Congenital Heart Disease and Pulmonary Hypertension

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KEYWORDS

- Congenital heart disease • Pulmonary hypertension • Eisenmenger syndrome • Management • Treatment

KEY POINTS

- Pulmonary hypertension is common in patients with congenital heart disease, even in those patients with previously repaired lesions, and can lead to considerable symptoms, including exertional dyspnea.
- Pulmonary hypertension in these patients can be caused by pulmonary arterial or pulmonary venous causes and requires heart catheterization for accurate diagnosis.
- Some patients may be able to be treated with catheter-based or surgical interventions, particularly when the disease is reversible.
- Some patients with pulmonary arterial hypertension with unrepaired shunt lesions progress to Eisenmenger syndrome (pulmonary vascular disease with reversed [pulmonary-to-systemic] shunting). These patients have severe functional limitation and complications from systemic cyanosis.
- Successful treatment with each therapeutic class of selective pulmonary hypertension therapy (endothelin antagonists, phosphodiesterase-5 inhibitors and prostacyclin analogues) has been reported, although the BREATHE-5 (Bosentan Randomized Trial of Endothelin Antagonist Therapy-5) study, using bosentan, remains the only randomized trial of selective therapy in Eisenmenger syndrome.
- Prevention of pulmonary hypertension through early identification and repair of congenital heart defects is the ideal patient management.

INTRODUCTION

In 1897, Victor Eisenmenger described a patient with dyspnea since infancy who died of massive hemoptysis and was found on autopsy to have a large ventricular septal defect associated with abnormal pulmonary vasculature. This finding was not further characterized until nearly 60 years

later. In the 1950s, more investigation gave further insight into the effect of congenital heart disease (CHD) on the pulmonary vasculature, and in 1958 Dr Paul Wood coined the term Eisenmenger syndrome to characterize patients with pulmonary hypertension (PH) caused by high pulmonary vascular resistance (PVR) associated with a large ventricular septal defect.¹ Multiple studies have

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since expanded our understanding of the syndrome to include other congenital heart defects.²⁻¹⁹ CHD is one of the world's leading birth defects and pulmonary arterial hypertension (PAH) associated with CHD is one of the most common causes of morbidity and mortality in this group of patients.²⁰

DEFINITION AND CLASSIFICATION

PH was most recently defined by the Fourth World Symposium on Pulmonary Hypertension as a mean pulmonary arterial pressure of 25 mm Hg or greater.²¹ PAH is usually defined as the following: (1) mean pulmonary artery pressure of 25 mm Hg or greater and (2) either pulmonary capillary wedge pressure (PCWP) of 15 mm Hg or less or left ventricular end-diastolic pressure (LVEDP) of 15 mm Hg or less or measured left atrial pressure of less than 15 mm Hg and (3) PVR of 3 Wood units or greater.²² It is inherent from these definitions that right heart catheterization is an essential test for the diagnosis of PAH.

The Fourth World Symposium on Pulmonary Hypertension in Dana Point, California, revised the classification of PH in 2008 (**Box 1**).²³ PH is classified into 5 different groups. The importance of the clinical system, as well as allowing a better understanding of pathophysiology, is to give a framework for understanding important branch points in the management and treatment of different conditions known to cause PH. Diseases that are predominantly associated with PAH are clustered in group 1, including idiopathic, heritable, drug-induced and toxin-induced and PAH associated with other conditions such as CHDs.²³ The reason for including CHDs in group 1 is because its histology and endothelial cell abnormalities are indistinguishable from other causes of PAH.²⁴

Classically, all congenital conditions are grouped together when considered as a cause of PAH. However, it is important to identify the underlying congenital defect, because this has important prognostic implications. To help in this task, the Fourth World Symposium on Pulmonary Hypertension updated the anatomic and pathophysiologic classification of CHDs. This classification encompasses the type and dimension of the defect, direction of the shunt, associated cardiac and extracardiac abnormalities and repair status (**Box 2**).²³ Its use is helpful in providing a more detailed description for each particular condition.

PAH associated with CHD (PAH-CHD) is generally classified as PAH associated with small defects (ventricular or atrial septal defects less than 1 and 2 cm, respectively; presenting in similar fashion to idiopathic PAH), PAH associated with

systemic-to-pulmonary shunts (moderate to large defects without cyanosis), Eisenmenger syndrome (large defects with severe increases in PVR and reversed or bidirectional shunting) and PAH after corrective surgery (PAH persists or recurs after surgery in the absence of postoperative residual lesions).²³

Not all CHDs with systemic-to-pulmonary shunts lead to significant PH. Truncus arteriosus, ventricular septal defects, atrial septal defects, and patent ductus arteriosus are the mostly commonly identified lesions associated with severe PH and the development of Eisenmenger syndrome.

Eisenmenger syndrome is generally the result of systemic-to-pulmonary shunts caused by large congenital heart defects that with time lead to reversed (pulmonary-to-systemic) or bidirectional shunting accompanied by oxygen-unresponsive hypoxemia. It represents the most advanced form of PAH-CHD. This syndrome manifests as a disease process and not as an isolated condition. The clinical scenario includes reduced functional capacity, worsening hypoxia, cyanosis, erythrocytosis, and multiple organ system involvement.

UNIQUE CHARACTERISTICS COMPARED WITH OTHER CAUSES OF PAH

Although PAH-CHD is similar in many ways to other causes of PAH, there are some important differences. Unlike other causes of PAH, congenital left-to-right shunts lead to a more progressive increase of right ventricular pressures early in life, allowing the right ventricle to remodel and accommodate for the increased afterload. This chronic course allows patients to reset their normal level of activity, adjusting it to help compensate for the chronic hypoxia.²⁵⁻²⁹ Therefore, they may not report the presence of significant symptoms with regular activity, underscoring the need for more objective assessment, as outlined later.

In addition, patients with PAH-CHD more commonly experience hemoptysis, cerebrovascular accidents, brain abscesses, erythrocytosis, coagulation abnormalities, and cardiac arrhythmias than other causes of PAH.³⁰ Adult patients with Eisenmenger syndrome have a more favorable hemodynamic profile and possibly a better prognosis than other groups of patients with PAH.¹⁹

EPIDEMIOLOGY

Congenital heart defects are usually reported in ~8 of 1000 live births.³¹ Although the prevalence of CHD in the Western world has remained fairly constant, the number of adults with congenital heart lesions has gradually increased, as a result

Box 1**Updated clinical classification of PH (Dana Point, 2008)**

1. PAH
 - 1.1. Idiopathic PAH
 - 1.2. Heritable
 - 1.2.1. BMPR2
 - 1.2.2. ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)
 - 1.2.3. Unknown
 - 1.3. Drug-induced and toxin-induced
 - 1.4. Associated with
 - 1.4.1. Connective tissue diseases
 - 1.4.2. Human immunodeficiency virus infection
 - 1.4.3. Portal hypertension
 - 1.4.4. CHDs
 - 1.4.5. Schistosomiasis
 - 1.4.6. Chronic hemolytic anemia
 - 1.5. Persistent PH of the newborn
 - 1.6. Pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis
2. PH caused by left heart disease
 - 2.1. Systolic dysfunction
 - 2.2. Diastolic dysfunction
 - 2.3. Valvular disease
3. PH caused by lung diseases or hypoxia
 - 3.1. Chronic obstructive pulmonary disease (COPD)
 - 3.2. Interstitial lung disease
 - 3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern
 - 3.4. Sleep-disordered breathing
 - 3.5. Alveolar hypoventilation disorders
 - 3.6. Chronic exposure to high altitude
 - 3.7. Developmental abnormalities
4. Chronic thromboembolic PH
5. PH with unclear multifactorial mechanisms
 - 5.1. Hematologic disorders: myeloproliferative disorders, splenectomy
 - 5.2. Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis
 - 5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
 - 5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

From Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2009;54:S45; with permission.

of the development of successful operative repairs at an earlier age. There are now estimated to be nearly a million adults with CHD in North America, and, for the first time in medical history, more

adults than children with congenital heart lesions.³²

It is estimated that 5% to 10% of adults with CHD develop PAH.^{22,33} Some studies estimate 4% to

Box 2
Anatomic-pathophysiologic classification of congenital systemic-to-pulmonary shunts associated with PAH

- 1. Type
 - Simple pre-tricuspid shunts
 - Atrial septal defect
 - Ostium secundum
 - Sinus venosus
 - Ostium primum
 - Total or partial unobstructed anomalous pulmonary venous return
 - Simple post-tricuspid shunts
 - Ventricular septal defect (VSD)
 - Patent ductus arteriosus
 - Combined shunts
 - Complex congenital heart disease
 - Complete atrioventricular septal defect
 - Truncus arteriosus
 - Single ventricle physiology with unobstructed pulmonary blood flow
 - Transposition of the great arteries with VSD and/or patent ductus arteriosus
 - Other
- 2. Dimension
 - Hemodynamic
 - Restrictive (pressure gradient across the defect)
 - Nonrestrictive
 - Anatomic
 - Small to moderate (ASD $\leq$ 2 cm and VSD $\leq$ 1 cm)
 - Large (ASD > 2 cm and VSD > 1 cm)
- 3. Direction of shunt
 - Predominantly systemic-to-pulmonary
 - Predominantly pulmonary-to-systemic
 - Bidirectional
- 4. Associated cardiac and extracardiac abnormalities
- 5. Repair status
 - Unoperated
 - Palliated
 - Repaired

Adapted from Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2009;54:S47; with permission.

10% of all patients with CHD develop Eisenmenger syndrome; however, this increases to as high as 30% in patients with unrepaired congenital defects.^{33–35} Worldwide, it is estimated that 3.2 million children are at risk for the development of PAH-CHD.²⁴ Most of them do not develop Eisenmenger syndrome, particularly if cardiac repair occurs within the first 2 years of life. Worldwide, because of inequality of access to medical care, only some patients (2%–15%) undergo reparative surgery.²⁴ A large outcome study in PAH-CHD showed a prevalence of PAH in CHD of 5.8% and its presence increased all-cause mortality and cardiac complications, including heart failure and arrhythmias, more than 2-fold and 3-fold, respectively.³⁶ In addition, the presence of PAH increased hospital days and intensive care unit days by more than 3-fold when compared with patients with CHD without PAH. Given the increased recognition of CHD in the pediatric population coupled with advances in surgical and medical management for congenital lesions, more patients with more complex congenital lesions are surviving to adulthood. These patients may present with various degrees of PAH in adulthood, underscoring the importance of adult cardiologists evolving their understanding of both CHD and PAH.

PATHOPHYSIOLOGY

Increased pulmonary blood flow from systemic-to-pulmonary shunts is responsible for initiating a series of events responsible for causing changes in the pulmonary vasculature that lead to pulmonary obstructive arteriopathy and to an increase in PVR and PAH.¹⁰ Main risk factors for the development of PAH include the type and size of the underlying anatomic defect and magnitude of shunt. Initial dynamic PAH is reversible, if corrective surgery is performed before vascular changes become permanent. The potential for reversibility is difficult to assess, and there is a paucity of information in this regard.²

Most of the pathophysiologic processes in PAH-CHD seem similar to the pathogenesis implicated in the development of other forms of PAH. The pathogenesis of PAH is explained by a persistent high flow and pressure in the pulmonary vasculature that causes endothelial damage, leading to loss of endothelial barrier function and imbalance of vasoactive mediators that favor vasoconstriction, inflammation, thrombosis, cell proliferation, apoptosis, and fibrosis and result in pulmonary vascular remodeling and irreversible PAH.³⁷ A more detailed description of the mechanisms involved in the development of PAH helps to understand current and potential future therapeutic interventions.

The destruction of the vascular endothelial barrier causes degradation of the extracellular matrix as well as release of growth factors such as fibroblast growth factor, angiopoietin-1 and transforming growth factor β , which induces smooth muscle hypertrophy and proliferation.³⁸ In addition, endothelial dysfunction leads to activation of cytokines and localized inflammatory cascades.³⁹

The pulmonary endothelium is responsible for the production of many vascular mediators. With endothelial cell dysfunction, there is a shift toward vasoconstriction, cellular proliferation, and apoptosis caused by increased production and decreased destruction of vasoconstrictors (ie, endothelin-1 and thromboxane A_2), as well as decreased production and increased destruction of vasodilators, such as nitric oxide (NO) and prostacyclin. Endothelin-1 is a potent vasoconstrictor that can cause smooth muscle proliferation as well, leading to vascular remodeling. Circulating endothelin levels have been found to correlate with disease severity and outcome in idiopathic PH,^{40–42} although this mediator has been less extensively studied in Eisenmenger syndrome.^{16,43–45}

The pulmonary endothelium is a major producer of NO. NO is endogenously synthesized by NO synthases and is a freely diffusible molecule that enters the pulmonary smooth muscle cells to produce guanosine 3', 5'-cyclic monophosphate (cGMP), resulting in vasodilation, helping keep the pulmonary vascular circuit at low pressure.^{46–48} Phosphodiesterases are responsible for breakdown of cGMP. With impaired production and normal degradation, cGMP levels decline, thereby decreasing cGMP-mediated vasodilation.^{16,49,50} Endothelial damage also causes a decrease in prostacyclin production, a potent vasodilator that also inhibits platelet aggregation and smooth muscle cell proliferation by increasing cAMP levels.^{8,16,21,51}

Recent research has revealed a genetic predisposition⁵² (because not all patients with CHD develop PAH) and suggests the presence of other potential pathways involved in the pathogenesis of PAH-CHD, including downregulation of potassium channels,⁵³ increased matrix metalloproteinases,⁵⁴ decreased vasoactive intestinal peptide,⁵⁵ increased serotonin⁵⁶ and transforming growth factor β levels,⁵⁷ among others.⁵⁸ Potential new biomarkers and lines of therapies could result from these discoveries.⁵⁹

CLINICAL PRESENTATION

The clinical presentation of PAH-CHD can be varied, and there is not a pathognomonic symptom pattern that can be easily identified. There are many

different factors affecting the presenting symptoms: the underlying congenital defect, the repair status, and the degree of initial and residual shunting. Symptoms from PH itself are also nonspecific and include breathlessness, fatigue, chest pain, and syncope. Depending on the severity of PH, there may be cyanosis and clubbing. Most left-to-right congenital shunts do not initially have cyanosis, but its presence is often the harbinger of increasing pulmonary pressures and the development of Eisenmenger syndrome.^{13,20,60} Complex congenital lesions may have some degree of chronic cyanosis, making the identification of worsening cyanosis difficult. In advanced stages, patients develop progressive right ventricular dysfunction, which may result in sudden death.

Exercise Intolerance

Dyspnea on exertion is the most common presenting symptom. Many patients with CHD have some degree of exercise intolerance, particularly those with PAH. Some estimates suggest that more than 90% of patients with PAH-CHD have New York Heart Association (NYHA) class II or worse symptoms. As mentioned earlier, these patients progressively restrict their regular activity, which complicates accurate estimation of their functional capacity.^{61–64} Exercise intolerance is a nonspecific symptom, because it can represent PAH itself, hypoxemia, worsening heart failure, or deconditioning.

Hemoptysis

Hemoptysis is another common symptom in PAH-CHD, and is most often present in patients with Eisenmenger syndrome. Hemoptysis is caused by the development of bronchial collaterals in patients with long-standing cyanosis.³⁰ Case series and retrospective studies indicate that anywhere from 11% to 100% of patients present with hemoptysis.^{1,25,65–67} Although unsettling for most patients, hemoptysis is generally not a cause of mortality for these patients.^{25,65–67}

Pulmonary Embolism

Given the extensive strain on the pulmonary arterial system, as well as turbulent flow, there is a higher risk of pulmonary thromboembolism in patients with PAH-CHD. Some case series report that up to 30% of patients with Eisenmenger syndrome present with clinically detectable intrapulmonary thrombus, usually manifested by rapidly worsening dyspnea, hemoptysis, chest pain, and tachycardia.^{68,69}

Hematologic Manifestations

There are a few major hematologic manifestations, including reactive or secondary erythrocytosis and chronic thrombocytopenia. Depending on the level of hypoxemia, patients with PAH-CHD develop compensatory erythrocytosis, which when severe can lead to hyperviscosity syndrome, the manifestations of which include headaches, blurry vision, dizziness, paresthesias, and myalgias.^{70–74} Patients with Eisenmenger syndrome are generally iron deficient, and iron supplementation (oral or intravenous) is often necessary.

Because of the chronic hypoxemia, the presence of PAH and the use of epoprostenol, most patients with Eisenmenger syndrome have chronic thrombocytopenia, platelet dysfunction, and difficulties with clotting.^{73–76} In addition, passive congestion of the liver because of worsening right heart failure can lead to deficiencies in clotting factor production. As a result, some patients may present with bleeding, although this is usually a late manifestation of the syndrome.

Infectious Considerations

Patients with congenital shunt lesions and coexistent cyanosis are at particularly high risk of bacterial endocarditis. Studies suggest that risk of development of endocarditis in unrepaired ventricular septal defects may be as high as 13% lifetime.⁴⁰ The risk in patients with Eisenmenger syndrome seems even more substantial (4% in 1 series over only 2 years of follow-up). Another infectious complication is cerebral abscess, presumably from septic emboli, with an incidence of more than 6% in patients with Eisenmenger syndrome followed for a 6-year period.⁶⁵

Arrhythmias

Arrhythmias are often a late manifestation in patients with Eisenmenger syndrome and the most common cause of death. Patients with Eisenmenger syndrome are at significantly increased risk of sudden cardiac death,⁶⁶ with ventricular arrhythmias being the presumed cause. These arrhythmias result from a multitude of factors including structural heart lesions, electrolyte abnormalities, and worsening heart failure. Supraventricular arrhythmias are also common, with 1 study reporting supraventricular arrhythmias in 42% of patients on 24-hour Holter monitoring.

Other

Less frequently reported complications associated with PH in patients with CHD include bile

stones, hyperuricemia and gout, acute renal injury associated with both hyperuricemia and glomerular injury, hepatic dysfunction, and cerebrovascular disease.^{76–79}

DIAGNOSIS

History and Physical Examination

The history and physical examination are often insufficient to tease out PAH-CAD as the cause of PH. However, they are helpful in identifying when further investigation is necessary. It is important to inquire into the onset, severity, and progression of symptoms, because it may help to assess the severity of the condition.^{20,60} In addition, associated symptoms may suggest a particular cause of PH.

Underlying conditions can give some insight into other causes of PH, such as a history of malignancy, which may be associated with chronic thromboembolic pulmonary disease, COPD, which can indicate PH associated with lung disease, and cardiovascular risk factors such as diabetes, which can point toward left heart failure. All of these conditions may also coexist with CHD.

Particular attention should be placed on determining the type of heart defect and the timing and nature of the corrective procedures, because these can alter the natural history of the disease. In general, patients with CHD have a more insidious course, thus a more insightful line of questioning may be necessary. For example, asking whether a patient is dyspneic may not be enough.^{20,60} On the other hand, asking what activities the patient was able to do a few months ago but is not able to do now may provide more detailed information.

Physical examination in a patient with CHD may show cyanosis and clubbing of the fingernails and toenails. If the unrepaired defect is a patent ductus arteriosus, the feet may be cyanosed and clubbed, whereas the right and possibly also the left arm may be spared (pink and unclubbed), depending on the location of the duct. This finding is pathognomonic for an Eisenmenger ductus. There may be a prominent second pulmonic sound associated with increased pulmonary pressures, although this finding is often subtle. It is important to assess for S3 gallops, suggestive of heart failure and other valvular heart defects.⁶⁰ It is also important to perform a thorough cardiopulmonary examination, specifically looking for the typical findings found with atrial septal defects, ventricular septal defects, and patent ductus arteriosus, taking into account that as the PVR increases, the shunt decreases and most of the classic murmurs disappear.

Routine Laboratory Testing

Every patient with CHD should undergo routine laboratory evaluation, including complete blood counts, serum electrolytes, blood urea nitrogen, serum creatinine, and liver function tests. Specifically, it is important to assess for erythrocytosis, because a hematocrit level greater than 65% can be associated with hyperviscosity.⁸⁰ Given the propensity for arrhythmias, it is important to check for serum electrolytes, specifically potassium, magnesium, and calcium. Evaluation of the patient's renal function and liver function tests is also important for therapeutic monitoring.

Brain natriuretic peptide (BNP) and N-terminal pro-BNP have both been shown to be increased in pediatric and adult patients with CHD, both with and without PAH.^{81,82} The lack of specificity makes these tests not particularly useful for the diagnosis of PAH. However, multiple studies have shown BNP to correlate with exercise capacity, response to therapy, and overall survival.^{41,81}

Chest Radiography

The chest radiograph (CXR) is a sensitive, albeit nonspecific test. It is not particularly useful for diagnosis, prognosis, or treatment monitoring. Some studies have suggested that ~90% of patients with PAH have an abnormal CXR at the time of presentation, most often increased central pulmonary vascular congestion with loss of peripheral vessels.⁸³ On occasion, an abnormal CXR may reveal intrinsic lung disease that can motivate further evaluation.

Echocardiogram

Every patient with CHD should have at the least a transthoracic echocardiogram performed, ideally with a performing sonographer and an interpreting cardiologist with CHD experience. This test is important not only in the evaluation for congenital defects but also to estimate pulmonary pressure and assess for right ventricular strain. In addition, it assesses left ventricular function as a cause or contributor to PH and facilitates noninvasive monitoring after initiation of therapy or when symptoms progress.^{22,84,85} Subcostal images from a transthoracic echocardiogram in **Fig. 1** show a large ventricular septal defect with evidence of bidirectional shunting, suggesting advanced PAH-CHD.

Cardiac Catheterization

Every patient with PH should be evaluated with a cardiac catheterization before initiation of PAH-specific therapy. The importance of this strategy

is most evident in the CHD population, in whom pure PAH is often the exception rather than the rule. In the original Boston Adult Congenital Heart Cohort more than 80% of patients with CHD had coexistent triggers for increased pulmonary pressure outside PAH. These triggers included increased left-sided pressures, pulmonary artery or vein stenoses, and thromboembolic disease (Dr Michael J. Landzberg, personal communication, 2011). Similarly, in our cohort of patients with presumed PAH-CHD at the Cleveland Clinic, we have found other causes responsible for pulmonary pressure increase in more than one-third of patients. Empiric therapy with a selective pulmonary vasoactive therapy in lieu of catheterization in such patients may be detrimental. Certain patient populations such as those with repaired tetralogy of Fallot deserve closer attention when increased right-sided pressure is found on echocardiography. In such patients, a variety of other associated lesions can be responsible for increased right-sided pressures, including unexpected right ventricular outflow obstruction, peripheral pulmonic stenosis(es), and aortopulmonary collaterals.

The cardiac catheterization in the patient with PAH-CAD should include a full oximetry run to assess for the presence of shunting and to quantify the direction of this shunt. **Fig. 2** shows the stages of progression in a patient with a large ventricular septal defect, with notation made regarding the expected saturations in each heart chamber. Early in the disease process (see **Fig. 2A**) the shunt is left to right and large resulting in a significant step up in oxygenation at the level of the right ventricle. As the disease progresses (see **Fig. 2B**), the shunt progressively decreases as the PVR rises. Late in the disease process (see **Fig. 2C**), the PVR is large and the shunt reverses (becomes right to left). Also the cardiac output is reduced, as shown by the decreased saturation of the mixed venous (right atrial) blood.

Ideally, a vasodilator challenge should also be performed during catheterization, with careful attention to the impact on the amount and direction of the shunt. In some cases, balloon occlusion of the defect can be helpful to assess the impact on pulmonary pressures. In such cases, simultaneous measurement of pulmonary and systemic pressures during the occlusion is essential. We have found that a significant decrease in PVR identifies patients in whom repair is still feasible, whereas a decrease in systemic pressure during occlusion should be an ominous sign and absolute contraindication to defect repair.

The vasodilator challenge also seems to predict prognosis in patients with CHD. Inhaled NO

Fig. 1. Subcostal images from a transthoracic echocardiogram in a patient with a large ventricular septal defect (arrow) and PH. Images are without (A) and with (B) color Doppler applied. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

Fig. 2. The stages of progression of pulmonary vascular disease in a patient with a large ventricular septal defect (the arrows signify the flow of blood across the ventricular septal defect). The chambers are annotated with the oxygen saturations. Early in the disease process (A) the shunt is left to right and large. The right atrial saturation (equal to the mixed venous saturation) is 75% and increases to 85% beyond the right ventricle because of the shunt. The left atrial and aortic saturations are the same because no right to left shunt is present. As the disease progresses (B), the shunt is progressively reduced as the PVR rises. The cardiac output is starting to decrease as a result of the development of right ventricular dysfunction (decreased to 65%). There remains some left to right shunting (pulmonary artery saturation is 75%) but the aortic saturation (90%) is now lower than the left atrial saturation (95%) because some right to left shunting (bidirectional shunt) is present. Late in the disease process (C), the PVR is large and the shunt is fully reversed (right to left). The cardiac output is now even more reduced (right atrial saturation is 60%) and no step-up in saturation is now seen. A substantial decrease in aortic saturation (75%) is present as a result of the large right to left shunt. (Courtesy of Cleveland Clinic Foundation, Cleveland, OH; with permission.)

combined with oxygen can help identify candidates for corrective cardiac surgery and in addition identify patients with better long-term clinical outcome.^{86–90}

Left heart catheterization may be necessary to confirm the LVEDP if the PCWP is difficult to obtain or interpret. Coronary angiography may also be needed to assess for atherosclerosis in older patients.

Current European and American College of Cardiology (ACC)/American Heart Association (AHA) guidelines strongly recommend a baseline right heart catheterization with a vasodilator challenge for both diagnostic purposes and before initiating therapy. In addition, monitoring for efficacy of PAH therapy invasively is suggested, although no time frame for repeating catheterization is provided.^{22,84,85}

Exercise Testing

Formal exercise testing serves multiple purposes, which include assessing the severity of disease, determining prognosis, and evaluating the effectiveness of therapy. Two methods to assess exercise tolerance are the 6-minute walk test (6MWT) and cardiopulmonary exercise testing. Motivated by its simplicity, most studies in PH use the 6MWT to assess response to therapy.^{62–64,91} Current guidelines recommend exercise testing before initiating therapy and at 3-month to 6-month intervals thereafter.^{22,85}

Advanced Studies

More advanced studies such as transesophageal echocardiography, cardiac magnetic resonance imaging, V/Q scanning, and pulmonary function testing should be performed only if clinically indicated and if they are not part of the routine workup.^{22,85}

TREATMENT

General Principles of Therapy

Patients with PAH-CHD should be monitored at regular intervals by experienced physicians to assess for changes in symptom profile, vital signs, complete blood counts, and electrolytes. The treatment strategy is for the most part based on clinical experience rather than being evidence-based.³⁰ Patients with Eisenmenger syndrome, in particular, should be managed in centers with experience in the treatment of this syndrome.²²

A treatment approach for PAH-CHD similar to other causes of PAH has recently been proposed (Fig. 3).⁹² Parts of this algorithm have been derived primarily from studies in idiopathic disease and

PAH associated with connective tissue disease, therefore care should be taken when extrapolating these data to PAH-CHD.³⁰

Oxygen therapy

Most patients with CHD, depending on the degree of shunting, have a degree of chronic hypoxia. Oxygen therapy does not improve exercise tolerance or survival in these patients; however, some patients still receive oxygen to use with exertion or on a nocturnal basis, based on symptom relief.⁹³ Care should be exercised not to overoxygenate these patients, because this may depress their respiratory drive and lead to further hypoxia. Also because these patients are prone to bleeding, because of the hematologic issues mentioned earlier, high-flow nasal cannula oxygen can result in epistaxis, with all of its attendant problems.

Aerobic exercise

Aerobic exercise is often avoided by patients with CHD because of worsening dyspnea. However, it is important to encourage continued aerobic exercise to improve exercise tolerance. However, it is recommended to avoid strenuous exercise.²²

Anticoagulation

There is a paucity of evidence regarding anticoagulation in patients with PAH-CHD. Therefore, current practice is varied and fragmented. Most centers anticoagulate these patients given their prothrombotic propensity.^{25,68,69,73} However, because of the increased risk of hemorrhage and hemoptysis, anticoagulation should be carefully monitored.^{22,25}

Antibiotic prophylaxis

Patients with CHD are at a markedly increased risk of infectious complications, specifically bacterial endocarditis.^{40,66} Current ACC/AHA guidelines recommend antibiotic prophylaxis for invasive dental procedures (any procedure involving gum manipulation) in unrepaired patients with cyanotic CHD, patients with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device that prevents endothelialization after repair, and for any patients within 6 months of surgical or percutaneous repairs using prosthetic materials or devices.^{84,94,95} We further propose that any patient with CHD, repaired or unrepaired, who has associated PH should receive appropriate prophylactic antibiotics before dental procedures, given their complexity and poor clinical reserve.

Fig. 3. Treatment algorithm for PAH-CHD. (1) Because of the complexity of the condition and the multiple treatment options available, expert referral is recommended. (2) Patients can remain clinically stable for prolonged periods and the efficacy/safety ratio of different therapies in these groups is not clear. (3) More evidence supports the use of bosentan. (4) Unstable patients should be treated with intravenous prostacyclin analogues, based on expert opinion. (5) In the absence of improvement or deterioration, combination therapy should be considered. (Reproduced from Galie N, Manes A, Palazzini M, et al. Management of pulmonary arterial hypertension associated with congenital systemic-to-pulmonary shunts and Eisenmenger's syndrome. *Drugs* 2008;68:1062; with permission.)

Diuretics, digitalis, antiarrhythmics, and calcium-channel blockers

Diuretics and digitalis are often used on an individual patient basis in Eisenmenger syndrome, with the precaution of avoiding dehydration, which can worsen hyperviscosity and produce hypotension.²⁹ Supraventricular and ventricular arrhythmias are common and may lead to hemodynamic decompensation and sudden death.⁶⁰ Amiodarone is often used, and the role of implantable defibrillators is unknown.⁶⁷ None of these approaches has significantly modified survival or risk of deterioration.⁶⁶ Calcium-channel blockers are generally contraindicated in patients with Eisenmenger syndrome because of their negative inotropic effects and systemic vasodilation (which increases right-to-left shunt and can worsen cyanosis).^{22,92,96}

Treatment of hyperviscosity syndrome

Patients with hematocrit levels greater than 65% are at increased risk of hyperviscosity syndrome. When clinical judgment warrants phlebotomy for relief of symptoms of hyperviscosity, care needs to be taken to avoid air embolization and the risk of stroke.^{70,73,77} Also, because these patients are sensitive to volume, adequate volume replacement is an important part of this therapy. Routine phlebotomy in cyanotic patients with CHD is associated with worsening exercise tolerance and increased risk of stroke, and therefore should be avoided.⁷⁰ In addition, monitoring for and treatment of iron deficiency is important, to ensure adequate hematopoiesis and erythrocytosis that is appropriate to the level of hypoxemia.^{22,29}

Avoidance of pregnancy

CHD associated with PH is associated with a significantly increased risk of maternal and fetal morbidity and mortality. Some estimates suggest up to a 50% risk of maternal mortality and 40% risk of spontaneous abortion in patients with Eisenmenger syndrome.^{97–99} These patients have an increased risk of cardiovascular events during birth, manifested as a higher incidence of arrhythmia, heart failure, and embolic events.¹⁰⁰ Therefore, pregnancy should be strongly discouraged in these patients. In individuals who become pregnant and do not wish to undergo elective abortion, careful monitoring and a multidisciplinary approach are essential.

For contraception, intrauterine devices impregnated with progesterone may be the best option, given their overall effectiveness and decreased risk of systemic thrombosis. Oral estrogen-based contraception is associated with an increased risk of thromboembolic events, and therefore is not ideal in these patients. Oral progesterone-

based contraception has a high failure rate, and surgical options carry with them considerable perioperative risk.

Specific PH therapeutic options

Randomized controlled trials that have shown benefits of PH-specific therapies in patients with PAH have included a few individuals with Eisenmenger syndrome. This important limitation complicates the treatment strategy for these patients. PAH-specific therapies center around 3 major pathways: endothelin, NO, and prostacyclin.

Endothelin receptor antagonists Endothelin receptor antagonists (ERAs) are the most extensively studied class of medications for PAH-CHD. Three drugs in this class have been studied in patients with PAH: bosentan, ambrisentan, and sitaxsentan.³⁰ Bosentan (Tracleer) is a dual ERA that acts on both endothelin A and B receptors. Until recently, there had only been small-scale, open-label trials, which suggested efficacy of oral bosentan in patients with PAH-CHD.^{87,101–108} The BREATHE-5 (Bosentan Randomized Trial of Endothelin Antagonist Therapy-5) trial was the first large (bosentan $n = 37$, placebo $n = 17$), randomized, double-blind, placebo-controlled trial looking at bosentan in World Health Organization (WHO) class III Eisenmenger syndrome. At 16 weeks, bosentan significantly improved exercise capacity (patients were able to walk 53.1 m more during 6MWT) and reduced PVR index (-472 dyn s/cm^5) and mean pulmonary artery pressure (-5.5 mm Hg) compared with placebo. In addition, bosentan did not worsen oxygen saturation.¹⁰⁹ A post hoc analysis showed no difference in efficacy within different types of congenital defects.¹¹⁰ Long-term data have shown that the improvement on bosentan can be maintained without safety or tolerability issues.^{111–116} A more recent randomized controlled trial of bosentan in patients with NYHA functional class II PAH included patients with PAH-CHD ($n = 32$ of 185 individuals). At 6 months, PVR significantly decreased from baseline but 6MWT distance change did not reach statistical significance (mean treatment effect 19.1 m, $P = .076$).¹¹⁷ There appeared to be no difference in the short-term clinical response between adults and children with PAH associated with systemic-to-pulmonary shunts. Several studies have shown continued benefit in exercise tolerance (6MWT), NYHA functional class, and physical/mental health (Short Form-36 score), as far as 5 years from initiation of therapy. This benefit is more robust in patients with PAH-CHD without Down syndrome.^{118–121} The predominant adverse reaction of bosentan is increased hepatic transaminases, which can be

seen up to ~10% of patients.^{105,116} However, the distinct benefit is that it is an oral agent and simple to administer. Dosage is generally initiated at 62.5 mg twice daily and uptitrated to 125 mg twice daily after 4 weeks.

Ambrisentan (Letaris) is a single ERA with preferential activity on the endothelin A receptor. It was studied in 2 large randomized, double-blind, placebo-controlled trials with improved exercise tolerance (6MWT), functional class (WHO), health survey score (Short Form-36 score), dyspnea score (Borg) and B-type natriuretic peptide in patients with PAH after 12 weeks of treatment.^{122,123} Patients with PAH-CHD were excluded from this study; however, a recent single-center study involving 17 patients showed short-term (~6 months) improvement in exercise capacity (6MWT). This beneficial response diminished during long-term follow-up (~2.5 years).¹²⁴ Overall, there have been limited data with the use of this medication in PAH-CHD. Its benefits include better tolerance and less drug-to-drug interaction than other ERAs.¹²⁵

Phosphodiesterase type-5 inhibitors Phosphodiesterase type-5 (PDE-5) inhibitors, such as sildenafil (Revatio) and tadalafil (Adcirca), inhibit the breakdown of cGMP in smooth muscle cells, leading to enhanced cGMP-mediated vasodilation. In a large randomized, placebo-controlled study, patients with PAH (including patients with PAH-CHD) reported improvements in exercise capacity, WHO function class, and hemodynamics after 12 weeks of treatment.¹²⁶ There have been limited data on PDE-5 inhibitors specifically in patients with Eisenmenger syndrome.^{126–133} A recent large prospective, open-label trial of sildenafil in PAH showed significant improvements in functional class, oxygen saturations, and cardiopulmonary hemodynamics after 6 months of treatment.¹²⁷ Longer-term studies have suggested sustained benefits.

In a preliminary study, tadalafil showed efficacy and safety in a small group of symptomatic patients with Eisenmenger syndrome.¹³² There have also been multiple small trials with sildenafil used in addition to prostanoids, with improved exercise capacity and hemodynamics shown as well.

Prostacyclin analogues Intravenous epoprostenol (Flolan) is the most extensively studied medication in patients with PAH-CHD, particularly in patients with Eisenmenger syndrome.^{134,135} Several small studies have shown that continuous intravenous epoprostenol used in patients with Eisenmenger syndrome significantly improved function class, oxygen saturation, and exercise capacity and decreased PVR.^{134–137} Treprostinil (Remodulin) is another effective therapy with an acceptable

safety profile in patients with PAH. A randomized multicenter, double-blind study using treprostinil in PAH included 109 (of 469) patients with congenital systemic-to-pulmonary shunts. Improvement in exercise capacity was greater in sicker patients and was dose-related. Disease cause showed no significant interaction with the change in exercise capacity (+16 m on 6MWT).¹³⁸ Beraprost (an oral prostanoid that is not commercially available in the United States) showed no improvements in exercise capacity in PAH causes other than idiopathic PAH.¹³⁹

Inhaled prostanoids are also available (iloprost [Ventavis] and treprostinil [Tyvaso]), which have improved safety profiles, but their efficacy in PAH-CAD has not been well established.^{136,138–141} The use of subcutaneous or inhaled route of administration of prostanoids could prevent the risks associated with central lines in patients with Eisenmenger syndrome, including paradoxical embolism and sepsis, and deserves further study.^{134,135}

Combination therapy A few studies have reported benefit to adding sildenafil to either bosentan¹⁴² or prostacyclin analogues.^{143–146} However, there has been no direct comparison among different classes of PH-specific therapies or between monotherapy or combined therapy in patients with Eisenmenger syndrome. Because of the limited data available, the use of combination therapy should be considered on a case-by-case basis.⁹²

Transplantation

Transplant-free survival is difficult to predict in patients with Eisenmenger syndrome. Some patients have prolonged survival despite severe hypoxemia.⁶⁶ Before PAH-specific therapy became available, patients with Eisenmenger syndrome had improved survival compared with idiopathic PAH (3-year survival of 77% vs 35%).²⁷ This improved survival likely resulted from congenital adaptations of the right ventricle (the chamber remains hypertrophied after birth) and the presence of a shunt that prevented the development and limited the impact of suprasystemic pressures on the right ventricle.²⁶ Recent data from the US Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) analyzed 1-year survival data from 2176 consecutive patients with PAH. Of patients with PAH, 11.8% had PAH-CHD. Overall 1-year survival was 91%, worse for patients with heritable, portopulmonary, and connective tissue disease-related PAH. CHD did not confer the expected survival advantage, regardless of the type of defect or the repair status.¹⁴⁷ This finding suggests that

withholding PAH-specific therapy to patients with PAH-CHD because of presumed stability is a flawed strategy.

PAH-specific therapies seem to stabilize patients with PAH-CHD as assessed by 6MWT, mean pulmonary arterial pressure, and PVR.¹⁴⁸ Furthermore, 1 recent retrospective study has shown a substantial survival benefit (in both unadjusted and adjusted analyses) with PAH-specific therapies (73.5% of patients received bosentan, 25% sildenafil, and 1.5% epoprostenol) in patients with Eisenmenger syndrome followed in a large tertiary referral center. The overall 5-year mortality was 23.3%, and of the 52 patients who died, only 2 were on PAH-specific therapy.¹⁴⁹

Perioperative mortality for transplantation is higher in CAD-PAH, but after this period some patients have an excellent response, with dramatic improvements in symptoms and quality of life.^{42,150–152} Transplant options include heart-lung or lung transplantation, with concomitant heart defect repair. These options are reserved for special patients not responsive to medical treatment who have indicators of poor prognosis (syncope, refractory right heart failure, function class III/IV, or severe hypoxemia).¹⁵³ By the time patients with PAH-CHD are considered for transplantation, they are usually poor candidates because of multiple organ system failure.^{29,154}

Shunt closure in patients with Eisenmenger syndrome

This is a controversial topic and there are only scattered case reports to assist in the decision of whether to close a hemodynamically significant shunt.¹⁵⁵ Potential candidates may be patients with right-to-left or neutral shunt that receive PAH-specific therapy and subsequently experience a reversal of shunt (becoming left-to-right) both at rest and during activities. This intervention (treat-and-repair) may improve oxygenation and pulmonary artery pressure at the expense of decreasing cardiac output. A careful selection of patients based on age, type of defect, resting, and exercise shunt hemodynamics is critical.^{155,156} Some experts suggest a PVR less than 6 Wood units per m² and a PVR/systemic vascular resistance ratio of 0.3 or less, after initiation of PAH therapy, to consider shunt closure in previously inoperable CHD.¹⁵⁷ In our personal experience, we have yet to witness a patient with true Eisenmenger syndrome who improved with therapy to the point that their lesion could be successfully repaired.

Prevention

Access to medical therapy is the single most important factor to prevent the development of

irreversible PH.²⁴ It is recommended that children with large left-to-right shunts or increased PVR undergo operative closure of the defect in the first 12 to 18 months of life to prevent development of Eisenmenger syndrome.¹⁵⁸ In children younger than 2 years, pulmonary vascular remodeling is usually reversible after the repair of the heart defect.¹⁰ Some conditions such as truncus arteriosus or transposition of the great arteries with ventricular septal defect are repaired during the first months of life, because they have higher propensity to develop PAH.²⁴ The level of PVR that precludes the safe closure of a heart defect varies with the age of the patient, type of lesion, PVR, and the presence of vasoreactivity.^{86,159–161} This topic remains a matter of significant controversy and outside the scope of this article.

SUMMARY

PAH-CHD is common among the different subtypes of PAH. Its severity depends on the type and size of the defect as well as the flow rate of the shunt. Cardiac catheterization is necessary for proper diagnosis and evaluation of severity. When reversibility is suspected, surgical or percutaneous correction is the treatment of choice. New PAH-specific therapies have proved beneficial, although further research is needed to determine optimal treatment of PAH-CHD. Lung or heart-lung transplantation remains an option for recalcitrant patients. More importantly, PAH may be preventable in many cases if the congenital heart defect(s) is identified and treated early.

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