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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]

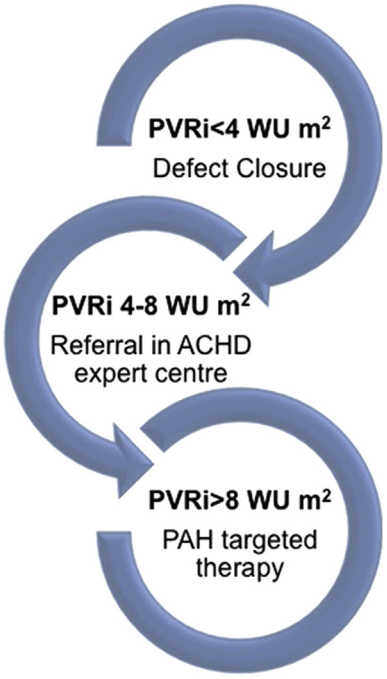

Figure 1 Recommendations for shunt closure based on the baseline indexed pulmonary vascular resistance (PVRi).

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

Table 1 Pulmonary hypertension in congenital heart disease. Prevalence and pathophysiology.

Location of defect	Type of defect	Prevalence of PAH*	Pathophysiology
Shunt at atrial level	Atrial septal defects	8% in secundum ASDs 7% in primum ASDs	Volume overload is the initial stimulus. Presents later in life. Development of PAH is idiosyncratic (possible genetic predisposition). Maladaptive response of the RV resembles that of idiopathic PAH, with dilation and progressive systolic dysfunction. Prognosis is worse than that of post-tricuspid shunts.
	Partial and total anomalous pulmonary venous drainage	NA	
Shunt at ventricular level	Atrioventricular septal defects	41%	Volume and pressure overload early in life (in large shunts). Lower right atrial pressures suggest better RV diastolic properties. Higher prevalence of patients with Down syndrome (especially AVSD).
	Ventricular septal defects	11%	
	Single ventricle with unobstructed pulmonary blood flow	7% in DILV, 17% in DORV, 11% in other UH	
Shunt at arterial level	Aortopulmonary window	100%	Same pathophysiology with shunts at the ventricular level. Aortopulmonary shunts and collaterals may cause segmental hypertension, which is a challenging diagnosis.
	Persistent ductus arteriosus	3%	
	Truncus arteriosus	6%	
	Surgically created systemic arterial to pulmonary shunts	9%	
	Aortopulmonary collaterals		

*Retrospective echocardiographic data from a Dutch registry.[22]
PAH: pulmonary arterial hypertension, NA: not available, DILV: double inlet left ventricle, DORV: double outlet right ventricle, UH: univentricular heart, RV: right ventricle, AVSD: atrioventricular septal defect.

these patients with ACHD-PAH proactively as with patients with idiopathic PAH. Although the positive impact of disease targeting therapies in ACHD patients with PAH is now well recognized and has been confirmed by recent studies, there are areas of uncertainty, such as the initiation of medical therapy early in the course of the disease (WHO class I/II), optimal use of combination medical therapy (upfront versus sequential), administration of parenteral prostanoids and use of novel treatments based on alternative pathophysiology pathways, which are prominent in PAH in ACHD (e.g., inflammation). Furthermore, disease targeting therapies in ACHD patients with PAH and net left-to-right shunts have not been fully explored. Theoretically, the administration of targeted PAH therapies to further augment pulmonary blood flow may accelerate the progression of pulmonary vascular disease. Physicians have remained somewhat hesitant to treat such patients, although data from the Bologna group suggest that they respond well to PAH-specific therapy in an intention-to-treat protocol. Other unexplored areas are the administration of targeting therapies in patients with complex disease, such as those with univentricular heart and PAH, as these patients have been excluded from major trials thus far, as well as in patients with segmental PAH.[12]

Although the treatment recommendation for PAH-ACHD has recently been published (Table 2),[13] it is currently unclear as to whether these patients should be treated with a goal-oriented strategy (as has been proposed for idiopathic PAH) and what these treatment targets should be. The optimal use of antiplatelet and oral anticoagulation therapy in Eisenmenger patients, who are prone to both thrombosis and bleeding, also remains unknown.[14] Furthermore, additional data are needed on the role of physical rehabilitation, exercise prescription, iron supplementation, long-term oxygen therapy, and so on.[15] Finally, it remains unclear which clinical endpoints should be used in trials on PAH-ACHD, especially in adult patients with Eisenmenger syndrome.[16] In fact, the relative stability of adults with Eisenmenger syndrome, in some, up to the fourth decade of life, makes hard endpoints, such as mortality or morbidity, difficult to implement in such an uncommon disease. Therefore, there is a need to strengthen the networking between ACHD-PAH expert centers, build multicenter collaborations and facilitate randomized trials with the aim of increasing the sample size. Finally, in line with the PAH paradigm, harder study endpoints that represent clinical parameters, beyond those of an improvement in exercise capacity, should be validated preferably if they reflect the quality of life and overall clinical outcome.[17]

Lately, the utilization of PAH-specific therapies in populations beyond the Eisenmenger complex has gained increased interest. Indeed, a large patient group, which remains untreated, is the Fontan population. These patients, strictly speaking and according to the international guidelines for PAH, do not meet the diagnostic criteria for PAH; however, recent evidence suggests abnormal vasculature in the Fontan circulation of chronic low cardiac output and a relatively increased pulmonary vascular resistance, which in theory, could be modulated by PAH-specific therapy. Although recent controlled randomized trials have shown that bosentan or other pulmonary vasodilators have small but significant beneficial effects on important cardiopulmonary measures,[18] there is still

Table 2 Treatment of pulmonary hypertension in congenital heart disease.

PAH targeted therapy	Bosentan is recommended in WHO-FC III patients with Eisenmenger syndrome
	Other ERAs, PDE-5 inhibitors and prostanoids should be considered in patients with Eisenmenger syndrome
	A combination drug therapy may be considered in patients with Eisenmenger syndrome
	The use of calcium channel blockers is not recommended in patients with Eisenmenger syndrome
Anticoagulation	In the absence of significant hemoptysis, oral anticoagulation may be considered in patients with pulmonary arterial thrombosis or signs of heart failure
Oxygen	The use of supplemental oxygen therapy should be considered in cases in which it produces a consistent increase in arterial O_2 saturation and reduces symptoms
Phlebotomy	Routine phlebotomy should be avoided. If symptoms of hyperviscosity are present, phlebotomy with isovolumic replacement should be considered, usually when the haematocrit is >65%
Iron	The use of a supplemental iron treatment may be considered in patients with low ferritin plasma levels
Other general measures	Dehydration should be avoided
	Pregnancy is contraindicated
	Immunization of PAH patients against influenza and pneumococcal infection is recommended
	Psychosocial support is recommended in ACHD PAH patients
	Supervised exercise training should be considered in physically deconditioned patients, while excessive physical activity that leads to distressing symptoms is not recommended
	In elective surgery, epidural rather than general anesthesia should be preferred whenever possible

uncertainty, and future research is needed to identify which Fontan patients are true responders and whether an earlier rather than a later treatment initiation will lead to a maximum efficacy effect.

There are inherent difficulties in performing randomized controlled trials in the field of ACHD-related PAH, which are needed to overcome areas of controversy and those that lack evidence. Blinding is extremely difficult, and it is not clear how such trials can be funded in the future unless a strong case for greater cost-effectiveness against the standard therapeutic protocols can be supported or the industry develops an intense interest. Therefore, there is a need for collaborative clinical research between specialist centers, to organize international registries and to strengthen expert opinion.[19] It is paramount for ACHD patients with PAH to be followed in tertiary centers and benefit from a multidisciplinary approach, including areas such as complex electrophysiology, anesthesia, hematology, gynecology, high-risk obstetrics, dentistry, and so on.[20] The improvement of referral patterns will lead to diminishing numbers of patients who are lost to follow-up or may present late with advanced disease, while at the same time, a closer collaboration between CHD and PAH centers will eventually improve the clinical outcome of this population. Patients who are lost to follow-up globally should be referred back to tertiary healthcare centers and be offered PAH-advanced therapy, especially those of WHO class III or greater. Globally, the inappropriate practices of the past, such as routine venesections and absolute exercise restriction should be abandoned. Education in ACHD, specifically in the field of PAH, is a key task.[21] There is clearly a need for a wider engagement, including education on PAH-ACHD for a broader healthcare professional audience, with direct links to tertiary centers to achieve optimal patient care in this complex area, minimizing risks through safety mechanisms and avoidance of pitfalls. One

Table 3 Future global prospects in the field of PAH associated with CHD.

Provide an early diagnosis and timely repair of congenital heart lesions that are prone to PAH development, especially in developing countries (thus preventing the development of PAH)
Improve transition patterns in tertiary centers from pediatric care
Patients lost to follow-up should be brought back into expert care and offered PAH-specific therapy when they are in functional class III or greater
Develop registries/genetic databases to elucidate the pathophysiologic mechanisms (e.g., patients who develop late PAH despite early intervention)
Organize multicenter collaborations between centers of excellence in developed countries and improve the infrastructure in developing countries
Organize collaborations and alliances between research organizations and scientific societies that share the common interests
Support the development of national/international registries (e.g., anticoagulation and hemoptysis in Eisenmenger patients, parenteral prostanoids in CHD-related PAH, other)
Study pathophysiology pathways (e.g., inflammation) to develop novel therapeutic modules
Encourage the design of multicenter randomized trials in new territories (e.g., early, targeted PAH treatment in Eisenmenger syndrome, potential role of supplemental oxygen, targeted PAH therapy in the Fontan population)

of the future aims should be a coordinated effort in support of PAH-ACHD in developing countries through a greater allocation of resources, with the collaboration and support of the PAH-CHD community worldwide, targeting a better awareness and an earlier diagnosis, followed by a wider availability of targeted-PAH therapies.

Medical and scientific research in this field over the past few years has gradually become more globalized, inclusive and collaborative. Looking ahead, national and international registries should provide a better understanding of the epidemiology, genetics, natural history, and therapeutic outcomes of the heterogeneous PAH population (Table 3). The registries should focus on areas such as the safety and efficacy of anticoagulation, clinical significance and management of hemoptysis, pregnancy, and management of patients with shunts and moderately elevated pulmonary vascular resistance as well as perform a long-term assessment of the "treat and repair" approach in carefully selected subgroups. Finally, we urge that randomized controlled trials assessing the benefits of PAH-specific therapy should be extended to include less symptomatic Eisenmenger patients, those with a pre-Eisenmenger physiology with moderately elevated pulmonary vascular resistance and those with a Fontan circulation. Adoption of a standardized assessment approach for Eisenmenger syndrome, as presented here and according to the international guidelines, should be applied widely and validated prospectively so that more patients with PAH associated with CHD will benefit and reach their full life potential.

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