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REVIEW

Pulmonary arterial hypertension: a comparison between children and adults

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ABSTRACT: The characteristics of pulmonary arterial hypertension (PAH), including pathology, symptoms, diagnosis and treatment are reviewed in children and adults.

The histopathology seen in adults is also observed in children, although children have more medial hypertrophy at presentation. Both populations have vascular and endothelial dysfunction. Several unique disease states are present in children, as lung growth abnormalities contribute to pulmonary hypertension.

Although both children and adults present at diagnosis with elevations in pulmonary vascular resistance and pulmonary artery pressure, children have less heart failure. Dyspnoea on exertion is the most frequent symptom in children and adults with PAH, but heart failure with oedema occurs more frequently in adults. However, in idiopathic PAH, syncope is more common in children. Haemodynamic assessment remains the gold standard for diagnosis, but the definition of vasoreactivity in adults may not apply to young children.

Targeted PAH therapies approved for adults are associated with clinically meaningful effects in paediatric observational studies; children now survive as long as adults with current treatment guidelines.

In conclusion, there are more similarities than differences in the characteristics of PAH in children and adults, resulting in guidelines recommending similar diagnostic and therapeutic algorithms in children (based on expert opinion) and adults (evidence-based).

KEYWORDS: Congenital heart disease, paediatrics, pulmonary arterial hypertension

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Pulmonary arterial hypertension (PAH) is a chronic disorder of the pulmonary vasculature, characterised by a progressive increase in pulmonary vascular resistance leading to right heart failure and death. PAH can be idiopathic or associated with underlying conditions [1]. Independent of the aetiology, the pathogenesis of PAH includes a combination of vasoconstriction, inflammation, structural remodelling of pulmonary vessels and *in situ* thrombosis involving dysfunction of underlying cellular pathways [2, 3], as well as an imbalance of vasoactive mediators [4–6]. PAH may present at any age from infancy to adulthood [7]. Abnormalities of lung development may contribute to pulmonary hypertension in children, as alveolar growth and pulmonary vasculature growth are intrinsically linked to each other [8]. In the last decade, treatments that target disease-specific abnormalities have been developed that improve exercise capacity, haemodynamic parameters, World Health Organization (WHO) functional class, overall quality of life and survival in adults [9–17]. The efficacy of these therapies in adults and the poor prognosis in the absence of treatment have led to the inclusion of these new agents in the current recommendations by the paediatric pulmonary hypertension community for treating paediatric PAH [18, 19]. However, there is currently limited information from published randomised controlled trials in children evaluating the safety and/or efficacy of these medications [20].

The purpose of this review is to compare the pathology, pathobiology, symptoms, diagnostic work-up and therapy of PAH in adults and in children. Additionally, we evaluate the current treatment approach in children based on extrapolation from the evidence-based adult algorithm. Due to limited data, many of the statements on paediatric PAH in this review article are based on the consensus opinion of the authors.

DEFINITION AND CLASSIFICATION OF PAH

The definition of PAH, *i.e.* pulmonary vascular obstructive disease, established at the 4th World

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Conference on pulmonary hypertension in Dana Point, CA, USA in 2008, is the same for children as for adult patients: mean pulmonary artery pressure ($\bar{P}_{pa}$) $\geqslant$25 mmHg, normal pulmonary capillary wedge pressure ($\leqslant$15 mmHg) and an increased pulmonary vascular resistance (PVR) [21]. However, whether this definition should apply to infants is debatable. Because children not infrequently have a mean systemic blood pressure <70 mmHg [22], it may be more appropriate to define pulmonary hypertension according to the value of the ratio of the $\bar{P}_{pa}$ to the mean systemic artery pressure (derived from pressures measured during right heart catheterisation) or the ratio of the pulmonary artery systolic pressure to the systemic arterial systolic pressure, with a ratio of either one >0.4 indicating pulmonary hypertension. For children with congenital cardiovascular disease undergoing surgical repair, a $\bar{P}_{pa}$ $\geqslant$25 mmHg or a ratio of the $\bar{P}_{pa}$ to mean systemic artery pressure >0.5 is indicative of post-operative pulmonary hypertension [23]. Additionally, although a specific threshold value for the increase in PVR is no longer in the definition of PAH, the consensus amongst the paediatric pulmonary hypertension community is to continue to include PVR index >3 Wood units·m^2 in the definition. This point is particularly important in patients with unrepaired congenital heart disease, *i.e.* PAH should only refer to pulmonary vascular obstructive disease and not to hyperkinetic pulmonary hypertension due to increased pulmonary blood flow due to a left-to-right systemic to pulmonary shunt [21].

According to the current diagnostic classification established for adults and children [1], PAH is classified as Group I pulmonary hypertension; it is either idiopathic or heritable (IPAH or HPAH), or associated with congenital heart disease (APAH-CHD), connective tissue disease (APAH-CTD), portal hypertension, HIV infection, drugs and toxins, or diagnosed as persistent pulmonary hypertension of the newborn (PPHN). HPAH includes sporadic HPAH and familial HPAH. In children, APAH-CHD and IPAH/HPAH account for the majority of PAH cases, whereas APAH-CTD is frequent in adults [24]. However, sometimes it may be difficult to classify paediatric patients as they may present with multiple problems, as described by VAN LOON *et al.* [25]. Some children with CHD appear not to have the normal decrease in PVR that occurs after birth. They do not develop failure to thrive and/or congestive heart failure during infancy, and can be inoperable from a pulmonary vascular disease standpoint. Whether these infants should be classified as PPHN that does not resolve, IPAH/HPAH or APAH-CHD remains controversial. Although PPHN is classified as Group I PAH, it will not be discussed in depth due to its specificity to infants and its natural history, with the majority of cases either completely resolving or resulting in death. Congenital diaphragmatic hernia can be a cause for PPHN. This condition involves pulmonary hypertension due to a respiratory disorder, *i.e.* Group III pulmonary hypertension, while it also belongs to Group I PAH. Bronchopulmonary dysplasia is another disease of the lung that is increasingly viewed as a cause of pulmonary hypertension in paediatrics. Both congenital diaphragmatic hernia and bronchopulmonary dysplasia are unique causes of pulmonary hypertension in children that do not easily fit into the Dana Point classification [1]. These disorders are intrinsically linked to lung growth and development, as alveolarisation and vasculature development are intertwined.

HISTOPATHOLOGY

The classification of pulmonary hypertension aetiologies into Group I PAH relies on the observation that all subsets of Group I have the same spectrum of histopathological lesions. The grading of pulmonary vascular alterations introduced by HEATH and EDWARDS [26] in 1958, and modified by RABINOVITCH *et al.* [27] in 1978 was developed in APAH-CHD patients, and subsequently adapted to include all Group I PAH patients [28]. However, a single grading/scoring system cannot convey the complexity of the pulmonary vascular lesions, and is not reliable for assessment of disease severity and surgical operability in patients with congenital systemic-to-pulmonary shunts [29]. A better assessment of overall pulmonary vascular disease can be obtained from haemodynamic assessment. Nevertheless, histopathological pulmonary vascular changes in all forms of PAH are qualitatively similar and only show quantitative differences in the distribution and prevalence of the pathological changes [28]. The localisation of plexiform lesions can be different according to aetiology. In congenital left-to-right systemic-to-pulmonary shunts, these lesions tend to occur in arteries 100–200 μm in external diameter, whereas in IPAH they tend to occur in arteries <100 μm [30, 31].

Similarities are observed between the vasculature in children and adults with PAH [32, 33]. In both age groups, the first observed change appears to be an extension of muscle into peripheral, nonmuscular arterioles. Intimal fibrosis, plexiform and thrombotic lesions, and fibrinoid necrosis may subsequently develop. Studies performed on lung tissue obtained at biopsy, pneumonectomy, or autopsy in children ($\geqslant$6 yrs of age) and adult patients with IPAH or HPAH reported that all patients, whether paediatric or adult, had pulmonary artery medial hypertrophy [33]. However, only 43% of all patients had plexiform and/or thrombotic lesions (patient age 10–57 yrs). Adults with IPAH/HPAH often have severe intimal fibrosis, plexiform lesions and what appear to be ''fixed'' irreversible pulmonary vascular changes. In contrast, children with IPAH/HPAH have more pulmonary vascular medial hypertrophy, less intimal fibrosis and fewer plexiform lesions [4]. In a study by WAGENVOORT and WAGENVOORT [34], medial hypertrophy was severe in patients <15 yrs of age, and was most often the only abnormality seen in infants; and among 11 children <1 yr of age at the time of death, all had severe medial hypertrophy, yet only three had intimal fibrosis, and none had plexiform lesions. With increasing age, intimal fibrosis and plexiform lesions were seen more frequently. In infants with complex congenital heart defects, medial hypertrophy and intimal proliferation can evolve very rapidly, and abundant cellular intimal proliferation can obstruct small pre-acinar and terminal bronchiolar arterioles, resulting in increased PVR and death before intimal fibrosis has developed [35]. These features are consistent with clinical observations that infants with PAH are more likely to die from sudden death than adults. Paediatric patients also have more acute pulmonary vasoreactivity with an increased prevalence of acute pulmonary hypertensive crises, *e.g.* syncopal episodes with over-exertion or hypoxic ''seizures'' with even mild hypoventilation during sleep.

Heterogeneity is also observed within and among families with familial HPAH: LOYD *et al.* [36] examined the lesions in 23

affected members of 13 families with known familial HPAH and found marked heterogeneity in the presence of thrombotic and plexiform lesions. Pulmonary histopathology is highly variable even in patients developing HPAH from the same risk factor.

These observations suggest that there is a great degree of histopathological heterogeneity among patients with PAH, regardless of age at onset or aetiology. However, a broad spectrum of histopathological lesions does not necessarily imply different primary mechanisms but rather could be the ''footprints'' of the pulmonary endothelial cell injury and dysfunction associated with PAH, a disease with wide biological variability. In particular, the rapidity of disease progression may be quite variable in the developing lung in children compared with the fully developed lung in adults.

PATHOGENESIS

The precise mechanism(s) of PAH development in adults and children is not thoroughly understood. Nevertheless, endothelial cell dysfunction is thought to play a key role in addition to smooth muscle cell migration and dysfunction, and abnormal apoptosis [2]. Smooth muscle cells de-differentiate, achieving a more synthetic than contractile phenotype, grow into the subendothelial space, and appear to produce the fibrous material responsible for intimal fibrosis [3]. Important vasoconstrictive and proliferative mediators implicated to date in paediatric and adult PAH include thromboxane (TX)A_2 and endothelin-1 (ET-1), opposing vasodilator and antiproliferative vasoactive mediators, such as prostacyclin and nitric oxide (NO) [4–6]. Many of the pertubations in the vasoactive mediators also appear to play a role in the pathobiology of PPHN and in the failure of the normal transition from fetal to post-natal physiology [4].

Because TXA_2 is a potent pulmonary vasoconstrictor and a stimulus for platelet aggregation [37], whereas prostacyclin produces the opposite effects [38, 39], an imbalance between these two vasoactive mediators in favour of TXA_2 could contribute to both pulmonary vasoconstriction and local thrombosis *in situ*. CHRISTMAN *et al.* [40] reported that adult IPAH/HPAH patients have an elevated ratio of the urinary metabolites of TXA_2 to prostacyclin, due to increased release of TXA_2 and decreased release of prostacyclin. TUDER *et al.* [41] observed diminished prostacyclin synthase expression in the lung vasculature of patients (23 adults and one child aged 2 yrs) with PAH. BARST and STALCUP [42] reported increased TX levels in 16 PAH patients aged 1.5–23 yrs. In a case study of a 17-month-old child with IPAH presenting an elevated TXA_2 to prostacyclin ratio (measured as their stable metabolites, TXB_2 and 6-keto-prostaglandin (PG)F1α, respectively), PAH was reduced with prostacyclin infusion (*i.e. i.v.* epoprostenol) and with calcium channel blocker administration, which increased 6-keto-PGF1α levels and decreased TXB_2 levels, respectively [43]. An imbalance favouring TXA_2 production has also been observed in children and adolescents with APAH-CHD [44, 45]. This imbalance is usually restored to normal after corrective open-heart surgery [44].

ET-1 is a potent vasoconstrictor and a mitogen for smooth-muscle cells [46] and fibroblasts [47]. Elevated plasma ET-1 levels have been reported in adult PAH patients [48, 49] with increased pre-proET-1 gene expression in pulmonary vascular endothelial cells [50]. Similar alterations of ET-1 signalling have been reported in infants and children with PAH [51–54]. Children with APAH-CHD also have increased ET-1 immunoreactivity and endothelin receptor type A (ET_A) density in the pulmonary arterial wall [55].

NO is a potent endothelium-derived vasorelaxant substance and an inhibitor of smooth muscle cell growth [56, 57]. NO is produced in various cell types by the action of NO synthase (NOS) [58]. Adults with PAH have impaired endothelium-dependent relaxation of pulmonary arteries and decreased endothelial NOS (eNOS) gene expression [59, 60]. Additionally, studies of endogenous NOS inhibitors, such as asymmetrical dimethylarginine (ADMA), support the hypothesis that eNOS is important in maintenance of normal pulmonary vascular tone. This has been observed in adults with IPAH [61], and children and young adults with APAH-CHD [62]. Structural abnormalities of pulmonary vascular endothelial cells are present in children with APAH-CHD [63]. Impaired endothelium-dependent vasorelaxation is already evident in some children with CHD with increased pulmonary blood flow prior to the development of established PAH, suggesting that endothelial dysfunction is an early event in these patients. The vascular responses of children with PAH are abnormal, with impaired responses to both endothelium-dependent and -independent agents [64]. In children with CHD undergoing cardiopulmonary bypass, the capacity for smooth muscle relaxation and pulmonary vasodilation could not be induced by acetylcholine, suggesting that the surgery and/or bypass caused the pulmonary endothelial dysfunction and transient post-operative pulmonary hypertension [65].

In addition to regulating vasoreactivity and cellular mitogenesis, the endothelium also modulates local haemostasis. Von Willebrand factor (vWF), a large multimeric plasma glycoprotein produced by endothelial cells [66], is involved in platelet adhesion [67]. vWF has been proposed as both a marker of endothelial dysfunction and a prognostic parameter in PAH [68]. In children and adults with PAH, plasma vWF is increased but dysfunctional because of a loss of its high molecular weight multimers, resulting in reduced platelet binding [68–70]. In a cohort of 64 children and adults with IPAH/HPAH, FRIEDMAN *et al.* [71] reported that 87% of adults and 79% of children had abnormal platelet aggregation at the time of diagnosis. Additionally, factor VIII, vWF and ristocetin cofactor levels were increased in 92, 72 and 52% of the adults, respectively, and in 29, 16 and 16% of the children, respectively. However, with continuous *i.v.* epoprostenol treatment for 1 yr, platelet aggregation normalised in 83% of the adults and in 80% of the children who had platelet aggregation abnormalities at baseline; factor VIII, vWF and ristocetin cofactor levels also decreased in both groups. These studies suggest that *i.v.* epoprostenol can restore endothelial function in children and adult patients with PAH. Improvement in fibrinolysis and ET-1 clearance with *i.v.* epoprostenol is also consistent with epoprostenol improving endothelial function [72, 73].

In summary, in both adults and children, PAH development involves complex molecular and cellular abnormalities, resulting in vascular remodelling in which fibroblasts, smooth muscle cells, endothelial cells and platelets all appear to play a

role. Abnormalities of vascular and endothelial haemostasis, including reduced prostacyclin and NO production, increased TXA_2 synthesis, increased circulating levels of vWF and ET-1 have all been identified in children and adults with PAH.

GENETICS

Genetic factors play a role in PAH development by predisposing some individuals to develop the PAH phenotype. Mutations in receptors for the transforming growth factor (TGF)-β family, including bone morphogenetic protein receptor (BMPR)2, activin receptor-like kinase (ALK)-1 and endoglin receptor, have been reported [74]. Mutations in BMPR2 have been identified in approximately 50–70% of familial HPAH patients [75] and 10–40% of patients previously classified as IPAH but who now would be classified as sporadic HPAH if a mutation is identified [61]; additionally ALK-1 mutations have been detected in adults and children with hereditary haemorrhagic telangiectasia (Osler–Weber–Rendu disease) and coexistent PAH [76]. ALK-1 mutations can also be present in children with PAH who do not present the clinical characteristics of hereditary haemorrhagic telangiectasia [77] but they may develop the condition as they get older. In a study of 18 children with PAH (16 with IPAH and two with APAH-CHD) [78], mutations in BMPR2, ALK-1 and endoglin were identified in four (22%) patients, demonstrating significant genetic heterogeneity for PAH development in childhood-onset PAH, as has been observed in adult-onset PAH. Once a mutation is identified in a patient considered to have IPAH, the classification is changed to sporadic HPAH. ROBERTS *et al.* [79] also identified BMPR2 mutations in 6% of a cohort of adults (n=40) and children (n=66) with APAH-CHD (with mutations identified in both the paediatric- and adult-onset PAH patients). ROSENZWEIG *et al.* [80] reported that 23 (16%) out of 147 IPAH/familial HPAH patients were BMPR2 mutation-positive: eight (10%) out of the 78 children and 15 (22%) out of the 69 adults. In contrast with the above studies, a study of 13 children <14 yrs of age diagnosed with IPAH did not detect BMPR2 or ALK-1 mutations; those authors suggested that some IPAH cases could have a different genetic background in childhood and adulthood [81].

In addition to being detected in children and in adults with PAH, BMPR2 mutations seem to have similar clinical implications in both. In particular, BMPR2 status appears to predict the response to acute vasodilator testing. ELLIOTT *et al.* [82] reported that adult patients with BMPR2 mutations were less likely to respond to acute vasodilator testing than BMPR2 mutation-negative patients. ROSENZWEIG *et al.* [80] subsequently confirmed the results of ELLIOTT *et al.* [82] in adult patients and extended the observation to paediatric patients. Additionally, in both paediatric and adult cohorts [80], patients with BMPR2 mutations appeared to have more severe disease at diagnosis. These observations further support the premise that whether PAH develops clinically during childhood or adulthood, it has similar predisposing genetic factors. Although BMPR2 mutations may be present from conception, the disease may only present later in life; it remains unclear why it takes decades in some patients for the disease to become clinically manifest, yet only months in others. This variability could be related to polymorphisms in the renin–angiotensin–aldosterone system, which is associated with age at PAH diagnosis [83].

Other genetic loci may also be implicated in PAH development in adults and children. A role has been suggested for the serotonin transporter gene in PAH adults [84]; similarly, a study in children found that homozygosity for the long variant of the serotonin transporter gene could be associated with IPAH [85].

These studies indicate that, as seen for PAH adult patients, some cases of PAH presenting in childhood also appear attributable to TGF-β and serotonin receptor defects. The observation that familial HPAH displays age- and sex-dependent incomplete penetrance with genetic anticipation is consistent with the requirement for additional environmental and/or genetic modifiers for disease development.

EPIDEMIOLOGY

The frequency of IPAH/HPAH in children and adults remains unknown. Estimates of incidence range from one to two new cases per million per year in the general population [86] and are thought to be similar in children. The prevalence of IPAH/HPAH in children was estimated to be $\geqslant$2.2 cases per million, and the overall prevalence of PAH (excluding PPHN and PAH caused by CHD) was $\geqslant$3.7 cases per million [87]. However, the true incidence of APAH-CHD has not been established.

The sex balance in adults with IPAH/HPAH reported in the National Institutes of Health (NIH) registry of primary pulmonary hypertension conducted in the mid-1980s was 1.7–1.8/1 females/males [88, 89], and was similar to that reported for children (1.8/1) with no apparent differences between younger and older children [90, 91]. However, in the Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL), an increase in female preponderance was observed in adults (3.9/1 in PAH patients, 4.1/1 in IPAH/HPAH patients and 3.8/1 in APAH patients) and to a lesser extent in children (2.0/1 in PAH patients) [92]. The development of hormonal replacement therapy may have played a role in this increased female preponderance in the adult PAH population, but this has not been confirmed.

NATURAL HISTORY AND SURVIVAL WITH TREATMENT

There is significant biological variability in the natural history of PAH in both adults and children: some patients have rapidly progressive deterioration resulting in death within weeks of diagnosis, but others survive for a decade or longer. Although similarities are observed between PAH aetiologies in terms of clinical features, pathobiology and histopathology, prognosis may be different depending on aetiology. Whereas the natural history of untreated IPAH/HPAH is most often rapidly progressive and fatal, patients with unrepaired APAH-CHD, *e.g.* Eisenmenger syndrome, can survive significantly longer without treatment; familial HPAH, regardless of age at diagnosis, is a prognostic parameter for poor outcome in PAH [93].

Historically, untreated PAH leads to progressive deterioration and death. Survival has been evaluated primarily in IPAH/HPAH patients and APAH-CTD patients. The prognosis for children with IPAH/HPAH initially appeared worse than that for adults; in a 1965 series of 35 children with IPAH/HPAH, 13 (37%) survived >1 yr and none survived >7 yrs [94]. Studies of adult IPAH/HPAH patients from the 1950s to 1990s reported survival estimates at 1, 3 and 5 yrs of 68–77, 35–48

and 21–34%, respectively [89, 95, 96]. In the same era, in children, the 1-, 3- and 5-yr survival rates were comparable: 66, 52 and 35%, respectively [10]. SANDOVAL *et al*. [97] reported an estimated median survival of 4.12 yrs (95% CI 0.75–8.66 yrs) in children with IPAH/HPAH treated with conventional therapy, *i.e.* prior to the availability of targeted PAH therapies, and 3.12 yrs in adults (95% CI 0.5–13.25 yrs; Chi-squares log-rank 0.81; not statistically significant).

Although overall care for patients, both paediatric and adult, is likely to have improved over the past few decades, based on observational uncontrolled data, the availability of the prostacyclin analogue epoprostenol (administered by continuous *i.v.* infusion) in the late 1980s in clinical studies, and its approval in 1995, had a significant impact, with higher survival estimates reported in adults (80–91, 49–65, and 47–55% at 1, 3 and 5 yrs, respectively) [98–102] and children (94, 88 and 81% at 1, 3 and 5 yrs, respectively) [103]. With the availability of oral agents in the past decade, HAWORTH and HISLOP [24] reported IPAH survival rates of 86, 80 and 72% at 1, 3 and 5 yrs, respectively, in children receiving *i.v.* epoprostenol, bosentan or sildenafil as monotherapy or in combination. Similar estimates were subsequently observed for children with IPAH/HPAH or APAH in a French registry [87] and in a retrospective study conducted in two US centres [104]. It is possible that children, who may have greater vasodilator responsiveness and more reversible lesions, respond better to treatment than adults.

These findings support the hypothesis that, despite earlier reports in untreated patients of a higher mortality in children than adults with IPAH/HPAH, the outcome of treated children is now at least as good as that of adults (if not better).

PATHOPHYSIOLOGY AND SYMPTOMS

PAH in adults and children is characterised by an increase in PVR causing an increased right ventricular workload, impaired left heart filling and, eventually, right heart failure [18, 105]. Overall, children with IPAH/HPAH have better preserved cardiac output with lower right atrial pressure and higher mixed venous oxygen saturation at diagnosis compared with adults, although, like adults, they have increased PVR and $\bar{P}_{pa}$ (table 1) [80, 91, 97]. Paediatric patients appear able to withstand the increased right heart workload better than adult patients. This is consistent with later development of right heart failure in paediatric IPAH/HPAH, even though the disease is at least as severe, if not more so, in children as in adults, as indicated by higher ratios of $\bar{P}_{pa}$ to mean systemic blood pressure and PVR index to systemic vascular resistance index at diagnosis. The explanation could be that the right ventricle may compensate better during childhood than later in life for the increased right ventricular workload. Children with IPAH/HPAH or APAH-CHD also appear to have a better clinical status at diagnosis, as indicated by a lower functional class [106, 107].

The overall clinical presentation of PAH in children is similar to that in adults, with dyspnoea on exertion and fatigue remaining the most frequent presenting symptoms; near-syncope, syncope, chest pain and right heart dysfunction occur in both adult and paediatric patients of all ages. However, in our experience with patients with IPAH/HPAH, near-syncope and syncope are more common in children, while right heart failure with peripheral oedema occurs more frequently in adults [108]. As the disease progresses, the adult with right heart dysfunction [109] more often self-limits his physical activity to minimise dyspnoea, whereas the child who can still increase cardiac output with normal daily activities is more likely to become symptomatic with over-exertion, resulting in increased dyspnoea or syncope.

DIAGNOSIS

The diagnostic evaluation of children with a clinical suspicion of PAH is based on the European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines for adult patients [19]; the recommendation to use the same diagnostic work-up proposed for adults is ranked Class IIa (*i.e.* the weight of evidence/opinion is in favour of usefulness/efficacy) and the level of evidence is grade C (*i.e.* it corresponds to a consensus of opinion of the experts and/or small retrospective studies or registries). The diagnosis of IPAH/HPAH is made when all other known causes of pulmonary hypertension have been excluded [110, 111]. The nonspecificity and the subtle presentation of PAH symptoms present difficulties in establishing a diagnosis in adults [112], and even more so in children [113]. Children are not always reliable in reporting symptoms and it is often necessary to rely on parental observations. PAH is often not diagnosed until after an upper respiratory tract infection: the patient does not appear to fully recover from the illness and a chest radiograph is obtained, revealing an enlarged heart. Because children are more exposed to upper respiratory tract infections and are more physically active than adults, they may be more likely to present with symptoms at an earlier stage of the disease. As a consequence, they tend to be diagnosed earlier, prior to the development of right heart failure, than adults who may not be aware of their slowly increasing physical limitations. This is

TABLE 1 Haemodynamic parameters at the time of diagnosis for children and adults with idiopathic or heitable pulmonary arterial hypertension

Parameter	Adults	Children
Subjects n	69	78
$\bar{P}_{pa}$ mmHg	56±13	62±22
Mean SBP mmHg	90±13	75±12
Mean RAP mmHg	10±7	5±3
Mean S_{v,O_2} %	58±10	64±9
Mean S_{a,O_2} %	93±5	94±4
PVR index U·m^2	25±15	20±13
SVR index U·m^2	39±18	24±11
$\bar{P}_{pcw}$ mmHg	9±5	8±4
CI$^{\#}$ L·min^{-1}·m^2	1.9±1.7	2.8±1.2

Data are presented as mean±SD unless otherwise stated. Paediatric and adult patients were consecutively enrolled in one centre between 1991 and 2005. $\bar{P}_{pa}$: mean pulmonary artery pressure; SBP: systemic blood pressure; RAP: right arterial pressure; S_{v,O_2}: mixed venous oxygen saturation; S_{a,O_2}: arterial oxygen saturation; PVR: pulmonary vascular resistance; SVR: systemic vascular resistance; $\bar{P}_{pcw}$: mean pulmonary capillary wedge pressure; CI: cardiac index. $^{\#}$: n=129. Reproduced and modified from [80] with permission from the publisher.

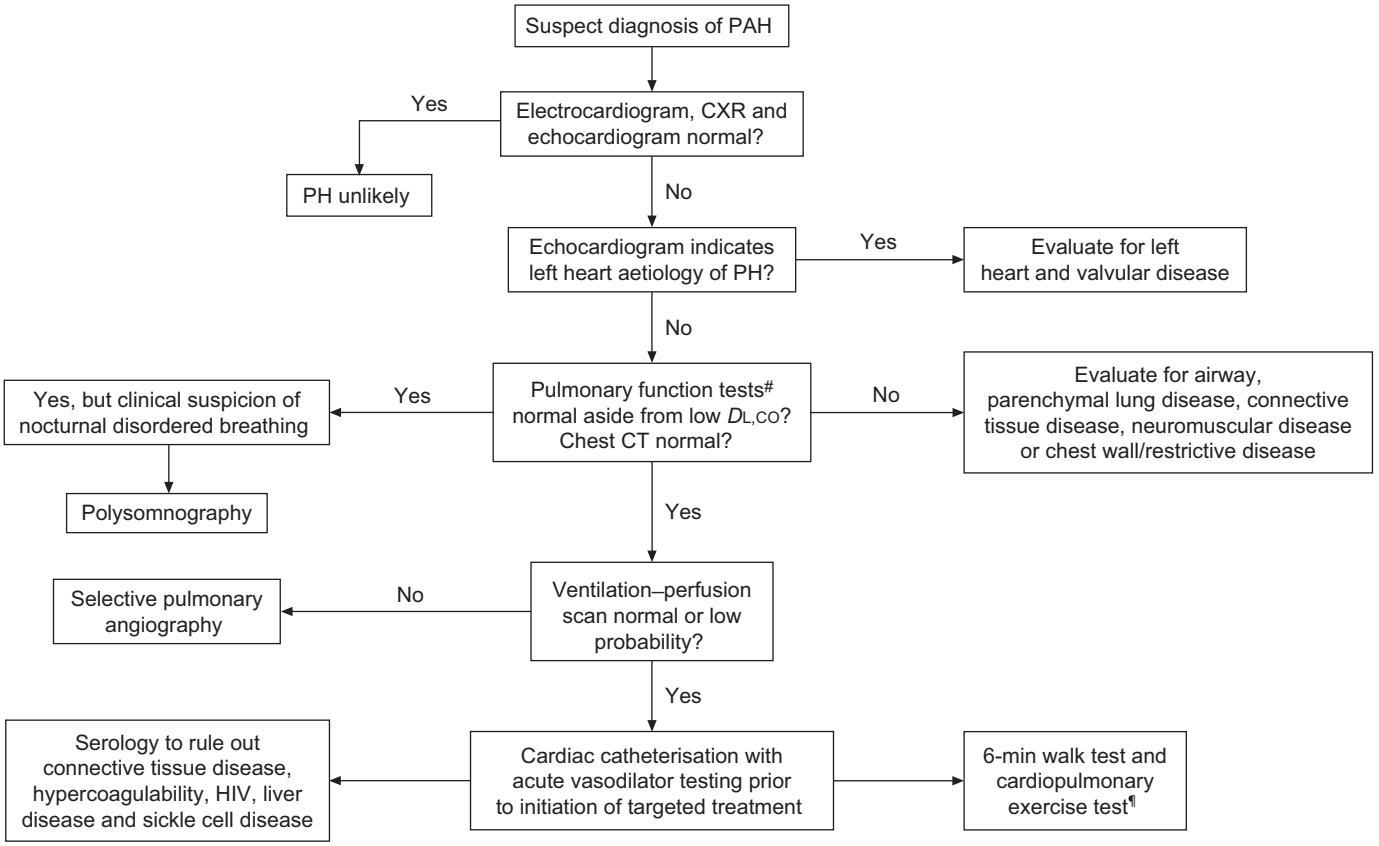

FIGURE 1. Paediatric pulmonary arterial hypertension (PAH) diagnostic work-up. CXR: chest radiography; PH: pulmonary hypertension; $D_{L,CO}$: diffusing capacity of the lung for carbon monoxide; CT: computed tomography. #: if unable to obtain a reliable test in a young child and there is a high index of suspicion for underlying lung disease, the patient may require further lung imaging; ¶: children >7 yrs of age can usually perform reliably to assess exercise tolerance and capacity in conjunction with diagnostic work-up. Reproduced and modified from reference [114] with permission from the publisher.

supported by results from the US multicentre, observational REVEAL registry indicating that, upon diagnosis, adults with IPAH/HPAH or APAH-CHD have worse functional class and haemodynamics than their paediatric counterparts [106, 107].

Figure 1 is illustrative of a diagnostic algorithm. Routine investigations include a chest radiograph, surface electrocardiogram and transthoracic two-dimensional echocardiography. The patient should be evaluated for lung disease, an important cause of pulmonary hypertension. Chest computed tomographic scan and ventilation–perfusion lung scintigraphy are useful in the evaluation of thromboembolic disease (although rare in children), pulmonary interstitial lung disease and pulmonary fibrosis. Serological evaluation includes routine biochemistry and haematology tests. Thyroid function should be checked, as thyroid disease is not infrequently associated with PAH in both paediatric and adult patients [115, 116]. Certain conditions, such as autoimmune disorders and liver disease, are less common in paediatric patients than in adults [117, 118], yet still warrant assessment. Evaluation for a hypercoagulable state should be performed and includes screening for disseminated intravascular coagulation, deficiencies of antithrombin III, and proteins C and S, presence of factor V Leiden, anticardiolipin antibodies, lupus anticoagulant, and/or prothrombin gene mutation 20210 G/A [119]. Serological testing for autoimmune disorders involves measuring antinuclear antibodies (ANA), anti-DNA antibody, Sjögren's syndrome-associated antibodies A and B, anticentromere antibody, scleroderma antibody, rheumatoid factor, complement factor and erythrocyte sedimentation rate [120, 121]. Children are not infrequently ANA-negative at the time of IPAH/HPAH diagnosis but seroconvert over several years with increased environmental antigen exposure [122]. Thus, although the incidence of positive ANA tests in adult IPAH/HPAH patients approaches 40% in some series [123], its incidence is also significant in paediatric IPAH/HPAH patients (18%) [122]. Furthermore, there is an increased incidence of positive ANA tests in the parents of IPAH/HPAH children and, in particular, in their mothers (in the absence of a diagnosed CTD) [122]. Clinically significant chronic CTD can develop years after the diagnosis of IPAH/HPAH in both paediatric and adult patients. HIV infection is associated with an increased incidence of PAH [124, 125] and should be assessed in PAH patients. A toxicology screen should also be included as several exogenous substances (*e.g.* amphetamines, cocaine, metamphetamines, fenfluramines, St. John's wort and phenylpropanolamine) have been identified as risk factors (or potential risk factors) for PAH in adults and children [126, 127]. Portopulmonary hypertension should be ruled out by performing abdominal ultrasonography and liver function tests [128].

Noninvasive methods are valuable when PAH is suspected but right heart catheterisation is necessary, in both children and adults, to confirm the diagnosis of PAH (*i.e.* the elevation in PVR and $\bar{P}_{pa}$, and the absence of left-sided heart disease), and to determine the acute vasoreactivity of the pulmonary vasculature. An acute response to vasodilator testing is currently defined for adult PAH patients as a decrease of $\geqslant$10 mmHg in $\bar{P}_{pa}$ to an absolute level of $\leqslant$40 mmHg with a normal or increased cardiac output [129]. Whether this is the correct definition for children, and whether it can be used to predict efficacy with long-term calcium channel blockers in infants and young children, remains unclear. One of the objectives in ongoing PAH registries, including REVEAL and the paediatric multicentre, international observational Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension (TOPP) Registry, is to analyse the utility of definitions for acute reactivity and their ability to predict response to calcium channel blockers and/or long term outcomes regardless of treatment. Furthermore, whether the severity of the pulmonary vascular disease, as indicated by the PVR at diagnosis or after 3–12 months of a given PAH therapy, will predict prognosis is critical to determine in order to develop treatment algorithms for PAH in children. DOUWES *et al.* [22] have suggested that, regardless of the response with acute vasodilator testing, the PVR to systemic vascular resistance ratio, as well as the $\bar{P}_{pa}$ to mean systemic blood pressure ratio at diagnosis, appear predictive of outcome in patients with IPAH/HPAH and APAH. In general, the younger the children are at the time of diagnosis, the more likely they are to respond to acute vasodilator testing; however, there is wide variability, consistent with wide biological variability in paediatric, as well as in adult, patients [10, 130–133]. We have observed that children with symptoms suggestive of severe pulmonary vascular disease for several years may be acute responders to acute vasodilator testing and manifest near-complete reversibility with chronic oral calcium channel blockers, while others with only a brief duration of symptoms may have what appears to be irreversible pulmonary vascular obstructive disease [90]. The incidence of responders to acute vasodilator testing ranges from 11 to 40% in children with IPAH/HPAH [10, 87] and from 6 to 27% in adult patients [130–133]. Although patients (paediatric or adult) with IPAH/HPAH or repaired APAH-CHD may respond to acute vasodilator testing, patients with APAH-CTD, HIV or portal hypertension, tend to be nonresponders.

The assessment of WHO functional class for patients with pulmonary hypertension developed at the 2nd World Conference on Pulmonary Hypertension in Evian, France (1998) [125] remains widely used in adult PAH patients to evaluate functional impairment. It can also be useful in older children, but less so in infants or young children, for whom a specific scoring system for heart failure [134] may be more appropriate. WHO functional class may also be inadequate to characterise a child with preserved cardiac output and no, or limited, functional impairment at rest, but with syncope upon over-exertion or with even mild exercise. Whether such a child should be considered as functional class IV is a matter of controversy, but the consensus is that aggressive treatment should be considered to manage recurrent syncope. Standardised guidelines are needed for the physicians taking care of paediatric pulmonary hypertension so that WHO functional class is used reproducibly in children.

The 6-min walk test is another tool to assess disease severity that is widely used in adults and is in the process of being standardised in children. Standard references are now available in healthy children [135–137]. The 6-min walk test assesses exercise endurance. It is useful in PAH patients, both adults and older children, who have symptoms such as dyspnoea with walking. However, the test procedure is not always followed by younger children, who walk at whatever pace they choose. This results in data that may not be reproducible nor reliable, especially in children $<$7 yrs of age [134]. Moreover, for a child who can carry out normal daily activities but has syncope with over-exertion, the 6-min walk test may be ''normal'' for the child's age and sex and, thus, underestimate the child's exercise limitations; in this instance, it is less useful as a tool to assess exercise endurance.

Noninvasive cardiopulmonary exercise testing (CPET) with gas exchange can be utilised to evaluate ventilatory responses to exercise in adult [138] and most paediatric PAH patients over 7–8 yrs of age [139–142]. This maximal exercise test may allow the detection of patients in whom pulmonary artery pressures are normal at rest but increase abnormally during exercise (*e.g.* ''asymptomatic'' obligate carriers of BMPR2 mutations); CPET may prove useful to diagnose these patients based on abnormal ventilatory efficiency [143, 144]. In our experience, CPET, in contrast to the 6-min walk test, may be particularly relevant to identify those children who have an exaggerated response of the pulmonary vascular bed to exercise and appear to have good exercise capacity with normal activities of daily living, but have a history of syncopal episodes with over-exertion or in response to mild hypoventilation with sleep [90].

Various markers used in adults such as serum N-terminal pro-brain natriuretic peptide (NT-proBNP), brain natriuretic peptide (BNP), uric acid, noradrenaline and C-reactive protein may also provide additional information on both disease severity and prognosis in children [145–148]. Lower NT-proBNP and BNP concentrations have been reported in children [145, 146, 149] compared with adults [147, 148], consistent with right heart failure being less frequent in children as compared with adult patients.

In summary, noninvasive disease severity assessment tools used in adults, such as WHO functional class and CPET, can be difficult to perform and are, therefore, less reliable in infants and young children; thus, haemodynamic evaluation remains the gold standard for assessing disease severity and evaluating treatment responses in PAH children. Nevertheless, as the goals of treatment for paediatric and adult patients are to improve overall quality of life in addition to increasing survival, we need to develop and validate quality of life tools that can be utilised in children of all ages.

TREATMENT

Due to limited controlled data reporting the clinical responses in paediatric PAH patients, the current consensus opinion is to extrapolate treatment guidelines from the adult evidence-based algorithms to children [19]. The recommendation for considering, in children, the therapeutic algorithm proposed for adults is Class IIa (*i.e.* the weight of evidence/opinion is in favour of usefulness/efficacy) and the level of evidence is

grade C (*i.e.* it corresponds to a consensus of opinion of the experts and/or small retrospective studies, registries).

The data supporting the efficacy of anticoagulation in adults is based on observational data from patients with IPAH/HPAH [130] and anorexigen-induced PAH [150]. In children, even fewer data are available and the overall risk–benefit profile remains unclear. Thus, whereas anticoagulation with warfarin is usually prescribed for adult patients with IPAH/HPAH and can be considered for those with APAH, by consensus, it is recommended for children with right heart dysfunction, indwelling central venous lines or with a hypercoagulable state [151], with consideration for other PAH children on an individual basis.

Calcium channel blockade therapy is initiated in patients (paediatric and adult) who respond to acute vasodilator testing [10, 133]. Uncontrolled, open-label, prospective, observational studies have reported improved haemodynamics and survival with long-term administration of calcium channel blockers in adult [130, 133] and paediatric [10, 103] IPAH/HPAH. However, a significant number of patients lose their initial acute responsiveness within several years (or less), which portends deterioration. It is recommended for these patients to start PAH disease-specific targetted therapy [103, 131]. In addition, although the overall acute response rate appears greater in the paediatric population than in adults, responders remain a minority of patients in all age groups and, consequently, the majority of patients need additional PAH disease-specific therapy. These currently include *i.v.* epoprostenol and *i.v.*, subcutaneous of inhaled prostacyclin analogues, oral endothelin receptor antagonists and *i.v.* or oral phosphodiesterase type 5 (PDE5) inhibitors.

The rationale for the use of *i.v.* epoprostenol or another prostacyclin analogue for PAH treatment is based on the observed imbalance between TXA_2 and prostacyclin metabolites. The clinical indications for long-term continuous *i.v.* epoprostenol therapy are similar in children and adults [18]. Based on observational data, continuous *i.v.* epoprostenol appears as effective in children with PAH as in adults with respect to improving survival and haemodynamics, and relieving symptoms [10, 103, 152]. YUNG *et al.* [103] confirmed the significantly improved long-term survival in children with IPAH/HPAH treated with *i.v.* epoprostenol compared with children for whom *i.v.* epoprostenol was not available. At 10 yrs, survival was 61% for all children treated with *i.v.* epoprostenol. These data strongly support the use of epoprostenol in children despite the invasive nature of its delivery system. The side effects of the drug (nausea, anorexia, jaw pain, diarrhoea, and musculoskeletal aches and pains) experienced by children are similar to those seen in adults [4]. However, optimal dosing in children is frequently higher on a nanograms per kilogram per minute basis. Efficacy has also been reported in adults with PAH with the prostacyclin analogues inhaled iloprost, and subcutaneous, *i.v.* or inhaled treprostinil, but data in children are limited. IVY *et al.* [153] evaluated the long-term effects of inhaled iloprost in 22 children (age range 4.5–17.7 yrs) with PAH. As reported for adult patients [154, 155], inhaled iloprost appeared to improve functional assessments in some children with PAH, but poor compliance with the frequency of inhalations currently limits chronic treatment in children. Compliance appears to be more favorable with inhaled treprostinil than with inhaled iloprost. Studies including both children and adults [11, 156, 157] suggest that subcutaneous and *i.v.* treprostinil are effective PAH treatments with an acceptable safety profile. However, no controlled study has been performed exclusively in children. Small, uncontrolled studies suggest that selected paediatric patients can be safely transitioned to *i.v.* treprostinil from oral therapies in the case of clinical deterioration [158] or from *i.v.* epoprostenol (treprostinil dose approximately 1.5 to 3 times the dose of epoprostenol) to limit the side-effects of *i.v.* epoprostenol [159].

Another target for treatment of PAH is the vasoconstrictor/proliferative peptide ET-1. The dual oral endothelin receptor antagonist bosentan improves haemodynamics, exercise capacity and WHO functional class in adults with PAH, including patients with the Eisenmenger syndrome [13, 14, 160]. Observational data also demonstrate maintenance of improved exercise capacity at 1 yr [161–166]. In paediatric PAH patients, open-label uncontrolled studies [91, 104, 167–169] demonstrate improvements in haemodynamics and WHO functional class with bosentan treatment as monotherapy or in combination with another PAH therapy. VAN LOON *et al.* [170], however, suggest that the initial improvement in exercise capacity may not be maintained after 1 yr in children with severe disease. The efficacy and safety of the specific ET_A receptor antagonist ambrisentan has been demonstrated in the adult population [16], but data in children are limited.

PDE5 inhibitors have been evaluated in children and adults. In adults, sildenafil improved haemodynamics, exercise capacity and WHO functional class [171]. Open-label observational studies in children suggest a similar beneficial effect of oral sildenafil on haemodynamics and exercise capacity [172–174]. Based on these observational data, a randomised controlled study evaluating the safety and efficacy of escalating sildenafil doses in children further supported the safety and clinical benefit in paediatric patients (consistent with the experience with adult patients) [20]. Tadalafil, another oral PDE5 inhibitor, has also been shown to improve exercise capacity and functional capacity in adult patients [175], but data in children are lacking.

Available data suggest that targetted PAH therapies, including *i.v.*, subcutaneous or inhaled prostacyclin analogues, oral endothelin receptor antagonists and *i.v.* or oral PDE5 inhibitors, are generally well tolerated, safe and effective in both children and adults with PAH. However, efficacy may not be maintained over time, and disease severity and response to therapy should be reassessed using noninvasive tools in conjunction with repeat haemodynamic evaluation. Maintaining an optimal therapy may involve changing or combining PAH-specific treatments. In adults, combination therapy is recommended for patients treated with PAH monotherapy who remain in WHO functional class III, while continuous *i.v.* administration of epoprostenol remains the treatment of choice in WHO functional class IV patients [176]. We have been using a similar approach in children, but supportive data is limited.

Even if the disease overall is the same in children as in adults, controlled data are still necessary in paediatric patients. Pharmacokinetic and pharmacodynamic data are invaluable in optimising overall risk–benefit profiles for specific drugs

and for specific ages and weights. Furthermore, both short- and long-term safety data are essential to ascertain the risk–benefit relationship in children. Finally, assessing effects on lung growth and development are also needed, as controlled data from adult studies suggest that early initiation of treatment is beneficial [177].

CONCLUSION

In all studies published to date, PAH in children appears to have more similarities than differences compared to PAH in adults. The disease presents with a broad spectrum of clinical features in both children and adults that are manifestations of similar processes. The extrapolation of the definition and classification of PAH from adult patients to children is not always straightforward, especially for very young children. Children can be difficult to diagnose and additional challenges arise in the assessment of disease severity due to the inability of young children to perform exercise tests reliably or reproducibly, and the difficulty to use tools such as the WHO functional class in young children. However, with appropriate therapeutic strategies, many children are living longer with an excellent overall quality of life. Future studies in children should permit further adaptation of the adult diagnostic and treatment algorithms to optimise the management of paediatric patients, as well as develop novel innovations specifically for children.

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STATEMENT OF INTEREST

Statements of interest for all authors and for the manuscript itself can be found at www.erj.ersjournals.com/site/misc/statements.xhtml

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