Pulmonary Hypertension in Adults with Congenital Heart Disease

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KEYWORDS

• Adult congenital heart disease • Advanced medical therapy • Clinical management
• Eisenmenger syndrome • Pulmonary arterial hypertension

KEY POINTS

- Pulmonary arterial hypertension (PAH) related to congenital heart disease (CHD) is the result of pulmonary vascular remodeling due to chronic systemic-to-pulmonary shunting and is associated with increasing morbidity, mortality, and functional limitation.
- Eisenmenger syndrome is the most severe phenotype of PAH-CHD and is characterized by severe pulmonary vascular resistance elevation and shunt reversal (pulmonary-to-systemic shunting), leading to systemic cyanosis and various complications.
- Treatment strategies typically focus on medical management, although select patients with large shunts who have not yet developed severe PAH may be appropriate for either surgical or percutaneous defect closure.
- Women of childbearing age with PAH-CHD should be counseled about the risks of pregnancy and appropriate contraceptive strategies.
- Lung or heart-lung transplantation should be considered in patients with advanced disease.

INTRODUCTION

In 1897, Dr Victor Eisenmenger[1] published a postmortem examination of a patient with a ventricular septal defect (VSD), cyanosis since childhood, clubbing of the fingers and toes, polycythemia, and evidence of right heart failure. Although he did not at the time deduce that this patient's cyanosis was related to increased pulmonary vascular resistance (PVR) leading to right-to-left shunting, his publication represented the first description of pulmonary arterial hypertension (PAH) associated with congenital heart disease (CHD). It was not until more than 50 years later, in 1951, that Dr Paul Wood published the first case series of 5 patients with bidirectional shunt lesions who had pulmonary artery pressures at systemic levels.[2,3] In 1951, Dr Paul Wood published a textbook that used the term, *Eisenmenger syndrome* (ES), likely for the first time. He described ES as "pulmonary arterial hypertension with a reversed shunt."[3] Since that time, it has become well recognized that chronically increased flow and transmitted pressures to the pulmonary circulation resulting from chronic left-to-right shunting induces pulmonary vascular remodeling and in some cases leads to PAH. It is now recognized, however, that the pathophysiology of PAH-CHD likely is more complicated than just this process. In contemporary cohorts, PAH affects 5% to 10% of adults with CHD and is associated with significant morbidity, mortality, and functional limitation.[4–7] Women are affected more commonly by PAH-CHD and risk increases with

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increasing biological age and the age when defect closure occurred.[5] This review describes the pathophysiology of PAH-CHD, discusses the definition and classification of PAH-CHD, outlines how PAH-CHD is diagnosed, and summarizes current management strategies.

PATHOPHYSIOLOGY OF PULMONARY ARTERIAL HYPERTENSION ASSOCIATED WITH CONGENITAL HEART DISEASE

PAH-CHD develops as a consequence of intracardiac or extracardiac systemic-to-pulmonary shunts that lead to volume and/or pressure overload of the pulmonary circulation and subsequent pulmonary vascular remodeling over time. Early in this process, pulmonary vascular remodeling can be stabilized or reversed if the shunt lesion is closed either through surgical or percutaneous intervention. If the shunt is not addressed, however, adverse pulmonary vascular changes can become irreversible. Once present, PAH-CHD typically progresses over time, sometimes causing severe elevation in PVR that exceeds that of the systemic circulation and results in pulmonary-to-systemic (right-to-left) shunting with hypoxemia and central cyanosis.

The pathologic process underlying the development of PAH-CHD is similar to that observed in other forms of class 1 PH. Persistent volume and pressure overload of the pulmonary vascular system lead to increased shear stress and arterial endothelial damage. Endothelial damage is associated with degeneration of the extracellular matrix and release of vasoactive mediators, such as fibroblast growth factor, angiopoietin-1, and transforming growth factor ß. When pathologically upregulated, these growth factors induce smooth muscle hypertrophy and proliferation.[8] Endothelial dysfunction also leads to platelet adherence and activation, cytokine release and activation of local inflammatory cascades, and an imbalance of vasoactive mediators that favors vasoconstriction.[8–10] Long-standing PAH is associated with pulmonary arterial fibrosis that results in decreased pulmonary artery diameter and further increase in pulmonary artery pressure and PVR over time.[11]

DEFINITION AND CLASSIFICATION OF PULMONARY ARTERIAL HYPERTENSION ASSOCIATED WITH CONGENITAL HEART DISEASE

PAH is defined by the 6th World Symposium on Pulmonary Hypertension as a mean pulmonary artery pressure greater than 20 mm Hg in the setting of a pulmonary artery wedge pressure less than or equal to 15 mm Hg and PVR greater than or equal to 3 Wood units (WU).[12] Pulmonary hypertension (PH) has been categorized into 5 groups based on the World Health Organization classification system (**Table 1**). PAH-CHD is included in group 1. PH in CHD can result from several different etiologies, spanning all 5 PH groups. Although PAH-CHD appears to have the greatest impact on morbidity and mortality, awareness of and differentiation from the other classes are essential in providing the most appropriate clinical management.

The most common etiology of PH in CHD is related to diseases of the left heart, categorized as group 2 disease. Patients with CHD are unique, because they may have a systemic right ventricle (as in congenitally corrected transposition of the great arteries) or single-ventricle physiology (as in a Fontan-palliated anatomy). As such, referring to the *systemic ventricle* and *subpulmonary ventricle* (as subsequently is done in this review) provides greater clarity than describing right-sided or left-sided cardiac chambers. Systolic or diastolic function of the systemic ventricle or abnormalities in the aortic or systemic atrioventricular valves can lead to elevated pulmonary capillary wedge pressure and secondary elevation of the pulmonary arterial pressure. The PVR in such cases usually is less than 3 WU, differentiating this cause of elevated pulmonary pressure from other causes. In some cases, there can be mixed disease, in which the pulmonary capillary wedge pressure is elevated, but the pulmonary arterial pressure is elevated disproportionately. These can be among the most challenging patients to manage, due to their predilection toward pulmonary edema with targeted PAH therapies. In general, management of systemic ventricular etiologies of PH should precede any attempt to target the pulmonary arterial component.

Patients with CHD often are subjected to multiple sternotomies and thoracotomies related to surgical interventions, resulting in restrictive lung disease. This also can lead to PH, categorized as group 3 disease. Finally, patients with CHD may develop thromboembolic disease, which can lead to group 4 disease and/or can have concomitant systemic disease that leads to group 5 disease. The most complex forms of PAH-CHD have been classified as group 5. These include segmental forms of PAH (discussed later) and single-ventricle anatomy. Although the absence of a subpulmonary ventricle in Fontan-palliated patients precludes the development of high pulmonary pressures, the presence of increased PVR is a well-known cause of categorized as

Table 1
Classification of pulmonary arterial hypertension based on the 6th World Symposium on Pulmonary Hypertension

Pulmonary Hypertension Class	Etiologies
Class 1	PAH • CHD • Idiopathic • Heritable • Drug or toxin induced • Persistent PH of the newborn • Pulmonary veno-occlusive disease • Connective tissue diseases • Human immunodeficiency virus infection • Portal hypertension • Schistosomiasis • Chronic hemolytic anemia
Class 2	PH caused by left heart disease • Systolic dysfunction • Diastolic dysfunction • Valvular heart disease
Class 3	PH caused by lung disease or hypoxia • Chronic obstructive lung disease • Interstitial lung disease • Mixed restrictive/obstructive lung disease • Sleep-disordered breathing • Chronic exposure to high altitude
Class 4	Chronic thromboembolic PH
Class 5	PH with unclear multifactorial mechanisms • Hematologic disorders ○ Myeloproliferative disorders, splenectomy • Systemic disorders ○ Sarcoidosis, Langerhans cell histiocytosis • Metabolic disorders ○ Glycogen storage disease ○ Gaucher disease ○ Thyroid disorders • Others ○ Tumoral obstruction ○ Fibrosing mediastinitis ○ Chronic renal failure on dialysis

Fontan failure. Whether targeted PAH therapies are beneficial for such patients remains under active investigation. Further discussion of groups 2 to 5 PH is beyond the scope of this review.

PAH-CHD has been categorized into 4 clinical subgroups: ES, PAH associated with persistent systemic-to-pulmonary shunts, PAH with small/coincidental shunts, and PAH persisting or developing after defect closure (Table 2).[13] This classification system defines underlying etiology and physiology and assists in identifying targeted treatment options.

Eisenmenger Syndrome

ES is the most severe phenotype of PAH-CHD. It results from large systemic-to-pulmonary (left-to-right) shunts and is characterized by severe elevation of PVR, such that there is shunt reversal (right-to-left shunting) or bidirectional shunting that results in hypoxia and central cyanosis. Chronic, and sometimes severe, cyanosis is a distinct manifestation of ES among patients with PAH-CHD and unrepaired or partially repaired defects and is associated with multisystem sequelae, including erythrocytosis, thrombocytopenia, coagulation abnormalities, thrombosis, susceptibility to infection, cerebrovascular events (ischemic, embolic, and hemorrhagic), right heart failure, and early death.[9] Despite earlier detection of CHD and advances in pediatric surgical and medical interventions for shunt lesions that have led to decreased prevalence of ES, this disease process remains prevalent among adults with CHD and requires a multidisciplinary approach to management.

Overall, patients with ES are considered to have a better prognosis than other forms of PAH.[14,15] The presence of a right-to-left shunt allows for pressure unloading of the right ventricle and maintains cardiac output, although at the expense of cyanosis. Additionally, in some patients with congenital systemic-to-pulmonary shunts, the right ventricle does not remodel after birth and maintains the adaptive hypertrophy present as a result of fetal circulation, thus allowing better tolerance of elevated pulmonary arterial pressure over time.[16] This phenomenon seems to occur more commonly in patients with post-tricuspid shunts (eg, VSD) as opposed to patients with pre-tricuspid shunts (eg, atrial septal defect), in whom the right ventricular response to PAH more closely resembles that of patients with idiopathic PAH. The presence of a pre-tricuspid shunt has been demonstrated to be an independent predictor of early death in patients with ES.[17] Despite this, long-term prognosis remains poor compared with patients with congenital shunt lesions without PAH. Based on registry data, 5-year survival from the time of diagnosis ranges between 74% and 81%, whereas long-term survival is lower (64% at 7 years and 57% at 10 years).[18–20]

Table 2
Clinical classification of pulmonary arterial hypertension with congenital heart disease[19]

ES	• Large left-to-right shunt that leads to severe elevation in PVR and shunt reversal • Characterized by hypoxia and central cyanosis
Persistent left-to-right shunt	• Moderate to large left-to-right shunt resulting in increased PVR • May or may not be correctable/reversible
Coincidental CHD	• Elevation of PVR is out of proportion to the magnitude of shunt and the size of the congenital heart lesion. • The CHD is unlikely to be directly responsible for the develop of PAH.
Postinterventional	• PAH that either persists after shunt closure or develops months or years after the intervention

Chronic cyanosis is associated with secondary erythrocytosis, a physiologic adaptive measure to augment oxygen transport and delivery. Erythrocytosis has effects on multiple other organ systems and predisposes patients to hyperviscosity syndrome, hemostatic abnormalities leading to increased risk for both bleeding and clotting, iron deficiency, hyperuricemia, and cholelithiasis.

Pulmonary Arterial Hypertension Associated with Persistent Systemic-to-Pulmonary Shunts

Patients with moderate to large left-to-right shunts may have PAH without progressing to ES. In these patients, the PVR is mildly to moderately elevated; thus, systemic-to-pulmonary shunting predominates, and cyanosis is not present at rest. Early identification of patients with PAH-CHD and persistent systemic-to-pulmonary shunts is important because shunt closure potentially can halt or reverse the progression of pulmonary vascular disease.

Pulmonary Arterial Hypertension with Small/Coincidental Shunts

PAH with small/coincidental shunts form of PAH-CHD is diagnosed in patients with markedly elevated PVR despite the presence of only very small shunt lesions. In this class of PAH-CHD, the severity of PAH is considered out of proportion to the size of the left-to-right shunt. Consideration of other underlying causes of PAH, therefore, is strongly recommended. The prognosis associated with PAH with small/coincidental shunts is similar to that seen in patients with idiopathic PAH.[15,21]

Pulmonary Arterial Hypertension after Defect Closure

PAH after defect closure is relatively rare, with contemporary data suggesting a prevalence of 3% among patients with corrected, simple shunt lesions.[22] This group consists of 2 PAH-CHD phenotypes: those who with persistent PAH despite defect closure and those who develop PAH many years after defect closure. The former most likely occurs in the setting of late diagnosis and shunt intervention. The pathophysiology underlying the development of PAH in the latter phenotype remains unclear, although genetic predisposition has been hypothesized.[9] Clinical characteristics that predict development or persistence of PAH following defect closure include type of defect (complete atrioventricular septal defect, sinus venosus defect, large defect, or concomitant moderate or high complexity congenital heart defects), ratio of pulmonary-to -ystemic blood flow (Qp:Qs) greater than or equal to 3 or pulmonary artery systolic pressure greater than 40 mm Hg prior to closure, presence of an associated genetic syndrome, older age at repair, and female sex.[23] The prognosis associated with this form of PAH-CHD is considered particularly poor, with a clinical phenotype that often is aggressive.[15,21,22]

Segmental Pulmonary Arterial Hypertension

Segmental PAH is diagnosed when segments of the pulmonary vasculature, as opposed to the entire pulmonary vascular bed, are affected by pulmonary vascular remodeling and elevated PVR. This form of PAH-CHD occurs when there is increased blood flow to localized portions of the lung. Some examples of underlying etiologies that can cause segmental PAH include a large left-to-right shunt with peripheral pulmonary artery stenosis (either occurring natively or due to branch pulmonary artery banding), absence or atresia of a single pulmonary artery, anomalous pulmonary artery from the aorta feeding a single lung segment, and surgical shunts, such as the Waterston shunt or Potts shunt, that may supply only part of the pulmonary vasculature. Each portion of the involved pulmonary vasculature may be affected by PAH of differing severity. Symptoms typically are related to the severity of ventilation-perfusion

mismatch and the degree of right ventricular dysfunction.[24]

DIAGNOSIS

Clinical History and Presenting Symptoms

A diagnosis of PAH-CHD requires a high degree of clinical suspicion, because presenting symptoms typically are nonspecific. Exertional dyspnea and fatigue are the most common presenting symptoms but also can result from arrhythmia, heart failure, and/or deconditioning in patients with CHD. Exertional syncope also can occur and typically is a marker of severe disease with increased associated mortality. Patients also may experience chest pain, which can be ischemic in nature as a result of a hypertrophied right ventricle with increased metabolic demands, elevated right ventricular end diastolic pressure resulting in reduced coronary perfusion, hypoxia, or extrinsic compression of the left main coronary artery by a dilated pulmonary artery.[25,26] Suggestive physical examination findings include an accentuated P_2, a right ventricular heave, elevated jugular venous pulsation and signs of right heart failure. Patients with CHD who report any of these symptoms or have relevant physical examination findings (**Fig. 1**) should undergo further evaluation for the presence of PAH. The more extreme physical characteristics of a patient with ES are illustrated in **Fig. 2**.

Diagnostic Testing

In patients with CHD in whom there is concern for PAH, transthoracic echocardiography (TTE) is an important initial diagnostic testing modality. Ideally, TTE should be completed by a performing sonographer and interpreting cardiologist with expertise in CHD. In addition to being used to assess the location and size of underlying congenital cardiac defects, TTE can be used to estimate the right ventricular systolic pressure, which, in the absence of pulmonary stenosis, approximates the pulmonary artery pressure. TTE also is useful in assessing right ventricular dysfunction. Although not an integral part of the diagnostic evaluation for PAH, cardiac magnetic resonance imaging also may be useful to better determine the size and location of the congenital defect, the direction and quantity of shunting, and, when appropriate, the feasibility of percutaneous defect closure.

Right heart catheterization (RHC) is the gold standard for establishing the diagnosis of PAH. As discussed previously, patients with CHD may have other reasons for pulmonary artery or right ventricular systolic pressure elevation, such as left heart disease with elevated left-sided filling pressures, pulmonary artery or vein stenosis, subpulmonary ventricular outflow or pulmonary valve stenosis, and thromboembolic disease. In some of these patients, use of vasodilator therapy, the hallmark of PAH treatment, may be harmful. RHC also is instrumental in establishing the magnitude of right-to-left and left-to-right shunting, which is reported as Qp:Qs. Additionally, a vasodilator challenge during RHC can be helpful in assessing prognosis and predicting response to targeted medical therapy.

Assessment of exercise tolerance also has important prognostic value in patients with PAH. When chronically managing patients with PAH-CHD, the 6-minute walk distance (6MWD) is used most commonly and can assess baseline functional status as well as serial improvement with targeted medical therapy.[27–29]

MANAGEMENT

Patients with PAH-CHD should be managed at centers with multidisciplinary expertise, including CHD and PAH specialists, CHD imaging experts, cardiovascular surgery, congenital heart interventionalists, and advanced heart failure/transplant teams. The primary management strategy for most patients with PAH-CHD is medical therapy, although defect closure may be considered in select cases of PVR elevation that is not severe and still may be reversible (**Fig. 3**). Invasive hemodynamic assessment with cardiac catheterization is recommended prior to initiation of medical therapy or consideration of surgical or transcatheter intervention in all patients with PAH-CHD to confirm the diagnosis, evaluate safety of medical therapy, and determine suitability of defect closure.[23] The most appropriate management strategy depends on the direction and magnitude of shunting and severity of PAH.

Defect Closure

In appropriate patients with PAH-CHD, defect closure can halt the progression of PAH and, in some cases, lead to reversal of disease. Multiple studies have demonstrated a decrease in prevalence of PAH following ASD closure as well as a reduction in pulmonary arterial pressure.[30] Shunt closure is not appropriate in all patients, however. Among patients with ES who have PVR elevation such that there is significant right-to-left shunting, defect closure is contraindicated. In these patients, the right-to-left shunt serves as a relief valve, allowing blood to reach the left heart and systemic circulation despite the presence of very elevated PVR, albeit at the expense of systemic desaturation. The defect also serves to reduce right ventricular afterload and therefore

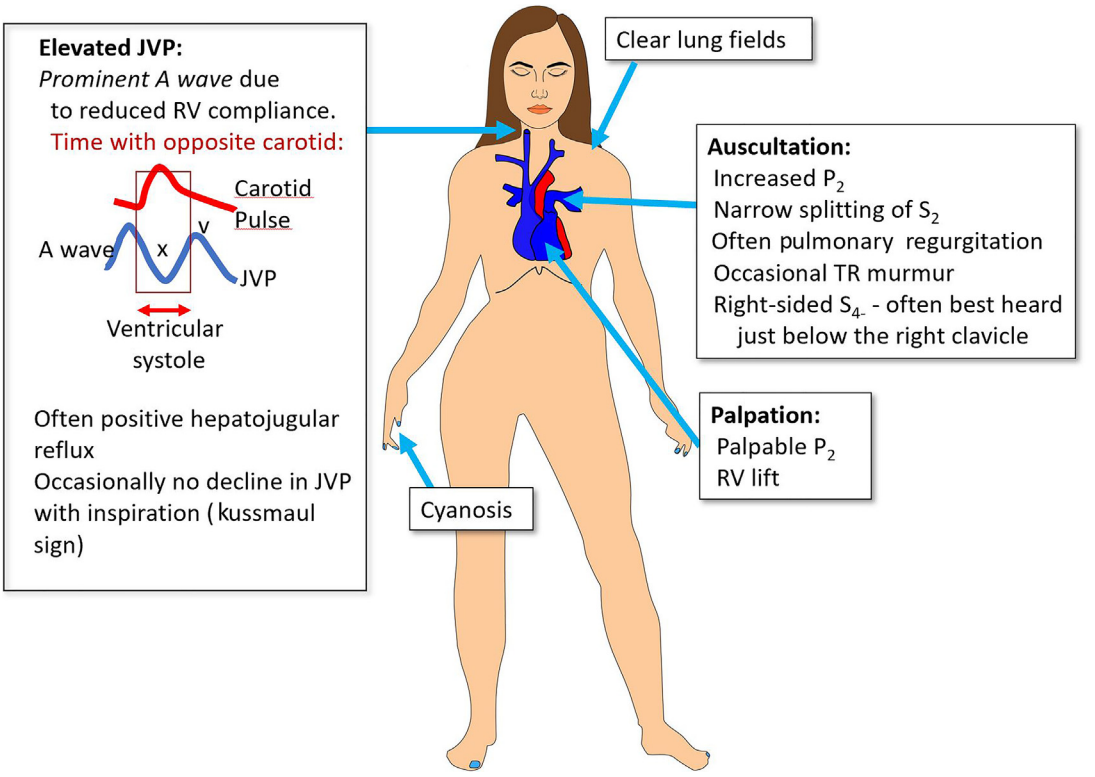

Fig. 1. Physical manifestations and common examination findings in a patient with PAH-CHD. JVP, jugular venous pulsation; RV, right ventricle; TR, tricuspid regurgitation.

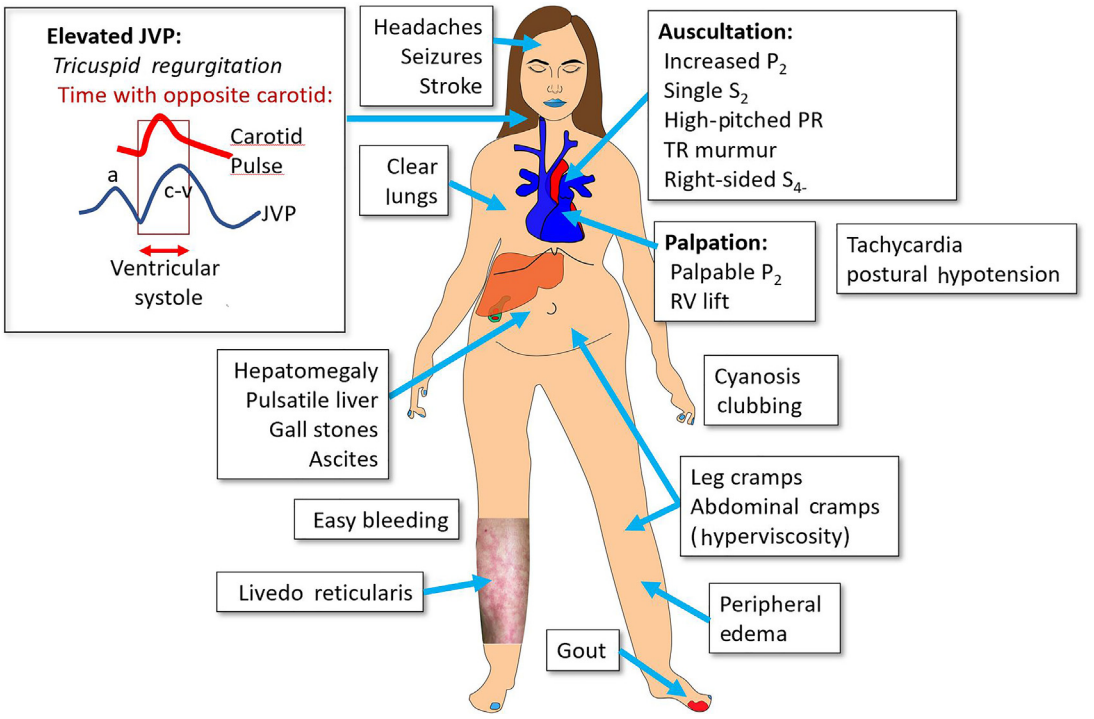

Fig. 2. Physical manifestations and common examination findings in a patient with ES. JVP, jugular venous pulsation; PR, pulmonary regurgitation; RV, right ventricle; TR, tricuspid regurgitation.

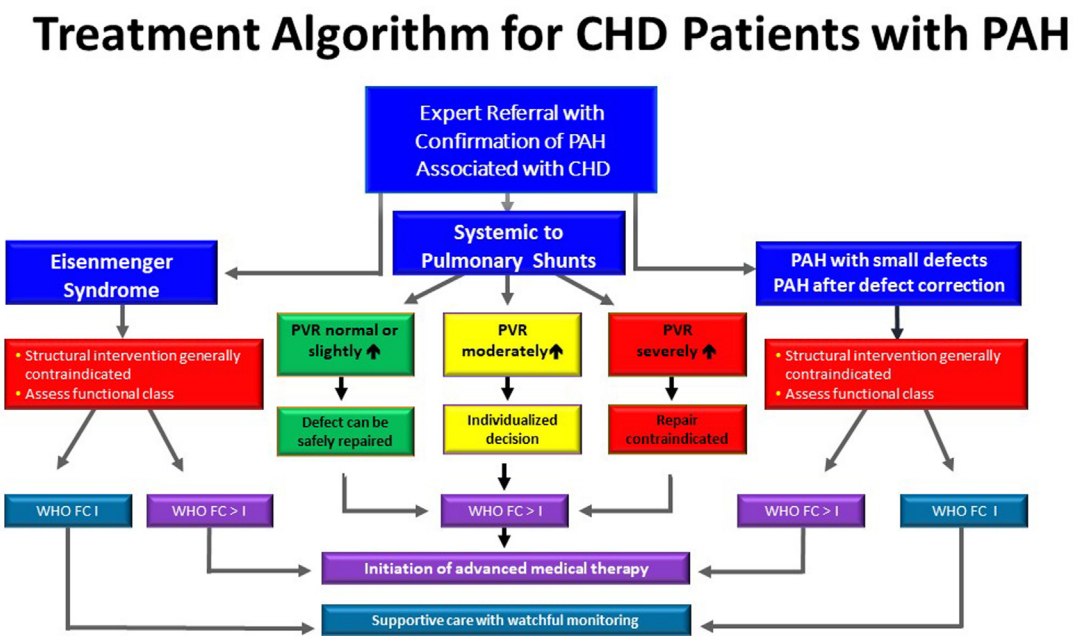

Fig. 3. A proposed treatment algorithm for patients with PAH-CHD arranged by subtype. For patients with unrepaired or residual shunts, defect correction should be considered, depending on the PVR. Larger left-to-right shunts with lower PVR should be closed, whereas smaller net left-to-right shunts with higher resistance should not be, because closure could be detrimental. For cases between these extremes, assessing response to vasodilators or reassessing hemodynamics during temporary balloon occlusion in the catheterization laboratory can be helpful. For patients with ES and corrected or small shunts, advanced medical therapies should be initiated in the presence of associated symptoms. FC, functional class; WHO, World Health Organization. (*Adapted from* Fathallah M, Krasuski RA. A Multifaceted Approach to Pulmonary Hypertension in Adults With Congenital Heart Disease. Prog Cardiovasc Dis. 2018 Sep-Oct;61(3-4):320-327.)

preserve right ventricular function. Closure of the defect may precipitate right heart failure and lead to cardiovascular collapse and death. In patients with desaturation with exertion suggestive of right-to-left shunting with exercise, device closure similarly is not recommended. Although assessment of upper extremity saturation is sufficient in patients with an atrial septal defect or VSD, it is important to assess for lower extremity hypoxia in patients with a patent ductus arteriosus, because the shunt may be located distal to the upper extremity blood supply. Finally, in patients with small/coincidental shunts, closure is not recommended, because it is unlikely to have an impact on the trajectory of PAH and potentially could be harmful if it is serving as a pressure relief valve for the right ventricle.

Some patients with a large shunt who have PAH but have not yet developed ES may benefit from defect closure. The 2018 American College of Cardiology/American Heart Association (ACC/AHA) Guideline for the Management of Adults with Congenital Heart Disease recommends surgical or percutaneous closure of large defects in patients with mildly or moderately elevated PVR who have evidence of significant left-to-right shunting. Specifically, defect closure is recommended only in patients with PVR less than one-third of systemic vascular resistance (SVR), pulmonary artery systolic pressure less than 50% systemic systolic pressure, and Qp:Qs greater than or equal to 1.5:1.[23]

The 2020 European Society of Cardiology Guidelines for the Management of Adult Congenital Heart Disease present a slightly different algorithm for selecting patients with PAH-CHD who may benefit from defect closure. The concept of treat to close, in which some patients with PAH-CHD initially ineligible for defect closure may become eligible with targeted PAH treatment, also is introduced. Shunt closure without preceding treatment of PAH is recommended in patients with a large shunt, PVR less than 5 WU, and Qp:Qs greater than 1.5. Among patients with PVR greater than 5 WU, a trial of PAH targeted medical therapy is recommended followed by reassessment of invasive hemodynamics. If after treatment the PVR is less than 5 WU and the Qp:Qs is greater than 1.5, defect closure with fenestration may be considered.[31]

Targeted Medical Therapy

For those patients with PAH-CHD and a large shunt in whom device closure is not recommended, medical therapy is the mainstay of management. Targeted medical therapy provides survival benefit in patients with ES and likely also in other forms of PAH-CHD.[32,33] Oral medications targeting the endothelin-1 receptor and the nitric oxide pathway as well as oral, parenteral, and inhaled formulations that target the prostacyclin pathway are commercially available. Although medical therapy typically is well tolerated in patients with pretricuspid shunts, those with post-tricuspid shunts require close clinical observation, because therapy can lead to left ventricular volume overload and left heart failure related to increased left-to-right shunting.

Endothelin-1 receptor antagonists work by blocking the binding of endothelin-1, a potent vasoconstrictor that is overproduced in the pulmonary vasculature in patients with PAH, to its receptor. Bosentan, a drug in this class, is the most extensively studied targeted PAH therapy for patients with CHD. Both short-term and long-term observational studies have demonstrated safety and tolerability of bosentan among patients with PAH-CHD, while also showing hemodynamic benefits and improvement in 6MWD.[34–40] The Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 (BREATHE-5) was the first multicenter, double-blind, randomized, placebo-controlled trial studying the benefits and safety of bosentan use in patients with PAH-CHD.[41] In this study, 54 patients with ES and advanced functional class were randomized to bosentan or placebo for 16 weeks. Those with patent ductus arteriosus, complex CHD, and/or concomitant treatment with other PAH medications were excluded. During the study period, 6MWD improved by 12% among patients treated with bosentan and decreased by 3% with placebo. Bosentan led to statistically significant reductions in PVR (9.3% reduction vs 5.4% increase with placebo) and mean pulmonary artery pressure (decreased by 5 mm Hg with treatment vs 0.5–mm Hg increase with placebo) and improved functional status. An open-label extension of BREATHE-5 followed 37 patients to 40 weeks of therapy and demonstrated sustained improvements in exercise and functional capacity.[42] Based on these data, current ACC/AHA guidelines recommend bosentan as first-line medical therapy in patients with PAH-CHD who are not eligible for defect closure.[23]

A second randomized controlled trial examining the use of a newer endothelin-1 receptor antagonist, macitentan, did not replicate the results of BREATHE-5. The Macitentan in Eisenmenger Syndrome to Explore Exercise Capacity (MAESTRO) study included 226 patients with ES and moderately to severely reduced functional status treated with macitentan or placebo for 16 weeks.[43] In addition to being a larger study that included patients with less severe PAH, MAESTRO included a more heterogeneous population of patients because it did not exclude those with severe congenital cardiac lesions or patients receiving other PAH therapies. MAESTRO failed to show a superior treatment effect of macitentan over placebo with respect to 6MWD or functional class, although the N-terminal fragment of the prohormone brain natriuretic peptide (NT-proBNP) levels were reduced and a hemodynamic substudy of 39 patients showed a reduction in indexed PVR.

Phosphodiesterase-5 (PDE-5) inhibitors, another targeted medication class used to treat PAH, function by blocking the action of PDE-5, an enzyme involved in the breakdown of nitric oxide. PDE-5 is present in high concentrations in the lung vasculature and is up-regulated in patients with PAH. The use of PDE-5 inhibitors, including sildenafil and tadalafil, has led to improvements in 6MWD and functional status among patients with PAH-CHD in observational studies.[44,45] The benefit of sildenafil also has been examined as an adjunctive therapy to bosentan in patients with PAH-CHD. One observational study evaluated bosentan-sildenafil combination therapy among patients who failed to respond to bosentan monotherapy.[46] After 6 months of combination therapy, there was a significant improvement in functional status, 6MWD, and hemodynamics. A randomized controlled trial assessing the effect of adding sildenafil after 9 months of treatment with bosentan did not demonstrate significant clinical improvements, although resting oxygen saturation did increase.[47] Guidelines currently recommend using PDE-5 inhibitors in patients with PAH-CHD without symptomatic improvement on single-drug therapy.[23]

Randomized, placebo-controlled studies focused on PAH-CHD are listed in **Table 3**. All these studies were conducted in ES. There are few data on the medical treatment of PAH-CHD with a coincidental shunt and patients with PAH-CHD after shunt closure. Most large, randomized studies of drug therapy in PAH have included a small subset of patients with repaired shunts. The largest such substudy examined the use of selexipag, a medication that selectively activates the prostacyclin receptor, thus inducing vasodilation and inhibiting proliferation of vascular smooth muscle cells. In the published post hoc secondary analysis of GRIPHON, a multicenter, double-blind,

Table 3
Randomized controlled trials investigating medical therapy in PAH-CHD

Study	Year	Drug (Class)	Population	N	Functional Class, % (II/III/IV)	Findings
BREATHE-5	2006	Bosentan (ERA)	ES	54	0/100/0	⇓ Indexed PVR ⇓ Mean PAP ⇑ 6MWD
Unnamed	2006	Sildenafil (PDE-5 inhibitor)	ES	10	30/60/10	⇓ Functional class ⇓ Mean PAP ⇑ 6MWD
Unnamed	2010	Bosentan (ERA) + sildenafil (PDE-5 inhibitor)	ES	21	43/48/5	⇑ Resting saturation ⇔ 6MWD
Unnamed	2011	Tadalafil (PDE-5 inhibitor)	ES	28	79/21/0	⇓ Functional class ⇑ 6MWD ⇓ PVR
MAESTRO	2017	Macitentan (ERA)	ES	226	60/40/0	⇓ Indexed PVR ⇓ NT-proBNP ⇔ Functional class ⇔ 6MWD

Abbreviations: ERA, endothelin receptor antagonist; PAP, pulmonary artery pressure.
A summary of randomized controlled trials investigating the effects of targeted advanced medical therapy in patients with pulmonary arterial hypertension with congenital heart disease. Studies are listed in chronologic order.

placebo-controlled study of the safety and efficacy of selexipag on morbidity and mortality in patients with PAH, patients with PAH-CHD after defect closure who were treated with selexipag experienced a lower combined endpoint of morbidity and mortality compared with those treated with placebo.[48] In general, given the similarities in disease progression and severity, it is recommended that patients with PAH-CHD with a coincidental shunt and PAH-CHD after shunt closure be treated with the same therapies used to treat idiopathic PAH.[9]

There also is a paucity of data dictating the appropriate medical management of patients with segmental PAH-CHD. Very small observational studies have demonstrated safety as well as improvements in 6MWD, symptoms, and hemodynamics with the use of both bosentan and sildenafil.[49–52] Other case reports, however, have noted worsening hypoxemia attributed to more pronounced ventilation/perfusion mismatching.[53,54] Patients with segmental PAH-CHD, should be followed closely after initiation of advanced medical therapies.

Organ Transplantation

Determining appropriate timing for when to consider organ transplantation in patients with ES and other forms of PAH-CHD can be difficult. Although some forms of PAH-CHD seem to mimic the expected disease progression seen in idiopathic PAH, those with ES and PAH-CHD with an uncorrected, large shunt appear to have a more unpredictable clinical course. Some patients can have prolonged survival before symptomatic deterioration or end-organ dysfunction occurs related to chronic hypoxia, whereas others deteriorate more rapidly.[55] Most patients with PAH-CHD who progress to end-stage disease require heart-lung transplantation. Discussion of the intricacies involved in the decision for lung transplant with congenital defect repair versus dual organ transplant is outside of the scope of this review. Early post-transplant mortality is higher among patients with PAH-CHD compared with other transplant recipients, but after the immediate post-transplant period PAH-CHD patients experience excellent clinical outcomes.[56]

Palliative Care

Palliative care is an important pillar of the management of patients with PAH-CHD and should be considered in patients with symptom burden such that their quality of life is affected. Primarily due to the young age of many patients with PAH-CHD, it is common to postpone discussions about palliative care and end-of-life decisions until all other treatment modalities have been exhausted. International guidelines, however, suggest that physicians caring for patients with PAH-CHD should be proactive in discussing advanced directives and end-of-life issues.

Additionally, following the initiation of end-of-life discussions by PAH-CHD specialists, referral to palliative care specialists should be considered early in the disease process alongside parallel multidisciplinary disease management and treatment with PAH therapies. Early palliative care involvement not only is helpful for symptom management but also can provide physical, psychological, and social support for patients and their families.[57] Timing of palliative care referral and services provided by palliative care specialists should be individualized to each patient's symptomatic and psychosocial needs.

PREGNANCY AND CONTRACEPTION

During pregnancy and the postpartum period, the maternal cardiovascular system must undergo profound and dynamic changes to support fetal growth and development that include increased cardiac output and circulating blood volume, decreased SVR and PVR, and increased heart rate. Although well tolerated in healthy women, these changes can be associated with catastrophic outcomes, including death, among patients with PAH. In the setting of PAH, the pulmonary vasculature already is maximally dilated and cannot undergo the necessary decrease in vascular resistance to permit the increased cardiac output that is needed during pregnancy. Additionally, patients with right heart dilation and failure typically are unable to tolerate the increased volume load that occurs during pregnancy and delivery. Related to this, patients with PAH are at risk for right heart failure, decreased cardiac output, PH crisis, hypotension, hypoperfusion, and end-organ compromise related to pregnancy. Contemporary observational studies report a 16% to 30% pregnancy-related mortality rate among women with PAH.[58–60] Although increased severity of PAH is associated more strongly with risk of death, patients with any degree of PAH are at increased risk for adverse outcomes.[59] The offspring of women with PAH also are affected, with increased rates of fetal and neonatal mortality, particularly in the setting maternal hypoxia, reduced cardiac output, and preterm delivery. As such, professional society guidelines recommend that women with PAH be counseled to avoid pregnancy, and termination should be discussed when pregnancy occurs.[61]

Among patients with PAH-CHD, those with ES experience particularly high mortality associated with pregnancy (20%–50%).[62] In patients with ES, the pregnancy-related reduction in SVR can lead to increased right-to-left shunting and decreased pulmonary blood flow that results in increased cyanosis, low cardiac output, and increased risk of paradoxic embolism in the setting of the hypercoagulability that occurs during pregnancy. Fetal and neonatal outcomes also are poor among offspring of mothers with ES, with 65% of pregnancies complicated by preterm delivery, 37% by small-for-gestational-age infants, and 28% by offspring death.[63] Avoidance of pregnancy is extremely important in these patients, because even the termination procedure itself can pose significant maternal risk.[61]

Counseling regarding safe and reliable contraception options should be pursued with all women of childbearing age with CHD but particularly in those with PAH-CHD. Combined hormonal contraception (ie, estrogen-containing oral contraceptive pill) use is associated with increased risk for thromboembolic events and, therefore, is not recommended in patients with PAH, cyanosis, or the potential for right-to-left shunting. Long-term reversible contraceptive methods that do not contain estrogen (levonorgestrel intrauterine device, copper intrauterine device, and tonogestrel subdermal implant) have a less than 1% failure rate and are favored in women with PAH-CHD.[64] The copper intrauterine device can be associated with heavier menstrual bleeding in some women and thus may be poorly tolerated in patients with PAH-CHD who are treated with anticoagulation or those with hemostatic derangements related to ES.

Patients with PAH-CHD who become pregnant and decide against termination should be managed at a multidisciplinary tertiary care center with experienced CHD, PAH, advanced heart failure, and cardiothoracic surgery specialists. Medical therapy is limited to phosphodiesterase inhibitors and prostanoids. Bosentan and other endothelin-1 receptor antagonists are thought to be teratogenic based on mouse data and, therefore, are contraindicated during pregnancy. Patients with PAH-CHD should be monitored closely throughout pregnancy with serial TTE and RHC when there is diagnostic uncertainty or invasive hemodynamic information is needed to make difficult therapeutic decisions. A detailed delivery plan, including timing of delivery, mode of delivery, and anesthetic plan, should be determined early in pregnancy in a multidisciplinary setting. Women are at highest risk for cardiovascular decompensation in the postpartum period, and most patients with PAH-CHD should be monitored in an intensive care setting, possibly with invasive hemodynamic monitoring, following delivery for close volume management and support of right ventricular function.[65] Patients with PAH remain at elevated risk for cardiovascular complications for many months after delivery and thus require close

follow-up after discharge.[61] Counseling about contraception and the risks of future pregnancies should be completed prior to discharge from the delivery hospitalization.

SUMMARY

PAH-CHD is a common complication seen in patients with CHD and is associated with increased morbidity and mortality. In patients with a large defect who have not yet developed ES physiology, surgical or percutaneous defect closure is the preferred treatment and may prevent progression to severe PAH. Although recent randomized controlled trials have begun to identify safe and effective targeted medical therapies in patients with PAH-CHD, more research is needed to determine the optimal treatment strategy. Lung or heart-lung transplantation should be considered in patients with advanced disease. Early involvement of palliative care specialists is recommended. Women of childbearing age with PAH-CHD should be counseled proactively about the risks of pregnancy and appropriate contraceptive strategies.

CLINICS CARE POINTS

- A diagnosis of PAH-CHD requires a high degree of clinical suspicion as presenting symptoms are non-specific.
- Right heart catheterization is the gold standard for establishing the diagnosis of PAH-CHD.
- Defect closure is contraindicated in patients with ES.
- Defect closure is recommended in patients with PVR < 1/3 of SVR, PAP < 50% systemic systolic pressure and Qp:Qs >/= 1.5:1.
- For patients with PAH-CHD and a large shunt in whom device closure is not recommended, medical therapy is the mainstay of management.
- Avoidance of pregnancy is recommended among patients with ES due to a high risk of maternal and fetal mortality.

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