafil in pediatric PH have not reported mortality or late adverse effects, but a group of PH experts still urge close monitoring of disease progression.[7] More recently, the FDA has modified its stance on the use of sildenafil in children with PH and the European Medicines Agency has approved sildenafil for use in pediatric PH.

Newer agents such as the PPARγ agonist, rosiglitazone, and the Rho-kinase inhibitor, fasudil, are promising but not studied in children.[71,72] Pulmonary vasodilator medications may have non-specific effects on the systemic vasculature resulting in systemic hypotension.[73,74] Finally, therapies targeting pulmonary vasodilation as the primary mechanisms of action may be ineffective in the setting of severe hypertensive vascular remodeling or structural lung disease, as seen in children with lung hypoplasia with decreased vascular surface area related to DLD such as BPD and congenital diaphragmatic hernia.[58]

Potential novel approaches to restore normal pulmonary vascular development

PVD in newborns, infants, and children often occurs in association with developmental arrest of lung vascular and alveolar growth, and past experimental studies have shown that disruption of angiogenesis impairs distal airspace growth and lung structure.[23] Thus, targeting mechanisms that preserve or augment lung vascular growth and development may enhance long-term outcomes.[75] It is thought that enhanced postnatal vasculogenesis or angiogenesis, such as through circulating and lung resident endothelial progenitor cells (EPCs), may provide a key strategy for regenerative mechanism.[76,77] In preterm infants who later develop moderate or severe BPD, the cord blood is deficient in late-outgrowth EPCs, also known as endothelial colony-forming cells (ECFCs), suggesting ECFCs may serve as early biomarkers of BPD risk.[78,79] ECFCs are highly proliferative, self-renewing, clonogenic, and form de novo vessels in vivo.[80,81]

In addition to studies that identify ECFCs as potential biomarkers for disease risk, preclinical studies suggest that cell-based therapies may promote lung repair and regeneration in animal models of neonatal lung disease and in ex vivo scaffolds.[82,83] For example, ECFCs and mesenchymal stromal cells (MSCs) prevent PH in neonatal rodents with experimental BPD.[84–88] MSCs prevent PH when administered intravenously[89] or intratracheally[86–88] to neonatal mice with experimental BPD. Furthermore, ECFC- and MSC-conditioned media (CM) prevent experimental BPD even when given via intraperitoneal administration, strongly suggesting that both cell types act via paracrine mechanisms.[86–90] A phase 1 clinical trial delivering a single intratracheal dose of MSCs suggests that MSC therapy may be safe for administration to preterm infants at risk for BPD,[91] and a phase 2 trial is now underway to determine efficacy. Nevertheless, how stem cell therapies can be utilized to restore pulmonary vascular growth in infants with PVD remains an area of ongoing inquiry, but has potential as a therapeutic breakthrough.[92] If successful, harnessing such novel therapies outside of the neonatal window could also prove useful for older children with PVD, particularly when related to pulmonary vascular insufficiency or developmental disorders.

Long-term implications for early diagnosis and treatment of pulmonary vascular disease in children

Several important considerations are relevant when considering the long-term consequences of pediatric PVD, but unfortunately, there are currently far more questions than answers. First, for infants and children who are diagnosed with PH, to what extent does early diagnosis and treatment impact long-term outcome, and what are the meaningful biomarkers or clinical endpoints that can predict improved outcome? Registry studies continue to be an important source of data regarding long-term outcomes and demonstrate improving overall survival in pediatric PAH, with 5-year survival estimates at 72–75%.[12,13,93] Adult PAH studies now suggest an additional survival benefit to upfront combination vasodilator therapies,[94,95] yet whether this strategy

will also be of benefit in children remains to be seen. Ultimately, the long-term goal for children with PHVD will be to maintain growth and development as well as RV function well into adulthood, yet identification of which specific strategies are most likely to accomplish this feat is lacking.

Second, to what degree are infants and children with PVD more susceptible to pulmonary vascular stressors, such as hypoxia, pulmonary infection, cigarette smoke, air pollution, or even hormonal changes of puberty? Several studies have identified increased susceptibility to vascular stressors, particularly hypoxia. For example, young adults with a history of PPHN have significantly greater pulmonary vasoreactivity in response to acute hypoxia at altitude when compared to controls, despite having normal PAP at sea level.[96] Similarly, a history of perinatal hypoxia has recently been shown to increase susceptibility to pulmonary vascular dysfunction and polycythemia more than sixfold in young adults living at high altitude.[97] In adults born premature, this interplay between perinatal insults and later hypoxic risk is further accentuated by evidence of impaired hypoxic ventilatory drive, thereby increasing their risk for clinically relevant hypoxemia.[98] Preclinical studies also demonstrate worsening PH after adult hypoxia exposure in an animal model of prematurity associated lung disease, though surprisingly, there appeared to be unique RV adaptive features that may mask the severity of PH.[99,100] If this extends to human exposures, diagnosis of PH may ultimately be delayed, as symptoms may not be obvious until the RV begins to fail.

Other vascular stressors, such as infection and cigarette smoke, likely contribute to ongoing vascular remodeling, though it is unclear if the risk in children is greater than adults. Infections are a well-known cause of acute PH crisis at all ages, and there are case reports of viral illnesses precipitating new presentations of PH in infants.[101,102] Regarding tobacco use, pulmonary vascular remodeling occurs in adult smokers even prior to the development of clinical lung disease,[103,104] but the effects of cigarette smoke exposure on the pediatric pulmonary vasculature remains largely unknown. Finally, registry data demonstrate a slight female predominance in pediatric PH, though less so compared to adult registries.[12,17] Although prolonged estradiol infusion causes sustained and remarkable pulmonary vasodilation in fetal lambs, the effects of estrogen may be strikingly different with maturation.[105] Given the potential for estrogens to accelerate pulmonary vascular remodeling in adults,[106] it is surprising that no studies have evaluated the effect of puberty on pediatric PAH. Acknowledging the associated risks in children with PVD, current clinical practice is strict avoidance of vascular stressors whenever possible, but clearly this requires early diagnosis for proper counseling.

Third, to what degree does pediatric PVD, particularly without clear PH (e.g. "subclinical" disease), predispose the pulmonary vasculature for later malfunction? Adult onset PH is typically thought to result from multiple insults to the pulmonary vasculature,[1] and developmental vascular abnormalities likely serve as an initial insult that could decrease the overall pulmonary vascular endowment for life (Fig. 5). Indeed, a growing body of evidence suggests that perinatal and postnatal events can prime the pulmonary vasculature and RV for later dysfunction, which may not be recognized until well into adulthood. Recently, young adults born preterm were found to have increased biventricular mass and reduced RV function when compared to age-matched term-born adults, with increasing severity when stratified by degree of prematurity, which may suggest persistent PVD.[49,107] No studies to date have evaluated long-term changes in PAP, PVR, or RV-pulmonary vascular interactions following premature birth in humans, though trials are now underway. However, a recent Swedish registry

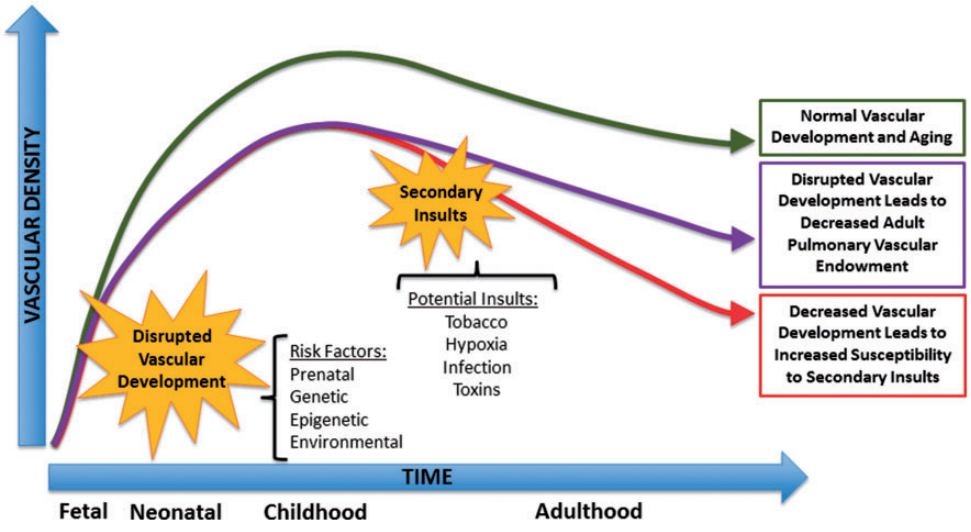

Fig. 5. Early life pulmonary vascular development impacts adult pulmonary vascular endowment and risk for pulmonary hypertension.

review of adults with PAH identified premature birth as an independent risk factor for the development of adult onset PAH.[108] It is highly probable that additional, currently unrecognized, perinatal and developmental factors also affect late development of PH.

Conclusion

Clearly, much remains to be elucidated regarding the characterization of the natural history, epidemiology, pathophysiology, co-morbidities, and other factors that contribute to the diverse phenotypes of pediatric PVD, which will undoubtedly impact pediatric PVD diagnosis, treatment, and long-term outcomes. Hopefully, ongoing studies will allow for enhanced recognition, diagnosis, and classification of pediatric PVD, and emerging treatment strategies will enhance pulmonary vascular development to improve long-term outcomes in children with PVD.

Conflict of interest

The author(s) declare that there is no conflict of interest.

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