



Registries for paediatric pulmonary hypertension

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Paediatric pulmonary arterial hypertension should be treated specifically and differently from adult pulmonary arterial hypertension <http://ow.ly/mzPDT>

Pulmonary arterial hypertension (PAH) is a progressive, angio-obliterative disease leading to increased pulmonary vascular resistance, right heart failure, and death in ~25–60% of PAH patients 5 years after diagnosis [1–3]. The estimated prevalence of PAH is 15–50 cases per million adults [4–6] and 2–16 cases per million children [7–9]. In certain at-risk groups, however, the occurrence of PAH is substantially higher. For example, the prevalence is 0.5% in HIV-infected patients [10] and 4–6% in schistosomiasis [11]. These diseases are far more common in developing countries with limited health care and, thus, the real burden of PAH worldwide is probably underestimated.

Historically, extrapolation from adult pulmonary hypertension studies has been used to make assumptions on the disease in children; however, this approach is neither validated nor appropriate [12]. The recent comprehensive analysis of paediatric registries allowed predictions on the epidemiology, clinical practice and outcome of PAH in childhood. In France, for example, the prevalence of paediatric PAH was estimated to be 2.2 cases per million children [7]. In the UK, the incidence and prevalence of idiopathic PAH (IPAH) was 0.48 and 2.1 per million children, respectively [8]. In the Netherlands, the incidence and prevalence of IPAH was 0.7 and 4.4 per million children, whereas PAH associated with congenital heart disease (PAH–CHD) had an incidence of 2.2 and prevalence of 15.6 per million [9]. Of note, the PAH disease spectrum may somewhat differ in the individual tertiary centre and in multicentre registries [13]. In a British cohort study, the 5-year survival for children with IPAH was only 75% with a freedom from death or transplantation of only 57% (1986 and 2000 with follow-up to 2007) [8].

Patients, family members and healthcare providers should be aware of the unique features of paediatric pulmonary hypertensive vascular disease (PPHVD) [14, 15]. These include the fetal origins, developmental and adaptive aspects of pulmonary vascular disease (PVD) and right ventricular dysfunction (RVD) in both childhood- and adult-onset disease. The proposal for a new classification of PPHVD (Panama, 2011 [14]) aims to incorporate such specific paediatric aspects that are not adequately addressed in the current classification of pulmonary hypertension (Dana Point, CA, USA, 2008) [16]. The Panama proposal of PPHVD is still very new, not broadly (internationally) accepted yet, and probably will undergo further modifications, according to international meetings (e.g., the PH World Symposium, Nice, France, 2013) and feedback from healthcare providers.

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PAH associated with congenital heart disease (CHD) is most commonly diagnosed in childhood. It is important to distinguish between CHD/left-to-right shunts with PVD (*i.e.*, PPHVD) and without PVD, because the latter PAH group benefits the most and primarily from shunt closure, be it interventional or surgically. In addition, in single *versus* biventricular circulations, PAH haemodynamics and physiology differ remarkably. While adults with Eisenmenger–PAH have a better survival than those with idiopathic/heritable PAH, children with PAH–CHD have a 5-year mortality that appears to be comparable to those with idiopathic/heritable PAH (29 *versus* 25%) [17]. The severity of adult PAH–CHD tends to be underestimated because adult patients probably represent a selection of “survivors”.

Interestingly, the sex ratio in prepubertal children with PAH is nearly even whereas 70–80% of adult patients with PAH are female. Potential environmental risk factors and disease modifiers such as cigarette smoke exposure [18], hormonal and metabolic abnormalities such as hyperandrogenaemia, dyslipidaemia and insulin resistance [19, 20], have been identified in adults with PAH recently, and should be studied systematically in children. However, sufficient recruitment of PAH children into classical randomised controlled trials (RCTs) is particular difficult. The challenging combination of an orphan disease with a complex, heterogeneous pathobiology has led to the search for alternative study modalities *versus* the traditional RCTs in PAH (*i.e.* “adaptive trial designs” [21]) although even those face the problem of sufficient recruitment.

Registries have become an important source of information in adult PAH (REVEAL (Registry to Evaluate Early And Long-term PAH Disease Management) [22], French Registry [23], COMPERA (Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension) [24], and more recently also in paediatric PAH (*e.g.*, REVEAL: survival in paediatric PAH [17]). The Tracking Outcomes and Practice in Paediatric Pulmonary Hypertension (TOPP) registry is a prospective registry that provides information on demographics, diagnostic evaluation, treatment and outcomes in paediatric pulmonary hypertension [25]. The recent TOPP analysis (31 centres in 19 countries; 2008–2010) identified important clinical features specific to the care of paediatric pulmonary hypertension, which drew attention to the need for paediatric data rather than extrapolation from adult studies [25]. In total, 317 of 362 pulmonary hypertension patients had PAH (PH Group 1, 88%), which was idiopathic or familial PAH in 182 (57%), and associated with other disorders in 135 (43%), of which 115 (85%) cases were associated with congenital heart disease. 42 (12%) patients had pulmonary hypertension associated with respiratory disease/hypoxaemia, with bronchopulmonary dysplasia being most frequent. Although such pulmonary hypertension registries are limited by the lack of randomisation, proper control groups and causal conclusions, they do yield very valuable information for the practicing physician.

In this issue of the *ERJ*, BEGHETTI *et al.* [26] (the TOPP registry investigators) report that most children with pulmonary hypertension (defined according to the Venice classification, 2003 [27]) do not undergo the diagnostic work-up recommended for adults, pointing towards the inappropriateness of adult guidelines for children and/or the incomplete awareness of the current guidelines for adults with pulmonary hypertension, or both. For example, brain natriuretic peptide (BNP) and N-terminal prohormone of BNP testing was performed in <25% of children with pulmonary hypertension, and the 6-min walk test and cardiopulmonary exercise testing were conducted in only 38 and 7% patients, respectively. Both exercise tolerance tests are probably not reliable in children <8 years of age and those with developmental delay, *e.g.*, in trisomy 21 (13% in TOPP [25]). Hence, these functional variables do not serve well as (the sole) primary outcome in paediatric RCTs.

BEGHETTI *et al.* [26] (TOPP registry) also report on the safety of invasive haemodynamic assessment in children with pulmonary hypertension and found that 7% (37 out of 554) of patients at diagnosis had significant complications within 24 h after heart catheterisation, including new inotropic support (3%, 14 out of 554), pulmonary hypertensive crisis (2%, 10 out of 554) and cardiac arrest (0.9%, 5 out of 554). For the total number of heart catheterisations (n=908) performed at diagnosis (n=554) and follow up (n=354), complications including pulmonary hypertensive crises, need for inotropic support and cardiac arrest were reported in 5.9% of cases; and there were five cases of procedure-related deaths [26]. The complication rate for cardiac catheterisation with or without anaesthesia is apparently higher in children than in adults [28], reminding us that we must weigh the risks and benefits of invasive procedures in this fragile patient population and that the care of children with PAH belongs in experienced hands. Nevertheless, cardiac catheterisation with vasodilator testing remains an essential part of the comprehensive PAH work-up at diagnosis.

An expert statement on adult pulmonary hypertension has been published by the American Heart Association and the American College of Cardiology in 2009 [29]. The European Respiratory Society and the European Society of Cardiology have published guidelines for the diagnosis and treatment of adult pulmonary hypertension in the same year [30]. Future guidelines on paediatric pulmonary hypertension

and RVD need to address the specifics of the disease in paediatric populations as well as concomitant disorders, expert clinical evaluation and future therapies [31, 32].

In summary, children are not simply young adults and PAH in children differs from PAH in adults. Physician scientists will need to determine the genetic, circulatory and environmental risk factors and disease modifiers of pulmonary vascular disease and right ventricular dysfunction, thus striving for “individual risk assessment”, “diagnostic evaluation” including better biomarkers, “clinical staging”, and “tailored therapy” of patients with PAH. The unique features and uncertainties of childhood PVD and RVD are evident and underline the need for significant and specific basic and translational research efforts, in addition to paediatric registries and clinical networks.

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