Pulmonary Hypertension in Children

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KEYWORDS

• Pulmonary arterial hypertension • Single-ventricle circulation • Bronchopulmonary dysplasia

KEY POINTS

- The prevalence of PH is increasing in the pediatric population, because of improved recognition and increased survival of patients, and remains a significant cause of morbidity and mortality.
- Recent studies have improved the understanding of pediatric PH, but management remains challenging because of a lack of evidence-based clinical trials.
- The growing recognition of developmental lung disease associated with PH requires dedicated research to explore the use of existing therapies as well as the creation of novel therapies.
- Adequate study of pediatric PH will require multicenter collaboration due to the small numbers of patients, multifactorial disease causes, and practice variability.

INTRODUCTION

Untreated, pulmonary arterial hypertension (PAH) in children carries a particularly poor prognosis. In the National Institutes of Health registry, the median untreated survival for children after diagnosis of idiopathic PAH (IPAH) was reported to be 10 months as opposed to 2.8 years for adults.[1] In 1999, further studies by Barst and colleagues[2] showed that survival for children with IPAH who were candidates for intravenous prostacyclin but were unable to be treated with this therapy was poor with a survival of 45% and 29%, respectively, at 1 and 4 years. Recent advances in the understanding of the pathobiology of IPAH and new treatment therapies have resulted in marked improvement in the prognosis for children with PAH (**Fig. 1**).[3,4] Similarities and differences persist in comparison of children and adults with PAH.[5] In both groups, disease progression is rapid, perhaps more rapid in children than in adults, and left untreated, elevation of pulmonary arterial pressure (PAP) and resistance leads to right ventricular (RV) failure, clinical deterioration, and death. In contrast, many aspects of pulmonary vascular disease of children are distinct from adult pulmonary hypertension (PH). Pediatric PH is intrinsically linked to lung growth and development in the younger child as defined in the Panama classification (**Box 1**, **Fig. 2**).[6] The onset of pulmonary vascular injury in the younger child may allow the possibility of greater reversal of pulmonary vascular disease, particularly in bronchopulmonary dysplasia (BPD) and other lung diseases of childhood. Medical management of children follows a similar algorithm to that of adults treated with idiopathic pulmonary vascular disease.[4,7,8] The resurgence of the Potts shunt, originally used to increase pulmonary blood flow in congenital heart disease (CHD) in the 1950s, has allowed for a surgical right-to-left shunt in the younger child failing medical management with end-stage disease.[9]

DEFINITION

Similar to adults, PAH is defined as a mean PAP greater than 25 mm Hg at rest, with a normal pulmonary artery wedge pressure less than 15 mm Hg and an increased pulmonary vascular resistance (PVR) greater than 3 Wood units × M^2.[4,10] Both the Nice and Panama classifications are

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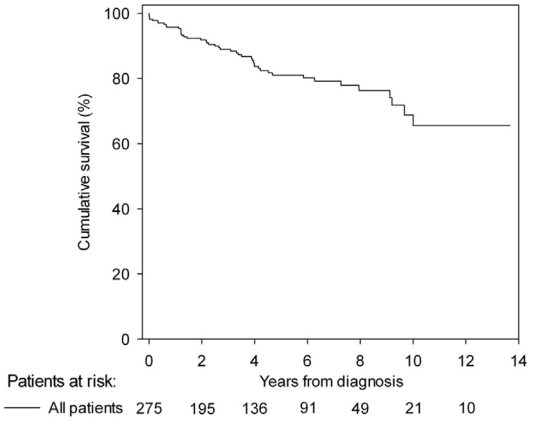

Fig. 1. Kaplan-Meier curves showing the survival pediatric PAH patients at 3 PH centers (NY, New York; NL, Netherlands): 1-, 3-, 5-, and 7-year transplantation-free survival rates were 96%, 89%, 81%, and 79%, respectively. (*From* Zijlstra WM, Douwes JM, Rosenzweig EB. Survival differences in pediatric pulmonary arterial hypertension: clues to a better understanding of outcome and optimal treatment strategies. J Am Coll Cardiol 2014;63(20):2159–69; with permission.)

appropriate for adults and children.[4,11] In younger children, the PAP is frequently referenced as a ratio to systemic arterial pressure with a significant difference being greater than 0.5. Pulmonary hypertensive vascular disease complicates the course of certain forms of single-ventricle heart disease in which mean PAP is less than 25 mm Hg, but PVR is high, leading to failure of the circulation.[6] PAH associated with CHD is heterogeneous and ranges from classic Eisenmenger syndrome with reversal of a central shunt and cyanosis to IPAH-like CHD with coincidental defects (**Box 2**).[11]

Box 1
Developmental lung diseases associated with pulmonary hypertension

- Congenital diaphragmatic hernia
- Bronchopulmonary dysplasia
- Alveolar capillary dysplasia (ACD)
- ACD with misalignment of veins
- Lung hypoplasia ("primary" or "secondary")
- Surfactant protein abnormalities
  - Surfactant protein B deficiency
  - Surfactant protein C deficiency
  - ATP-binding cassette A3 mutation
  - Thyroid transcription factor 1/Nkx2.1 homeobox mutation
- Pulmonary interstitial glycogenosis
- Pulmonary alveolar proteinosis
- Pulmonary lymphangiectasia

From Ivy DD, Abman SH, Barst RJ, et al. Pediatric pulmonary hypertension. J Am Coll Cardiol 2013;62(Suppl 25):D117–26; with permission.

EPIDEMIOLOGY

National registries from the United Kingdom, the Netherlands, and Spain have all shown a lower incidence for IPAH in children compared with adults. The incidence of IPAH in the national registry from the United Kingdom was 0.48 cases per million children per year, and the prevalence was 2.1 cases per million.[12] In the Netherlands, annual incidence and point prevalence averaged 0.7 and 2.2 cases per million children, respectively (**Fig. 3**).[13] Likewise, in the Spanish registry, the incidence and prevalence were 0.49 and 2.9 cases per million children.[14] PAH associated with CHD represents highly heterogeneous subgroups. Transient PAH is seen in children with CHD and systemic-to-pulmonary shunt, in whom PAH resolves after early shunt correction. However, in a small subset of CHD progressive PAH after surgical repair associated PAH (APAH)-CHD Group D (**Box 2**) has a particularly poor diagnosis (**Fig. 4**).[15] APAH-CHD occurs more frequently in children than adults with an incidence and

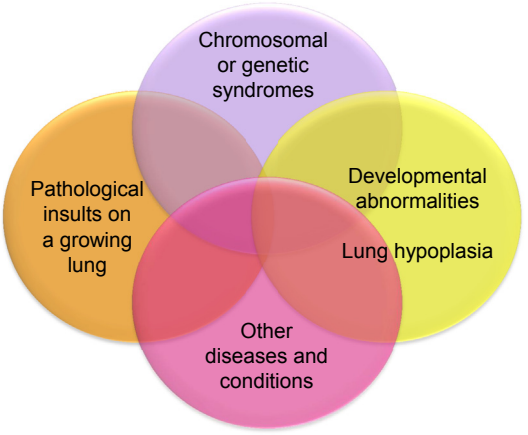

Fig. 2. Venn diagram illustrating the heterogeneity and multifactorial elements in pediatric pulmonary hypertensive vascular disease. (*Adapted from* Cerro MJ, Abman S, Diaz G, et al. A consensus approach to the classification of pediatric pulmonary hypertensive vascular disease: report from the PVRI Pediatric Taskforce, Panama 2011. Pulm Circ 2011;1(2):286–98; with permission.)