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REVIEW ARTICLE

Pulmonary arterial hypertension in congenital heart disease: Current perspectives and future challenges

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Abstract Medical and scientific research in the field of pulmonary arterial hypertension (PAH) in adults with congenital heart disease (ACHD) has gradually become globalized, inclusive and collaborative over the past few years. The education of physicians, health administrators and patients on congenital heart disease (CHD), specifically in the field of PAH, is of paramount importance. It is also crucial for ACHD patients with PAH to be followed in tertiary centers and to benefit from a multidisciplinary approach. Shared care models dictate a closer collaboration between tertiary expert centers and local non-specialist services, as well as networking between expert physicians in CHD and PAH and geneticists/epidemiologists, with the inclusion of PAH-CHD patients in national and international registries with a detailed genotypic/phenotypic characterization.

Pulmonary arterial hypertension (PAH) has received incremental attention over the past 2 decades from the medical profession, health administrators, patient associations and pharmaceutical industry. The design and completion of numerous multicenter randomized controlled trials and the development of new compounds has led to enhanced survival prospects and an improved quality of life for patients with PAH. However, the majority of randomized controlled

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studies excluded patients with Eisenmenger syndrome, namely, PAH related to bidirectional or right-to-left congenital heart shunts. Due to similarities with idiopathic PAH, PAH in adult patients with congenital heart disease (ACHD) and previous reparative surgery has been the only permissive ACHD subgroup included in major PAH trials. This ACHD subgroup represents a small proportion of PAH patients in such large PAH studies (less than 10% of the total population enrolled). It is, therefore, necessary to invest further in clinical research and collaboration between expert ACHD centers and address areas that are controversial and lack evidence.

Since 1897, when Viktor Eisenmenger first described a typical case of a syndrome that would later bear his name and provided a detailed anatomical and clinical description of a cyanotic male patient with a ventricular septal defect, significant academic advances in our understanding and management of PAH in ACHD have occurred. However, there are still numerous questions to be addressed.[1,2] First, we need robust data on the epidemiology of PAH in ACHD. For instance, the exact number of patients with Eisenmenger syndrome worldwide remains unknown.[3] Previous studies have based the diagnosis on echocardiography and included patients from previous eras in which early reparative or palliative surgery of congenital cardiac disease was not always available. This may still be a problem in some parts of the developing world. Moreover, little is known about the natural history and optimal management of pediatric patients with PAH, who have been reported to have a worse outcome compared with their adult counterparts.[4] Research is also required to understand how to best functionally assess patients with Down syndrome who constitute, at present, a significant proportion of the Eisenmenger syndrome cohort (up to a third).[5] Although the current guidelines and recommendations have proposed criteria for shunt closure in patients with net left-to-right shunting and PAH (Fig. 1), they still represent a management dilemma.[6] There are still unresolved issues, such as the management of patients with borderline pulmonary vascular resistance at rest; the long-term impact of reversibility studies using pulmonary vasodilators for the purpose of assessing operability; and the employment of a staged treatment approach, such as a partial defect closure with one-way flaps or the creation of a small fenestration in the patch repair that would permit a "pop-off" valve. Critically, the decision to intervene and close a defect should not be solely based on the procedural feasibility and technical aspects, as such a decision may compromise the long-term prospects for these patients by converting the disease to a more aggressive form of PAH. We submit that there is an urgent need for patients with PAH and left-to-right shunts to be followed in tertiary academic centers, where long-term follow-up clinical studies or international registries are present, as well as for expert opinions in this population of borderline patients. In general, with regards to PAH and left-to-right shunts, patients should only undergo defect closure if a certain and long-standing benefit from such intervention can be anticipated. The exact circumstances in which this can be sufficiently guaranteed are currently uncertain, and either surgical or catheter therapy may have long-term detrimental effects in these patients. Moreover, we need to gather expert opinions on the safety and efficacy of a "treat and repair" approach in this population (that is, to treat patients with PAH-specific therapy and, if they respond well, to then consider defect closure), as there is no substantive evidence to support this approach at the present time.[7]

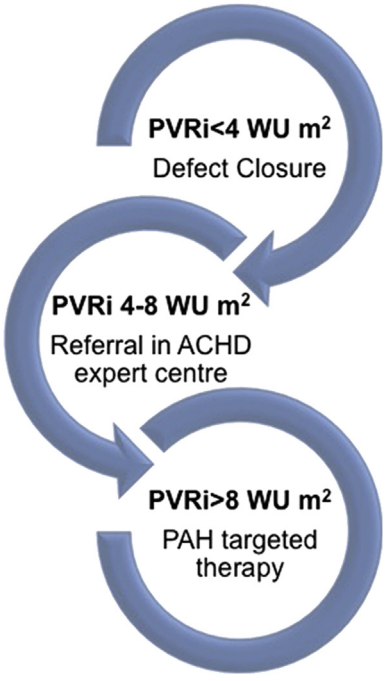

Figure 1 Recommendations for shunt closure based on the baseline indexed pulmonary vascular resistance (PVRi).

The varying responses of the pulmonary vascular bed to similar hemodynamic stimuli implies different underlying predispositions to pulmonary vascular disease relating to unknown genetic factors.[5] This may also be supported by the presence of different phenotypes/genotypes of patients with Down syndrome and of patients with ASD-related PAH.[8] Furthermore, some patients develop PAH later in life, even after timely early childhood repair of a defect and even in the absence of significant residual hemodynamic lesions (e.g., PAH in the setting of transposition of the great arteries). Much work is needed to understand the genetic and molecular mechanisms underlying the development of PAH, both in CHD and other types of disease, leading to a common endpoint of a histologically deranged pulmonary vascular bed (Table 1). Therefore, there is a need for a closer collaboration between CHD and PAH physicians and geneticists/epidemiologists towards this end, with the inclusion of PAH-CHD patients in national and international registries and with a detailed genotypic/phenotypic characterization.

The traditional belief that survival prospects are far superior in ACHD patients with PAH compared to other PAH etiologies is not always supported by recent studies.[9,10] In contrast, there is now evidence that at least patients at the extreme end of the spectrum of ACHD-PAH, namely, patients with Eisenmenger syndrome, respond well and safely to PAH specific therapy and demonstrate improved hemodynamics, 6-minute walking test distance, functional class and survival prospects.[11] It is therefore appropriate to treat

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