Title

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Journal

The European respiratory journal. Supplement, 63(6)

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Publication Date

2024-06-01

DOI

10.1183/13993003.01518-2023

Seeing pulmonary hypertension through a paediatric lens: a viewpoint

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Shareable abstract (@ERSpublications)
Paediatric pulmonary hypertension (PH) offers unique genetic and developmental insights that can help in the discovery of novel mechanisms and targets to treat adult PH https://bit.ly/3TMm6bi

Cite this article as: Agarwal S, Fineman J, Cornfield DN, *et al*. Seeing pulmonary hypertension through a paediatric lens: a viewpoint. *Eur Respir J* 2024; 63: 2301518 [DOI: 10.1183/13993003.01518-2023].

Received: 8 Sept 2023
Accepted: 16 March 2024

Introduction

Pulmonary hypertension (PH) is a life-threating condition associated with abnormally elevated pulmonary pressures and right heart failure. Current epidemiological data indicate that PH aetiologies are different between the adult and paediatric population. The most common forms of PH in adults are PH from left heart disease or chronic lung disease, followed by pulmonary arterial hypertension (PAH) [1]; in paediatric patients, PH is most often associated with developmental lung disorders and congenital heart disease (CHD) [2, 3]. In contrast to adults with PH, wherein patients worsen over time despite therapy, PH in children can improve with growth. For example, in infants with bronchopulmonary dysplasia (BPD) and PH morbidity and mortality are high, but with lung growth and ensuring no ongoing lung injury pulmonary vascular disease can improve as evidenced by discontinuation of vasodilator therapy in almost two-thirds of BPD-PH survivors by age 5 years [3, 4]. Improvement in pulmonary vascular tone and reactivity likely derives from ongoing angiogenesis, even well past the neonatal time frame. Indeed, abnormal lung growth and pulmonary hypoplasia are commonly present in PAH and PH associated with congenital heart disease (CHD) [5], Down's syndrome [6] and congenital diaphragmatic hernia [7], suggesting that limiting vascular and parenchymal injury, as well promoting longitudinal growth, can improve pulmonary vascular disease over time.

A link between fetal-neonatal lung disease and risk of PH in adulthood

In the 1980s, the British epidemiologist David Barker coined the concept of "fetal origins of adult disease", proposing that suboptimal intrauterine nutrient supply and subsequent low birth weight disrupt physiological morphogenic programming and predispose individuals to an increased risk of disease in adulthood [8]. This notion that there are fetal origins of adult disease has been increasingly accepted since Barker's report and expanded on development in general, giving rise to the concept of "developmental origins of health and disease". Development of pulmonary parenchyma and the microvasculature are integrally intertwined and codependent during the second and third trimesters of fetal life, followed by a roughly 20-fold increase in alveolar and vascular surface area after birth. Pharmacological manipulation in preclinical studies during the saccular or early alveolar stages (second and third trimester) demonstrate that inhibition of either the vascular or airway compartments can inhibit further development and growth of the other compartment [9]. CHD can entail a midline heart defect or patent ductus arteriosus that leads to an

increase in pulmonary blood flow and an increase in pulmonary vascular pressure and pulmonary vascular reactivity. In children with trisomy 21, the pulmonary circulation can include prominent intrapulmonary bronchopulmonary anastomoses and persistence of the double capillary network in the postnatal alveoli, suggesting delayed lung maturation [10]. In addition, genetics influence overall structure and development. Collectively, impaired development and genetic susceptibility may also lead to persistence of fetal circulation patterns, including patent ductus arteriosus (CHD leading to pulmonary over-circulation), or persistence of a double capillary network and prominent intrapulmonary bronchopulmonary anastomoses (common in Down syndrome) [10]. Thus, abnormal lung development or preterm birth span a spectrum of injury and may increase risk for multiple adult lung diseases. For example, extremely preterm-born infants and survivors of BPD have a higher risk of developing COPD later in life [11]. Although less documented, several longitudinal cohort studies have highlighted the long-term effects of *in utero* and early life factors on pulmonary vascular dysfunction in adulthood (figure 1) [12]. Jayet *et al.* [13] found that preeclampsia, a prenatal risk factor for chronic lung disease in very low birth weight infants, is associated with persistent pulmonary circulation dysfunction and approximately 30% higher pulmonary artery pressure in offspring than in control subjects. They also found greater increases in pulmonary artery pressure at high altitude in young adults who developed transient persistent pulmonary hypertension of the newborn (PPHN) compared to volunteers without any history of perinatal complications [14]. Similarly, in a prospectively followed US cohort, 45% of young adults born extremely preterm demonstrated early pulmonary vascular disease characterised by elevated mean pulmonary artery pressure >19 mmHg and right ventricular dysfunction [15].

Low birth weight is a surrogate marker of poor fetal growth (intrauterine growth restriction; IUGR) and a risk for preterm birth. Initial evidence also indicates that children with IUGR are also at risk for lung function trajectories below average and at risk for chronic lung disease later in life [16, 17]. Studies conducted in rodents also suggest that perinatal insults predispose to pulmonary vascular dysfunction in adulthood. Similarly, experimental models of IUGR demonstrate vascular and alveolar remodelling that could underlie the PH-associated mechanisms across the life span [18, 19]. On the contrary, initial experimental studies show that high calorie intake together with maternal obesity cause vascular muscularisation and PH in the offspring [20]. Postnatally, mice exposed to neonatal hyperoxia (100%

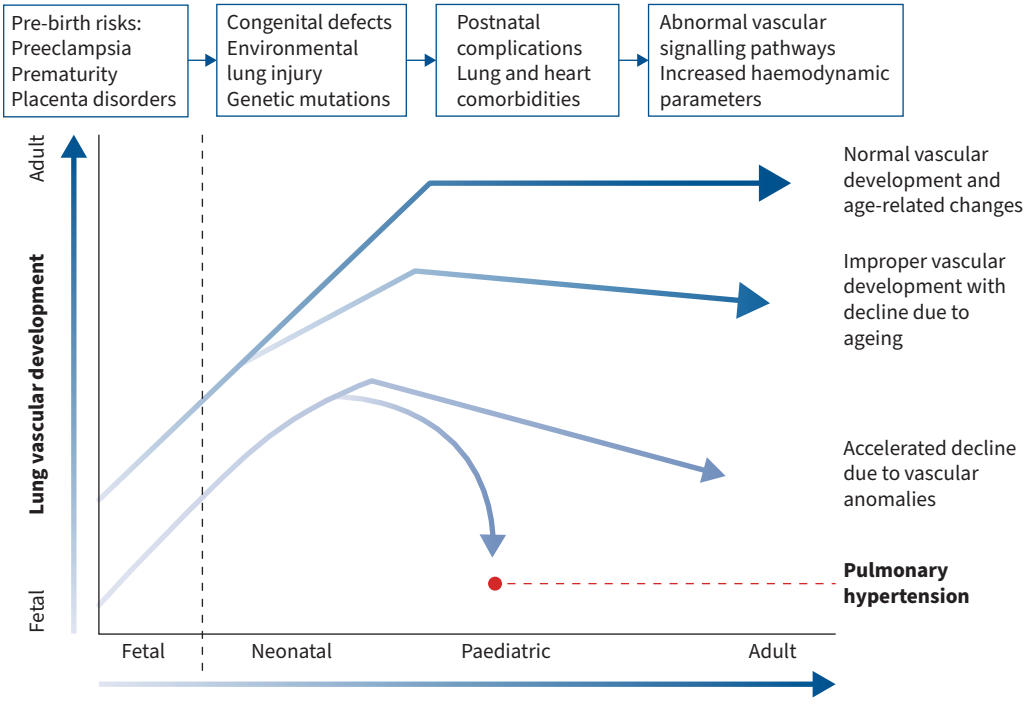

FIGURE 1 Mechanisms associated with the pathogenesis and evolution of paediatric pulmonary hypertension (PH) with relevance to adult PH. Prenatal factors (*e.g.* preeclampsia, premature birth) and genetic defects can adversely impact perinatal pulmonary vascular growth and increase susceptibility to PH with age, environmental stressors and systemic diseases. Modified from [12] with permission from the publisher.

oxygen between postnatal days 1–4) show a reduced lifespan, decreased lung elastance, right ventricular hypertrophy and PH at 67 weeks of age [21]. Rats exposed to a vascular endothelial growth factor receptor 2 antagonist perinatally and exposed to either hypoxia or hyperoxia demonstrate reduced pulmonary angiogenesis, increased pulmonary artery wall thickness and decreased alveolarisation, mirroring abnormalities encountered in premature newborns who develop BPD [22–25]. Despite catch-up growth, these abnormalities can persist into adulthood as diminished pulmonary artery density, increased pulmonary artery wall thickness, airspace enlargement and right ventricular hypertrophy, which were also detected in adult rats [26]. The Fawn-hooded rats (FHR) spontaneously develop PH at sea level, a phenotype amplified upon exposure to mild hypoxia. Compared to Sprague Dawley rats, the lung architecture of FHR pups exhibits a marked airspace enlargement characteristic of impaired alveolarisation. Moreover, oxygen therapy during the combined prenatal and early postnatal period significantly improved alveolarisation and reduced the development of PH in these rats, reinforcing the notion that PH detected in adult life originates at least partly from developmental defects [27].

The long-term pulmonary vascular and right ventricular consequences of early-onset paediatric pulmonary vascular disease remain unclear, but underscore the need for transition to adult care that is multidisciplinary. First, the disorders that lead to PH in children are often more multifactorial. With respect to the clinical classifications of PAH, this was recognised in the Panama classifications of paediatric PH, where there is frequently overlap between traditional groups from the World Symposium on Pulmonary Hypertension [28]. Moreover, there may be implications for the duration of even less severe PAH on right ventricle function and overall mortality. In adolescents and adults born prematurely, both echocardiogram and catheterisation studies demonstrated mild elevations in mean pulmonary artery pressure, particularly in those with a history of BPD [15, 29]. Given that mild elevation in mean pulmonary artery pressure is associated with increased mortality in adulthood [30, 31], these findings are expected to have significant clinical implications.

How do early insults like preterm birth or CHD directly influence the right ventricle? In the case of preterm birth, the heart is consistently smaller into adulthood, including reduced biventricular length and volumes [4, 32]. Functionally, this results in impaired stroke volume reserve during exercise [15, 33], and resting right ventricle function may be impaired, particularly in those with a history of BPD [34, 35]. Given the potential for airways, pulmonary vascular and cardiac involvement, cardiopulmonary exercise testing is particularly helpful in this population to define limitations. Intriguingly, rodent studies using postnatal hyperoxia to mimic BPD demonstrate that although the right ventricle maintains its function in early life, even mild pulmonary vascular disease can lead to right ventricular failure in adulthood [22]. However, relatively well-preserved function early in life may translate to difficulty determining appropriate screening intervals for extremely preterm-born individuals at the highest risk. On the converse, patients with CHD who develop Eisenmenger syndrome, associated with the reversal of left to right shunt in the setting of PH, demonstrate improved overall survival in adulthood compared to other PAH patients [36]. This survival advantage is thought to result from the persistence of the fetal right ventricle (*i.e.* wall thickness similar to the left ventricle) which helps the right ventricle adapt to high pulmonary pressures [37].

Genetic differences between paediatric and adult PH

Paediatric-onset PAH differs from adult-onset PAH in many important aspects, including clinical presentation, molecular mechanisms, genetic burden and the specific genes involved. Development of pulmonary vasculature comprises vasculogenesis and angiogenesis processes and occurs in proximity and in synchrony with airway development [3]. Pulmonary vascular development is tightly controlled by cell–cell and cell–environmental communications *via* a series of molecular cues, including vascular endothelial growth factor (VEGF) and its receptor VEGFR2, T-box 4 (Tbx4) and Tbx5, SRY-related HMG box17 (Sox17), fibroblast growth factors 9 and 10 and their counter receptors, Akt-endothelial nitric oxide synthase signalling, angiopoietin 1 and its receptor Tie2, and the mechanotransducers Yap/Taz [38–40]. It is also important to note that alveolar development continues after birth until at least 2 years of age. Not surprisingly, disturbance of normal embryonic lung and/or pulmonary vascular development, premature birth, prenatal conditions and postnatal interventions (preeclampsia, oxygen therapy, *etc*.) largely contribute to paediatric PAH (table 1). Paediatric PAH is associated with higher clinical severity, better response to treatment, and a profound genetic component, which contributes to approximately 35% of paediatric-onset idiopathic PAH compared with approximately 11% of adult-onset PAH [41].

Mutations in genes, many of which encode developmental proteins, have been detected in both adult and paediatric PAH. The most common genetic cause of hereditary and sporadic PAH in adults, also detected in children with PAH, are mutations in bone morphogenetic protein receptor 2 (BMPR2), which is

TABLE 1 Perinatal insults associated with pulmonary hypertension

Perinatal insult	References
Premature birth	[56–59]
Intermitted hypoxaemia	[60]
Hypoxia	[61]
Congenital diaphragmatic hernia	[7, 62, 63]
Bronchopulmonary dysplasia	[63, 64]
Drug exposure	[65–68]

essential for the maintenance of pregnancy and for post-implantation embryonic development [42]. Over the past 5 years, genetic screening of large PAH cohorts has led to the discovery of new genetic markers, including ATP13A3, GDF2 (BMP9), *Sox17*, AQP1, KCNK3 and CAV1 (figure 2, table 2) [41, 43, 44]. Whole genome sequencing has revealed kinase insert domain receptor (KDR), the gene that encodes for VEGFR2, to be associated with PAH [45, 46], and an independent predictor of PH in interstitial lung disease [47]. The genetics of paediatric PAH differs by enrichment in *de novo* and rare deleterious variants and in frequency of mutations of developmental genes encoding transcription factors, such as *Tbx4* and *Sox17* (figure 2, table 3). *Tbx4* and *Tbx5* are essential for trachea formation, proper lung branching morphogenesis, early stage lung development, and vascularisation that dictates microvascular density during lung development [39]. Interestingly, a clinical and histological analysis of 19 children carrying rare deleterious *Tbx4* variants revealed a high frequency of severe developmental defects of the lung, skeleton and heart [48]. 10 of the infants presented with PPHN which resolved; however, the children were subsequently diagnosed with PAH later in infancy or childhood. This points to an especially significant role for *TBX4* in paediatric-onset PAH.

Sox17 acts upstream of Notch signalling and plays an essential role in vascular network formation [49, 50]. Exome sequencing data in a cohort of 256 patients with PAH-CHD estimated that rare deleterious variants in *Sox17* contribute to approximately 7% of paediatric-onset PAH, especially PAH-CHD, compared with 0.4% of adult-onset PAH. In addition, common single nucleotide polymorphisms in a putative endothelial-acting enhancer region of *Sox17* are associated with PAH [51], suggesting that variation in *Sox17* gene expression may increase the risk for developing PAH. In addition to providing better understanding of PAH genetics, these studies strongly suggest the importance of transcription factor networks in angiogenesis and maintenance of vascular integrity in PAH and paediatric PAH.

Leveraging clinical and genetic differences in paediatric and adult PH in screening and treatment

Considering the similarities and differences in PH between paediatric and adult patients might inform the discovery of more effective and precise therapeutic tools that serve both groups. First, deep genotyping using next-generation strategies should be considered for every PH patient so that, as genetic discoveries unfold, the disease aetiology might be definitively identified in more of the children and adults with PAH presently considered idiopathic. In children a genetic basis for PAH has been identified in about 40% of paediatric cases, as opposed to only 12% in adults [44]. Second, innovative imaging strategies to identify abnormal pulmonary vascular development are needed. Whether novel therapeutics such as sotatercept, which acts as a ligand trap for transforming growth factor β superfamily activins and growth differentiation

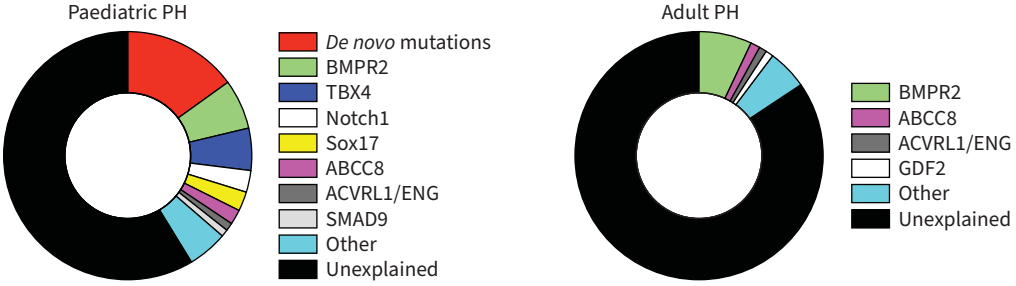

FIGURE 2 Distribution of genetic mutations in paediatric and adult pulmonary hypertension (PH) populations. Relative contributions of *de novo* mutations and 18 pulmonary arterial hypertension (PAH) risk genes in a cohort of 443 paediatric and 2628 adult cases from the Columbia University Irving Medical Center and the PAH Biobank. Reproduced from [41] with permission from the publisher.

TABLE 2 Genes associated with adult pulmonary hypertension

Gene	Function	References
BMPR2	Bone morphogenetic protein receptor 2, a member of the BMP signalling pathway	[69, 70]
EIF2AK4	Encodes GCN2, a kinase that phosphorylates the alpha subunit of eukaryotic translation initiation factor 2	[44, 71]
Tbx4	Member of the T-box gene family, encodes a transcription factor involved in lung development	[72]
GDF2	Encodes for BMP-9, a secreted ligand of the transforming growth factor (TGF)-beta superfamily of proteins	[73, 74]
SOX17	Encodes a member of the SOX (SRY-related HMG-box) family of transcription factors involved in endothelial regeneration and angiogenesis	[51, 75]
ENG	Endoglin, a member of the TGF-beta pathway; ENG mutations are associated with Osler–Weber–Rendu disease	[45]
KCNK3	A member of the superfamily of potassium channel proteins that acts as an outwardly rectifying channel	[45]
ABCC8	A member of superfamily of ATP-binding cassette (ABC) transporters that moves proteins across membranes	[76]
KLK1	Encodes a kallikrein involved in the release of Lys-bradykinin, a vasoactive peptide	[77]
GGCX	Endoplasmic reticulum protein that carboxylates glutamate residues of vitamin K-dependent proteins	[77]
SMAD9	Signalling mediator of the TGF-beta superfamily of proteins	[45]
AQP1	Membrane protein that acts as a water transport channel	[78]
BMP10	A secreted ligand of the TGF-beta superfamily of proteins	[44]
KDR	Vascular endothelial growth factor receptor 2, a gene involved in endothelial homeostasis and angiogenesis	[44]

factors [52–54], are equally tolerated by individuals with PAH related to developmental lung diseases remains to be studied. These observations suggest that in both adults and children, careful phenotyping superimposed on identifying molecular subtypes of PAH might result in better strategies to risk stratify and deliver more precise treatments.

Emerging high-throughput single-cell, proteomics and metabolomics technologies combined with machine learning provide new opportunities to accelerate biomarker discovery and prioritise some for further evaluation. Several recent studies using aptamer-based or antibody-based methods have identified novel plasma proteins that predict mortality in PAH patients [45, 46]. Unbiased approaches superimposed on expanding biomarker testing with sensitivity for low abundant proteins have motivated identifying specific factors or signatures that reflect disease severity and prognosis. Although high throughput technologies provide an unprecedented opportunity for the identification of markers of disease processes, a significant challenge will consist of filtering these many candidate biomarkers, adopting a consensus list, and demonstrating their utility and reproducibility in large, prospective and multisite studies using patients from different ethnic origins and using defined cut-off values. In addition, numerous confounding factors can cloud the clinical use of biomarkers, especially in paediatric PH (*e.g.* nutritional status, developmental stage, sex). Therefore, searching for an ideal set of biomarkers and potential applications in clinical medicine is ongoing and may benefit from collaboration between the PH community and industry.

Conclusions

For the past two to three decades, treatment for paediatric and adult PH has centred on vasodilators targeting the endothelin, nitric oxide and prostacyclin pathways [15]. However, as most clinical trials have

TABLE 3 Genes associated with paediatric pulmonary hypertension

Gene	Function	References
Tbx4	Member of the T-box gene family; encodes a transcription factor involved in lung development	[44, 79–82]
BMPR2	Bone morphogenetic protein receptor 2, a member of the BMP signalling pathway	[79, 80]
ACVRL1	Activin A receptor like type 1, a receptor belonging to the transforming growth factor (TGF)-beta superfamily of proteins; mutations are associated with Osler–Weber–Rendu disease	[79]
KCNK3	A member of the superfamily of potassium channel proteins that acts as an outwardly rectifying channel	[79]
SMAD9	Signalling mediator of the TGF-beta superfamily of proteins	[79]
ABCC8	A member of superfamily of ATP-binding cassette (ABC) transporters that moves proteins across membranes	[76, 83]
SOX17	Encodes a member of the SOX (SRY-related HMG-box) family of transcription factors involved in endothelial regeneration and angiogenesis	[55]
NOTCH3	Notch 3 receptor, a member of the Notch intercellular signalling pathways	[84, 85]
ATP13A3	A member of the P-type ATPase family of proteins that moves cations across membranes	[86]
CAV1	Caveolin-1, a scaffolding protein associated with plasma membrane caveolae	[87]
CPS1	Carbamoyl-phosphate synthase, a mitochondrial enzyme that catalyses synthesis of carbamoyl phosphate from ammonia and bicarbonate	[85]

been conducted in adults, it is unclear whether similar benefits are obtained in the paediatric population, resulting in major disparities in quality of life and outcomes between paediatric and adult populations. Moreover, the differences in the aetiology and clinical course of PH highlight the underlying differences in pathobiology and disease progression between adult and paediatric PH. In particular, the perinatal period of adverse influences and complications should be taken into account when considering the origins of PH. Emerging high-throughput omics approaches, including single-cell technologies, reveal progressive cellular heterogeneity and demonstrate new canonically distinct cellular subpopulations arising in PAH [55]. In revealing new cell populations with unique signalling pathways, these emerging platforms may facilitate the discovery of potentially exciting new targets for therapeutic intervention. Applying and unifying these approaches is an aspirational goal that will improve and inform our collective understanding of both shared and distinct aspects of adult and paediatric PAH pathogenesis.

Author contributions: S. Agarwal and V. de Jesús Pérez were responsible for conceptualising and drafting the manuscript, and overseeing manuscript organisation. All authors contributed to the planning, design, and drafting of the sections included in the manuscript. All authors were involved in reviewing and approving the final manuscript.

Conflict of interest: The authors have no potential conflicts of interest to disclose.

Support statement: This work was supported by NIH (R01 HL139664, R01 HL160018, R01 HL134776 and R01 HL159886, to V. de Jesús Pérez; R01 HL166932 to T.V. Kudryashova; and R01 HL130261 and R01 HL172488 to E. Goncharova). Funding information for this article has been deposited with the Crossref Funder Registry.

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