Evaluation and Management of Pulmonary Arterial Hypertension in Congenital Heart Disease

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ABSTRACT: Pulmonary arterial hypertension is a common complication in patients with congenital heart disease (CHD), aggravating the natural course of the underlying defect. Pulmonary arterial hypertension (PAH) has a multifactorial etiology depending on the size and nature of the cardiac defect as well as environmental factors. Although progress has been made in disease-targeting therapy using pulmonary vasodilators to treat Eisenmenger syndrome, important gaps still exist in the evaluation and management of adult patients with CHD-associated PAH (PAH-CHD) who have systemic-to-pulmonary shunts. The choice of interventional, medical, or both types of therapy is an ongoing dilemma that requires further data. This review focuses on the evaluation and management of PAH-CHD in the contemporary era.

INTRODUCTION

The population of adults with congenital heart disease (CHD) has significantly grown over the last few decades thanks to advances in cardiac and surgical care.[1] This increase in the number of patients is accompanied by an increase in complexity,[2] with patients requiring life-long specialized care and surveillance for complications. Pulmonary arterial hypertension (PAH) is a well-known complication of CHD. Population-based studies have reported that between 6% and 28% of adults with CHD are diagnosed with PAH.[3,4] We review the clinical implications, pathophysiology, clinical classification, diagnosis, and management considerations in dealing with CHD-associated PAH (PAH-CHD).

CLINICAL IMPLICATIONS

Pulmonary hypertension increases the all-cause mortality rate by two-fold and morbidity such as heart failure and arrhythmia by three-fold compared to patients without PAH. It also increases resource utilization and admissions to intensive care units. Clinical deterioration has even been reported after defect repair in some patients.[4,5]

PATHOPHYSIOLOGY

The mechanism behind the development of PAH-CHD is multi-factorial. The most frequent cause of PAH-CHD is unrepaired shunts, which is the incomplete separation of the pulmonary and systemic circulation. This leads to unrestricted flow from the systemic to the pulmonary circulation, with pressure and/or volume overload of the pulmonary circulation that, in turn, induces irreversible changes in the medium and small arteries; this inevitably leads to vasoconstriction, endothelial proliferation, and obstructive remodeling of the pulmonary vasculature as well as inflammation and thrombosis.[6] Consequently, there is an increase in pulmonary artery pressure (PAP). If the PAP reaches suprasystemic values, this can lead to shunt reversal (right-to-left shunt) and consequent cyanosis, a condition known as Eisenmenger syndrome.

CLASSIFICATION OF PULMONARY HYPERTENSION IN CHD PATIENTS

A clinical classification of PAH in CHD was presented during the 5th World Symposium of Pulmonary Hypertension in 2013 (Table 1).[7] This classification separates patients into four clinical and phenotypical groups. We will follow this classification to detail the characteristic of these phenotypes.

1. Eisenmenger Syndrome

Eisenmenger syndrome (ES) is the most severe form of PAH-CHD. It is the result of unrepaired, unrestricted left-to-right shunting that leads to severe PAH. Large unrestricted ventricular septal defects (VSDs) lead to ES more frequently than large atrial septal defects (ASDs). Initially, the hemodynamics are characterized by a significant left-to-right shunt that leads to a progressive increase in PAP due to the combined effect of volume overload and shear forces that elevate the pulmonary vascular resistance (PVR). As the PAP approaches the level of systemic pressure, the amount of the left-to-right shunt decreases. Once the PVR equals the systemic vascular resistance (SVR), the shunt becomes bidirectional. Finally, when the PVR is higher than the SVR, the shunt reverses to right-to-left, leading to cyanosis and ES (Figure 1).[11,12] Chronic cyanosis leads to erythrocytosis, coagulopathy, thrombocytopenia, and clubbing among other clinical features of ES. In these

EISENMENGER SYNDROME	• Includes all large intra- and extracardiac defects, which begin as systemic-to-pulmonary shunts and progress with time to severe elevation of PVR and to reversal (pulmonary-to-systemic) or bidirectional shunting. Cyanosis, secondary erythrocytosis, and multiple organ involvement are usually present.
PAH ASSOCIATED WITH PREVALENT SYSTEMIC-TO-PULMONARY SHUNTS	• Correctable • Noncorrectable • Includes moderate to large defects; PVR is mildly to moderately increased, systemic-to-pulmonary shunting is still prevalent. Cyanosis at rest is not a feature.
PAH WITH SMALL/ COINCIDENTAL DEFECTS	• Marked elevation in PVR in the presence of small cardiac defects (usually ventricular septal defects < 1 cm and atrial septal defects < 2 cm of effective diameter assessed by echo), which themselves do not account for development of elevated PVR; the clinical picture is very similar to idiopathic PAH. Closing the defects is contraindicated.
PAH AFTER DEFECT CORRECTION	• Congenital heart disease is repaired, but PAH either persists immediately after correction or recurs/develops months or years after surgery in the absence of significant postoperative hemodynamic lesions.

Table 1.
2013 clinical classification of pulmonary arterial hypertension associated with congenital heart disease. This classification remained unchanged in the 6th World symposium of Pulmonary Hypertension. Reprinted with permission from Elsevier.[7]
PVR: pulmonary vascular resistance; PAH: pulmonary arterial hypertension; HCV: hepatitis C virus

patients, shunt closure is contraindicated because it could lead to acute right ventricular failure and high mortality.

The prevalence of ES has decreased by 50% in the Western world due to advances in surgical care for CHD.[6] Most patients who develop ES reach adulthood, with reported survival between 25 to 75 years in population-based studies.[13]

2. Left-to-Right Shunts

Moderate-to-large, hemodynamically significant systemic-to-pulmonary shunts may lead to PAH when they are not repaired. These shunts can be intracardiac, such as ASDs and VSDs, or extracardiac, such as patent ductus arteriosus (PDA) and aortopulmonary windows. There is heterogeneity in the hemodynamic consequences depending on the location of the shunt, the size of the defect, and the genetic predisposition. Traditionally, small-to-moderate lesions are defined as ASD ≤ 2 cm and VSD/PDA ≤ 1 cm; large lesions are ASD > 2 cm and VSD/PDA > 1 cm. The pathophysiology of PAH differs in patients with pre-tricuspid defects compared to post-tricuspid shunts. Pre-tricuspid shunts include ASDs, sinus venosus defects, unroofed coronary sinus, and anomalous pulmonary vein return and cause volume overload of the pulmonary vascular bed, with associated enlargement of the right atrium and right ventricle. In these patients, the degree and duration of volume overload tend to be the key determinants of endothelial injury, and the PAP typically does not increase significantly until adulthood.[14] Post-tricuspid defects include VSDs, PDAs, and aortopulmonary window and lead to volume and pressure overload of the pulmonary vasculature and associated dilation of the left ventricle. Unrestrictive post-tricuspid defects expose the pulmonary circulation to higher pressures and are more likely to induce early and more severe pulmonary vascular disease, with high-pressure shear forces playing a crucial role.[14,15]

Notably, patients with Down syndrome develop accelerated pulmonary vascular disease compared with non–Down-syndrome patients who have similar cardiac defects.[16]

3. PAH With Coincidental Congenital Heart Disease

This group includes patients with significant elevation in PVR in the presence of small cardiac defects, which do not explain the degree of PAH. CHD has no causal relationship with PAH. This is a similar clinical picture to idiopathic PAH, and it is contraindicated to close the defects.[7]

4. Postoperative PAH

In these cases, PAH persists, recurs, or develops after surgical repair of the congenital defect. The clinical phenotype is often aggressive.[7]

OTHER CONGENITAL HEART DEFECTS ASSOCIATED WITH PAH

In addition to simple shunts, other complex unrepaired conditions are associated with PAH. Examples are unrepaired complete atrioventricular canal, transposition of the great arteries with a VSD, single ventricle physiology with unrestricted pulmonary flow, and unrepaired truncus arteriosus, among others.

Patients with Fontan Circulation

Patients with single ventricle physiology who have undergone a Fontan operation have passive circulation from the systemic veins to the pulmonary vasculature. This circulation system relies on low PVR. Adverse pulmonary vascular remodeling might play a role in the worsening hemodynamics that patients with a Fontan operation experience over time.[17] Even though the PVR may not meet the definition of PAH in these patients, data suggests that they benefit from treatment to lower the PVR.

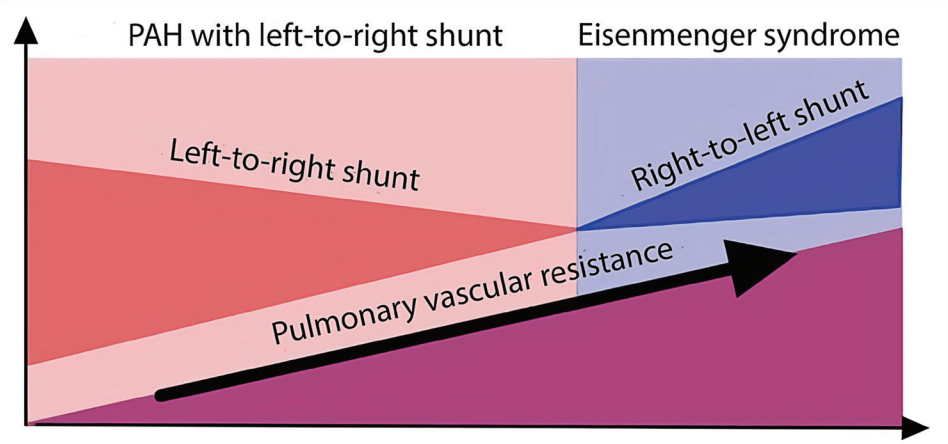

Figure 1.
Pathophysiology of pulmonary arterial hypertension in a patient born with a hemodynamically significant septal defect. Pressure and volume overload of the pulmonary circulation increases the severity of pulmonary vascular resistance, leading to an initial fall and eventual reversal of the shunt.

DIAGNOSIS AND EVALUATION OF PAH ASSOCIATED WITH CHD

Pulmonary hypertension–congenital heart disease should be suspected in all CHD patients with persistent cardiac shunt who present with a decline in functional status or right heart failure symptoms (lower extremity edema, abdominal distention, exertional syncope, weight gain). Most commonly, PAH-CHD comes to attention when estimated PAP is found to be elevated on routine echocardiographic assessment.[10] A comprehensive diagnosis and evaluation are warranted for all patients with suspected PAH-CHD. The following focuses on critical diagnostic tests including echocardiography, cardiac magnetic resonance imaging, and cardiac catheterization, all of which are helpful in making the diagnosis, defining the pathophysiology, evaluating the candidacy for either surgical or medical management, and evaluating prognosis and response to therapy.[18]

Echocardiography

Transthoracic echocardiogram (TTE) is the preferred imaging modality to screen for PAH in patients with CHD. TTE can estimate the subpulmonary ventricular pressure and PAP in the absence of obstructive disease of the right ventricular outflow tract (RVOT) or pulmonary valve using the Doppler velocity across the tricuspid valve. TTE is also the first step in visualizing the underlying cardiac anatomy, shunt defect size, and pressure gradient to determine (1) if the anatomy is restrictive, (2) the level and direction of shunting, and (3) ventricular size and function.[6,19] Detection of an intra- or extracardiac shunt may present a challenge when there is equalization of pressures between chambers and bidirectional shunting.

Pulmonary arterial hypertension is often suspected based on elevated tricuspid regurgitation peak velocity, which indicates elevated right ventricular systolic pressure (RVSP). Caution must be exercised in the CHD population because, in the presence of RVOT obstruction, elevated RVSP does not correlate with elevated pulmonary artery systolic pressure (PASP)[18,19]; PASP estimations must therefore account for any RV outflow gradient. In addition, PASP correlates with mean PAP (mPAP), which means that caution must also be observed with high-flow patients (eg, left-to-right shunt or pulmonary regurgitation) because under these circumstances, PASP increases disproportionally to mPAP. Right ventricular dysfunction is common with CHD, even in the absence of PAH, and consequently does not reliably identify PAH.

Cardiac Magnetic Resonance

Cardiac magnetic resonance (CMR) plays a valuable role in assessing RV size and function because it provides reproducible and reliable data.[20] CMR has a unique value in the assessment and serial follow-up of patients with ACHD because it offers unrestricted and noninvasive access to the heart and great vessels without the need for ionizing radiation.[10] In the presence of shunt lesions, we can quantify the net forward flow through the aortic valve and the pulmonary valve by using phase contrast technique and thus measure Qp:Qs noninvasively to assess the hemodynamic significance of the shunt.

Cardiac Catheterization

All symptomatic patients with PAH must undergo cardiac catheterization with shunt evaluation to confirm the diagnosis of PAH, delineate the underlying pathophysiology, determine the prognosis and response to therapy, and evaluate candidacy for operative/device closure in patients with shunt physiology.[10,21] Confounders such as pulmonary artery or pulmonary vein stenosis should be excluded during an invasive assessment.[6] Catheterization data is a snapshot of the resting hemodynamics at a single moment in time. Dynamic maneuvers, such as inhaled nitric oxide challenge, volume loading, and exercise, will help determine the prevailing pathophysiology in borderline or mixed PAH cases.[18] Obtaining accurate pulmonary artery and vein saturations is not a trivial task for CHD patients with any level of complexity. Even appropriately collected accurate data can unknowingly be misleading. As

such, catheterization should be performed by an experienced ACHD specialist.[10]

MANAGEMENT OF PAH IN CONGENITAL HEART DISEASE

Given that PAH-CHD is a very heterogeneous population that has been excluded from randomized clinical trials for pulmonary hypertension, the management guidelines are based mainly on clinical expertise rather than a strong level of evidence.[9,10,22,23]

Supportive Management

It is recommended that patients with PAH-CHD be assessed by a physician trained in ACHD. Pregnancy in this setting is associated with high maternal and fetal mortality, thus reliable contraception should be established to avoid pregnancy. Regular immunization with influenza and pneumococcal infections should be ensured. Appropriate diuresis should be instituted in patients exhibiting signs and symptoms of right heart failure. Patients with indications for anticoagulation (those with atrial fibrillation, mechanical valves, or pulmonary embolism) should receive it unless there are contraindications.[23] Anticoagulation in the absence of atrial arrhythmia, mechanical valves, or vascular prosthesis is not generally recommended in PAH-CHD and should be decided on an individual basis.[9] History of hemoptysis should be carefully assessed before initiation of anticoagulation.

Disease-Targeting Therapy

The mainstay of treatment in PAH-CHD is targeted PAH therapy, which works best when started early.[24] Targeted PAH therapy includes three classes of substances: (1) endothelin receptor antagonists (ERAs), (2) phosphodiesterase type 5 (PDE-5) inhibitors, and (3) prostanoids. The ultimate aim of therapy is to attain reasonable or appropriate exercise ability and quality of life and enhance or sustain ventricular function.[22]

PAH-CHD With Coincidental Defects or PAH After Defect Closure

The pathophysiology of this group is similar to patients with idiopathic PAH and should be treated as such. Defect closure in these patients is contraindicated.[16] Treatment includes targeted PAH therapy, with lung or heart-lung transplantation reserved for deteriorating symptoms despite maximized oral and intravenous therapy.

PAH With Systemic-to-Pulmonary Shunt

The 2018 American Heart Association (AHA)/American College of Cardiology (ACC) Guidelines for the Management of Adults with Congenital Heart Disease recommend that surgical or percutaneous closure of hemodynamically significant defects (Qp:Qs ≥ 1.5:1) is considered in patients with symptoms and ventricular dilation provided that the systolic PAP is less than 50% of the systolic systemic pressure and the PVR is less than one-third of the SVR.[10] Closure of defects in the presence of severe PAH (PAP > two-thirds systemic; PVR > two-thirds of the SVR in the AHA/ACC guidelines and PVR > 5 WU in the European guidelines) and/or a net right-to-left shunt is contraindicated.[9,10] This is based on the increased mortality after closure in patients with the described hemodynamics.[25]

Patients who do not meet the hemodynamic cutoff for intervention are in the "therapeutic gray zone" for defect repair. The AHA/ACC guidelines recommend that these patients be evaluated by an ACHD and PAH team to treat PAH before consideration for closure. The 2020 European Society of Cardiology guidelines for the management of ACHD have given a class IIB indication for fenestrated closure of septal defects in patients with severe PAH when the PVR falls below 5 WU after targeted PAH treatment and a significant left-to-right shunt is present.[9] However, given the lack of established markers of favorable prognosis in this group, decisions should be based on the patient's careful clinical and hemodynamic evaluation. Assessment of such patients should be performed in tertiary care centers with expertise in ACHD and PAH.[23]

Eisenmenger Syndrome

The management of patients with ES is limited to palliative measures and heart and lung transplantation for eligible patients.[12] Recent advances in management have focused on improving the quality of life of these patients. Adult patients with ES should be closely monitored and managed by ACHD specialists.[10] Supportive measures include maintaining hydration, treating iron-deficiency anemia, establishing contraception and avoiding pregnancy, and antiarrhythmic therapy. Routine phlebotomy is contraindicated because it may impair oxygen transport capacity, reduce exercise tolerance, induce iron deficiency, and increase the risk of stroke.[6,26] Phlebotomy should be reserved to relieve hyperviscosity syndrome and should be accompanied by appropriate volume replacement. Routine anticoagulation has not been shown to increase survival. Anticoagulation is only suitable in patients with another indication of anticoagulation in the absence of clinically significant hemoptysis.[27]

In the BREATHE-5 trial (Bosentan Randomized Trial of Endothelin Antagonist Therapy-5), bosentan showed improved exercise capacity (6-minute walk distance) and hemodynamics (mPAP and PVR index) in patients with New York Heart Association class III symptoms with ES.[28] Current clinical guidelines recommend initiating bosentan as a first-line therapy (class I) in symptomatic adults with ES.[10] Combination therapy with PDE-5 inhibitors is indicated (class IIa) in patients with

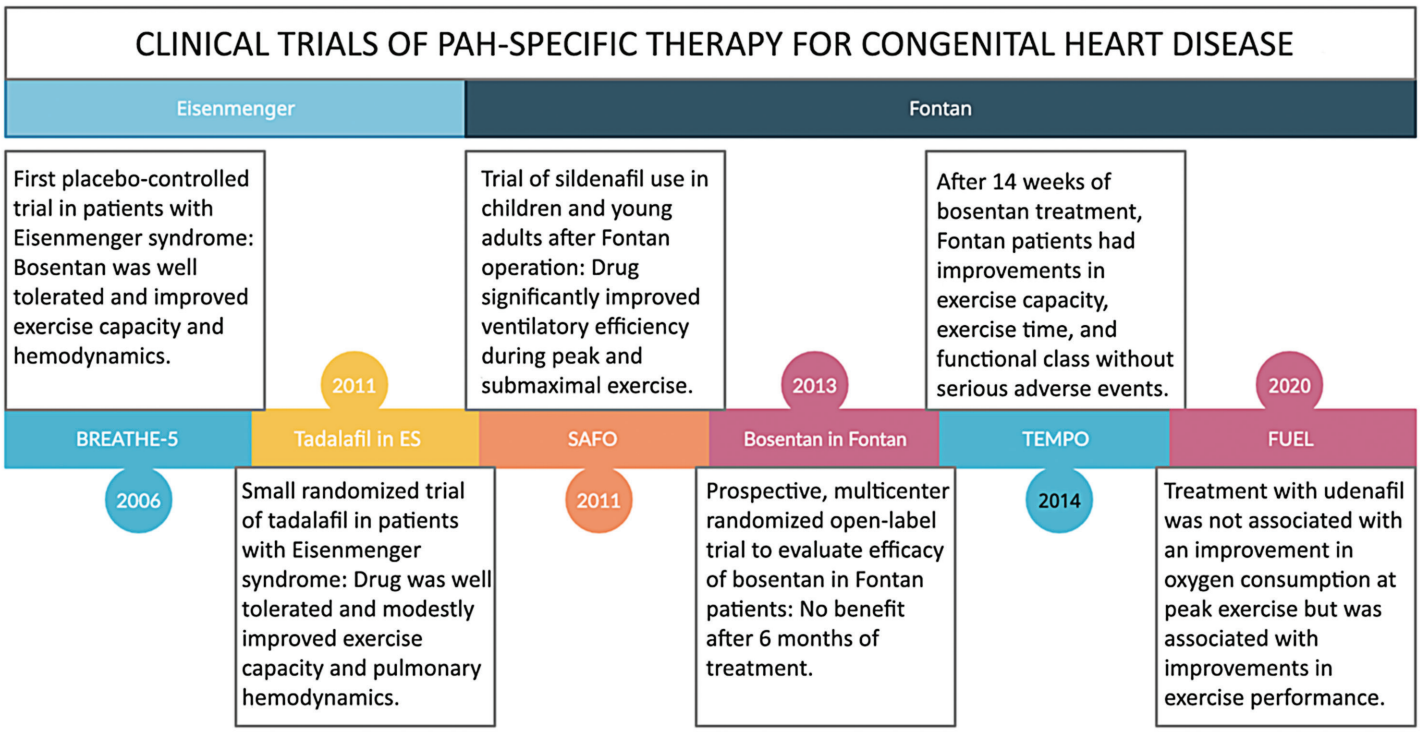

Figure 2.
Trials specific to pulmonary arterial hypertension therapy done in patients with congenital heart disease, specifically in those with Eisenmenger syndrome (ES) and with single ventricle physiology and Fontan operation.[28,29,35-38]

suboptimal responses to bosentan and has been shown in smaller trials to be beneficial for exercise capacity.[29] There is limited data on prostanoids; typically, continuous intravenous infusions are not routinely prescribed due to the risk for infection and paradoxical embolism.[30] Other agents have not shown consistent benefit.[31]

Most centers adopt a symptom-oriented care plan for ES, usually beginning with an ERA or PDE-5 inhibitor and escalating to combination therapy for persistent symptoms or in the event of clinical worsening. Patients with ES who receive disease-targeted therapy have better survival compared with those not on targeted therapies.[32]

Management of PAH in Fontan Patients

A Fontan operation redirects the superior and inferior vena cava flow to the pulmonary arteries in patients with single ventricle physiology without a subpulmonic ventricle. As such, the circulation is passive and dependent on low pulmonary pressures.[23] Even a slight rise in mPAP or PVR will lead to a failing Fontan circulation.[33] Because maintaining a low PVR is vital to the viability of Fontan circulation, PDE-5 inhibitors have been viewed as an appealing option for patients with high Fontan pressures and have been shown to improve cardiac output and functional capacity in Fontan patients.[34-36] In the FUEL (Fontan Udenafil Exercise Longitudinal) trial, udenafil did not show an increase in peak oxygen consumption but did show improvement in measures of exercise performance.[37] The use of ERAs has shown benefit in exercise capacity.[38] The clinical guidelines recommend the use of pulmonary vasoactive medications in Fontan patients (class IIa).[10] Figure 2 shows clinical trials evaluating PAP therapy in patients with congenital heart disease, including ES, single ventricle physiology, and Fontan operation.

CONCLUSION

Recent advances in diagnosis and management have significantly improved survival in the CHD population. Timely repair of hemodynamically significant shunts remains the cornerstone of therapy. Patients with significant shunts who have already developed PAH should be evaluated and treated at a center with ACHD and PAH expertise. Patients who develop ES have increased morbidity and mortality. There is growing evidence of the benefits of pulmonary vasoactive agents in patients with ES and Fontan circulation. Pregnancy remains a high risk in this patient population, and timely contraception counseling is indicated.

KEY POINTS

- The most frequent cause of pulmonary arterial hypertension (PAH) in adult congenital heart disease (ACHD) is unrepaired shunts.
- Timely repair of hemodynamically significant shunts remains the cornerstone of therapy.
- Patients with significant shunts who have already developed PAH should be evaluated and treated at a center with ACHD and PAH expertise.
- There is growing evidence of the benefits of pulmonary vasoactive agents in patients with Eisenmenger syndrome and Fontan circulation.

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