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A Multifaceted Approach to Pulmonary Hypertension in Adults With Congenital Heart Disease☆

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ABSTRACT

Advances in the management of congenital heart disease (CHD) in children have resulted in growing numbers of adults with CHD. Pulmonary arterial hypertension related to CHD (PAH-CHD) is a common complication, affecting up to 10% of patients; and can arise even after successful and complete defect repair, with severe and potentially fatal consequences. Careful work-up in these patients is essential, particularly hemodynamic assessment, and can help define the most appropriate therapeutic approach. Management can be challenging, but the therapeutic armamentarium is continually expanding and now includes surgical, transcatheter and medical options. Timely correction of defects along with early treatment with advanced medical therapies appears to improve quality of life and possible even improve survival. Interestingly most studies of PAH-CHD have focused on its most severely afflicted patients, those with Eisenmenger Syndrome, making it less certain how to manage PAH-CHD of milder degrees. This review summarizes our current understanding of PAH-CHD and emphasizes the need for close follow-up in specialized centers of care where close collaboration is common practice.

Contents

Nearly 1% of all neonates are born with congenital heart disease (CHD), making it the most common inborn defect.[1] Recent advances in screening and interventional techniques have significantly boosted the proportion of children with heart defects surviving and thriving into adulthood, with numbers approaching –90% over the last two decades.[2] Unfortunately most adults with CHD (ACHD) remain at risk of long-term sequelae and thus benefit from lifelong specialist care and possibly future interventions. Pulmonary arterial hypertension (PAH) is one of the more common complications seen in adults with CHD, having an incidence of approximately 3 to 10%.[3–5] In unrepaired CHD, PAH occurs in up to 30% of patients,[6] with nearly half of them progressing to Eisenmenger syndrome (ES), characterized by right to

Abbreviations and Acronyms: 6-MWT, six-minute walk test; ACHD, adult congenital heart disease; ASD, atrial septal defect; BNP, brain natriuretic peptide; cGMP, cyclic guanosine monophosphate; CHD, congenital heart disease; ERA, endothelin receptor antagonist; ES, Eisenmenger syndrome; LV, left ventricle or ventricular; PA, pulmonary artery; PAH, pulmonary arterial hypertension; PAH-CHD, pulmonary arterial hypertension related to congenital heart disease; PAP, pulmonary artery pressure; PDA, patent ductus arteriosus; PDE-5i, phosphodiesterase-5 inhibitor; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RA, right atria or atrial; RCT, randomized control trial; RV, right ventricle or ventricular; TTE, transthoracic echocardiogram; VSD, ventricular septal defect; WHO, World Health Organization.

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left shunting with consequent cyanosis and profound functional limitation.[7] Despite the compelling improvement in pediatric CHD care and the consequent decline in the prevalence of ES, the overall population of adults with PAH related to CHD (henceforth referred to as PAH-CHD) appears to be increasing.

PAH-CHD can result from any heart defect or palliative procedure that increases exposure to pressure and/or volume overload in the pulmonary circulation. It can develop at any point throughout the life of the patient; however, timing is usually influenced by the size and location of the defect and whether or when previous intervention has been performed. When PAH-CHD develops, it leads to an increase in morbidity, mortality, and healthcare spending.[8] It is therefore of utmost importance to identify and treat these patients in a timely manner. In this paper we will provide an up-to-date overview of PAH-CHD, including recent classification guidelines and relevant diagnostic and therapeutic considerations that target the various aspects of the disease.

Definition and classification of PAH-CHD

In general, pulmonary hypertension (PH) is defined as a mean pulmonary artery (PA) pressure (PAP) ≥25 mm Hg at rest. The World Health Organization (WHO) has classified PH into five groups based upon respective pathologies and potential therapeutic approaches. According to this classification, PAH-CHD falls under Group 1 together with idiopathic PAH, familial PAH and PAH associated with other conditions (such as connective tissue disease and HIV infection). This group is characterized by pulmonary capillary wedge pressure or left ventricular (LV) end-diastolic pressure ≤15 mm Hg and pulmonary vascular resistance (PVR) >3 Wood units. Despite significant overlap with the other types of PAH in terms of pulmonary pathology, PAH-CHD has key differences in pathophysiology as well as clinical outcomes. This stems from the fact that CHD is not a single entity, but rather a spectrum of diseases that vary widely based upon cardiac anatomy, type of previous interventions and associated comorbidities.

PAH-CHD is itself further described by two classification systems, clinical and anatomic-pathophysiologic, which are summarized in Table 1. The clinical classification system divides patients into four groups based upon the direction of blood flow through the defect, the size of the defect and history of corrective surgery(ies):

- Group A consists of patients with ES, in whom PAP have increased to systemic levels causing a reversal of shunt from left-to-right to right-to-left or bidirectional. It is the most extreme form of PAH-CHD with the highest PVR. Cyanosis is an important hallmark of this disease, which impacts multiple organ systems. This explains, at least in part, the significant morbidity and mortality seen in this patient population.[9–11]
- Group B includes patients with systemic to pulmonary (left to right) shunts that are moderate-to-large in size. PVR is mildly to moderately elevated, but not enough to result in shunt reversal. These patients are therefore not cyanotic at rest.
- Group C includes patients with small or coincidental defects, usually a ventricular septal defect (VSD) <1 cm or an atrial septal defect (ASD) <2 cm of effective diameter as measured by echocardiography. The marked increase in PVR seen in many of these patients appears due to an intrinsic predisposition of the pulmonary bed toward vascular dysfunction that is unrelated to the shunt lesion. Indeed, the clinical picture of these patients is very similar to idiopathic PAH, but with the advantage of having a 'relief valve' protecting the right ventricle (RV) from the detrimental effects of chronically elevated afterload. Hence, repair of these defects is often contraindicated, particularly when PAH is advanced and long-standing.[12]
- Group D includes the growing population of patients in whom PAH persists or develops after corrective cardiac surgery. Since the defect (s) have been corrected, the RV lacks a 'relief valve' and therefore the clinical presentation of these patients tends to be more severe and rapidly progressive, depending on the degree of PVR elevation.[13]

Table 1
Comparison of 2 classification systems for describing PAH-CHD. ASD, atrial septal defect; PAH-CHD, pulmonary arterial hypertension associated with congenital heart disease; PAPVR, partial anomalous pulmonary venous return; PDA, patent ductus arteriosus; VSD, ventricular septal defect.

Classification Systems for PAH-CHD	
Clinical	Anatomic-Physiologic
Group A: Eisenmenger syndrome	Pre-tricuspid shunts
- Cardiac defects with initial left-to-right shunts that have reversed into right-to-left or bidirectional - Cyanosis at rest	- ASD - PAPVR
Group B: Systemic to pulmonary shunts that are moderate-to-large in size	Post-tricuspid shunts
- No cyanosis at rest	- VSD - PDA
Group C: PAH with small or coincidental defects	Complex defects
- ASD < 2 cm or VSD < 1 cm	- Atrioventricular septal defects
Group D: PAH persisting or developing after closure	- Single ventricle physiology
- No residual shunting	- Combined shunts

The anatomic-physiologic classification system, on the other hand, divides patients into 3 groups according to the location of the defect: those with pre-tricuspid shunts such as atrial septal defect (ASD) and partial anomalous pulmonary venous return, those with post-tricuspid shunts such as ventricular septal defect (VSD) and patent ductus arteriosus (PDA) and those with complex defects such as atrioventricular septal defects, single ventricular physiology and combined shunts. While both classification systems currently remain in clinical use, the anatomic-physiologic classification appears to be better at predicting clinical outcome.[14] It is worth mentioning that many patients with CHD have lesions that result in elevated left-sided filling pressures. These often reflect back to the pulmonary circulation and can result in pulmonary venous hypertension (WHO Group 2 PH). The treatment of such patients should mainly be focused on correcting the underlying heart defect and reducing the left-sided pressures through pharmacological or mechanical means.

Pathophysiology

PAH-CHD, like its counterparts in Group 1 of the WHO classification, is a disease of progressive vascular remodeling with resultant increase in PVR. Within PAH-CHD, the mechanism of damage to the pulmonary vasculature differs between pre-tricuspid valve (TV) and post-TV defects. While the degree and duration of volume overload appears to be the main determinant of vascular injury in patients with pre-tricuspid defects, high pressure shear forces play an important role in those with post-TV defects. Hence, with pre-TV defects, the pulmonary vasculature is usually able to accommodate increases in volume by vasodilating and recruiting previously under-perfused vessels until late in the disease process. This explains why PA pressures do not typically rise to significant levels in most patients with ASD until adult life and why these patients rarely progress to ES.[15] On the other hand, patients with large, non-restrictive post-TV shunts tend to develop severe PAH early. The combined effect of volume overload and shear forces significantly elevates the PVR; and without treatment the left to right

shunt progressively decreases and eventually reverses, resulting in right-to-left flow and consequent hypoxemia.[15,16]

The mechanism by which pulmonary vascular remodeling occurs is thought to begin with endothelial injury. Injured endothelial cells in patients with CHD release factors that contribute to PAH such as endothelin, a potent vasoconstrictor and stimulant of vascular smooth muscle cell proliferation, and thromboxane B2, which causes platelet activation and constriction of pulmonary arterioles.[17,18] Other molecules released include fibroblast growth factor and transforming growth factor-β, both of which induce smooth muscle cell hypertrophy and proliferation.[19] Simultaneously there is a decrease in production and release of potent pulmonary vasodilators by the injured endothelial cells, most important of which are prostacyclin and nitric oxide.[20] The end result is a shift in the balance toward vasoconstricting factors, which eventually leads to progressive narrowing of the pulmonary vasculature and consequent PVR elevation.

Approach to patient diagnosis and evaluation

PAH should be suspected in patients with CHD who have any of the following: decline in functional status, signs and symptoms of right-heart failure such as jugular venous distention, hepatic congestion and lower extremity edema, cyanosis in the context of an unrepaired cardiac shunt or syncope. Such patients should undergo a comprehensive work-up including a thorough history and physical exam, laboratory testing, a chest radiograph, an electrocardiogram and, most importantly of all, diagnostic cardiovascular imaging.[2] Table 2 lists the various components of the initial diagnostic evaluation of PAH-CHD, as well as potential key findings.

Comprehensive two-dimensional transthoracic echocardiography (TTE) with Doppler is the most commonly used diagnostic test for initial evaluation of PAH-CHD. It can help characterize the underlying heart defect and previous corrective interventions, provide an estimate of PAP and determine biventricular function and extent of cardiac chamber remodeling. Additionally, echo has significant value in determining prognosis and assessing response to therapeutic interventions. Signs of PAH on echo include RV hypertrophy and dilatation, right atrial (RA) enlargement, flattening of the interventricular septum and increased tricuspid and pulmonary valve regurgitant velocities. Additional imaging by computed tomography or cardiac magnetic resonance is generally indicated when the cardiac anatomy and function cannot be adequately assessed by echo.

Right heart catheterization is strongly recommended before therapy initiation, ideally at a center with expertise in PAH with an operator experienced in the catheterization of patients with CHD. Hemodynamics are critical, as most CHD patients have a pulmonary venous etiology to PH.[2] A thorough shunt run should be performed in all CHD patients, whether or not a shunt has previously been detected. The presence of a concomitant ASD, stretched patent foramen ovale or partial anomalous pulmonary venous return is not uncommon and may be a correctable source of increased pulmonary blood flow. A shunt should be suspected in any patient with hemodynamics suggesting advanced PAH but cardiac output by Fick method that is either normal or increased. PA saturations should be sampled bilaterally to exclude PDA. Bilateral PAP measures also help to detect segmental PH. The latter patients may benefit from interventions to restore balanced perfusion to the various lung segments. After PAH has been confirmed, vasoreactivity testing should also be performed. Treatment with calcium channel blockers is generally not advised in this patient population, and so testing is performed mainly to assess response to medical therapy and help determine prognosis. Responsiveness to inhaled nitric oxide has been shown to be associated with improved mid-term outcome in adults with PAH-CHD[21] and to long-term outcome in ES patients receiving advanced PH therapy.[22]

Additional studies may also help to assess the severity of the disease and monitor progression and response to therapy. Brain natriuretic peptide (BNP) levels in PH correlate with PVR, mean PAP, RA pressure and RV mass.[23] Moreover, the degree of elevation of BNP in PAH-CHD reflects the degree of hemodynamic derangement and provides prognostic information.[24] A six-minute walk test (6-MWT) should also be performed at baseline for all patients to determine functional limitation and degree of oxygen desaturation with exertion.[25] Maximal cardiopulmonary exercise testing with measurement of gas exchange is a valuable prognostic tool that can be very useful for assessing dynamic shunting and ventilatory efficiency. Because of its more cumbersome nature, however, cardiopulmonary exercise testing is less frequently utilized for serial follow-up of PAH-CHD than the 6-MWT.

Approach to treatment of patients with PAH-CHD

The ultimate goal of CHD management should be the prompt repair of defect(s) before long-term sequelae develop. In patients with significant shunt lesions, this involves surgical or transcatheter repair prior to the development of irreversible pulmonary vascular disease. Early correction of such shunts (i.e. within nine months of age) has been associated with normalization of PVR one year after repair, suggesting reversal of early changes in the pulmonary vasculature.[26] If repair is delayed until after two years of age, PVR rarely falls to normal levels and PAH typically ensues over time.[26]

Management of PAH-CHD patients should ideally take place at specialized centers under the care of cardiologists with training and experience in ACHD and PAH.[2,12] The approach to treatment depends on each patient's unique medical and surgical history, hemodynamics and clinical state. Treatment options include supportive care, percutaneous or surgical interventions and advanced PAH-specific medical therapy.

Supportive care

Supportive measures are usually targeted to treat or avoid the complications of PAH-CHD. Patients with ES are typically cyanotic; and it is this state of chronic hypoxemia, along with low cardiac output and PAH, that is responsible for the numerous complications that can develop. The degree of hypoxemia is inversely related to red blood cell count, and thus secondary erythrocytosis is commonly present.[27] However, contrary to previous belief that routine phlebotomy could avoid hyperviscosity symptoms and reduce thrombotic events, current practice has moved away from phlebotomy, which is now reserved for patients with severe hyperviscosity symptoms in the absence of dehydration.[12]

Table 2
Components of the initial workup that should be performed in all patients with suspected PAH-CHD, as well as the key findings expected with each type of study. CT, computerized tomography; MRI, magnetic resonance imaging.

Initial Workup	Key Findings
History and physical exam	Signs and symptoms of right heart failure, cyanosis, decrease in functional capacity
Laboratory testing	Erythrocytosis, iron deficiency
Chest radiography	Pulmonary arterial and hilar dilation, right heart enlargement, variable pulmonary vascularity (dependent on presence of shunting)
Electrocardiography	Right axis deviation, right atrial enlargement, RV hypertrophy
Diagnostic cardiac imaging (echo, MRI, CT)	Right ventricular hypertrophy in early disease. Right ventricular dilatation and systolic dysfunction in more advanced disease. Right atrial enlargement. Tricuspid regurgitation and hepatic congestion. Pulmonary vascular pruning.

Erythrocytosis is now believed to be a beneficial compensatory mechanism that serves to increase tissue oxygen delivery. In addition, routine and unnecessary phlebotomy can result in significant iron deficiency anemia, further impairing oxygen delivery and reducing exercise tolerance.[28] Thus avoidance of dehydration, maintenance of euvolemia and repletion of iron stores are now critical aspects of ES care.

ES patients are also at an increased risk of stroke and PA thrombosis due to blood stasis, endothelial injury and prothrombotic material.[29,30] This is countered by an increased risk for bleeding and hemoptysis, which makes use of anticoagulants in these patients controversial. In general, oral anticoagulation is recommended for ES patients with intrapulmonary thrombi, confirmed paradoxical embolism, in the presence of atrial flutter or fibrillation and for patients requiring indwelling lines for medication administration or intracardiac pacing leads.[12] In patients with very high hemoglobin levels (>20 mg/dl), standard INR measures have been found to be less accurate and the amount of sodium citrate in test tubes should be adjusted to ensure accuracy for appropriate warfarin dosing adjustments.

In women of childbearing age and PAH-CHD, contraception is a critically important issue. Maternal and fetal mortality is prohibitively high in this population, in addition to the greater risk of CHD in fetus, particularly in syndromic CHD.[31] Prevention of pregnancy should be stressed with the use of safe and effective methods of contraception. Estrogen-containing compounds should be avoided due to an increased promotion of thrombosis. In the event that a woman with mild to moderate PAH-CHD becomes pregnant, she should be followed by a cardiologist with expertise in the management of PAH-CHD as well as a maternal-fetal medicine specialist to reduce peripartum risk. In the presence of severe PAH-CHD, early pregnancy termination should ideally be recommended.

Long-term oxygen therapy, despite modestly increasing arterial oxygen saturation and improving symptoms in some patients with ES, has not been shown to alter survival.[32] Its use is suggested for selected patients with intrinsic lung disease, advanced respiratory symptoms and/or those with marked hypoxia who ascend to high altitudes or travel by air. Finally, patients with cyanotic CHD are at risk of infective endocarditis during invasive dental procedures and should receive antimicrobial prophylaxis.[33]

Interventional approach

Surgical and percutaneous techniques can be performed to repair or palliate most cardiac defects with fairly low periprocedural risk in the absence of significant comorbidities, providing that the indexed PVR is <4 Wood units/m^2. For patients with indexed PVR of 4–8 Wood units/m^2, further testing and consideration on a case per case basis is generally recommeded.[12] Shunts that are not hemodynamically significant (low pulmonary to systemic flow ratio and in the absence of heart chamber enlargement or increased PVR) generally will not require closure in the absence of related pathology (such as paradoxical embolic stroke).

Early attempts at surgical closure of shunts in patients with group A PAH-CHD (ES) resulted in very high rates of mortality, and this practice was quickly abandoned. Acute and short-term results of some interventional therapies in subsets of ES appear promising; however, the long-term consequences remain largely uncertain.[34–36] As such, structural intervention in this population should be considered contraindicated, short of enrollment into prospective clinical studies.

As with surgical approaches, management of Group B patients (moderate-to-large defects with prominent systemic-to-pulmonary flow leading to mild-to-moderate increases in PVR) should be based upon indexed PVR (Table 3). With normal or slightly increased PVR, the defect can be safely repaired. Fig 1 demonstrates echocardiographic images from a 65-year-old patient who presented with moderately severe PH. Panel A shows the dominant RV, as seen in PAH, and in panel B the estimated RV systolic pressure calculated to 81 mm Hg (4 × velocity^2 + 10 [RA pressure estimated based upon a dilated but normally collapsing inferior vena cava]). Both defects are visualized by color Doppler on apical 4 chamber transthoracic echo in Panel C and by intracardiac echo in Panel D. At catheterization the cardiac output was very high (due to prominent left to right shunting) and the pulmonary vascular resistance was calculated at 2.2 Wood units. The patient tolerated simultaneous balloon occlusion of the defects and both defects were successfully closed using 30 mm Gore Cardioform Devices (Gore Medical; Flagstaff, AZ); Panels E and F. Closure resulted in return to a dominant LV (Panel G) and RV systolic pressure on 1-year follow-up echo was down to 51 mm Hg (Panel H). The echo showed well seated devices and no shunting by color Doppler (Panel I).

Table 3
Guideline-based approach to repair of shunt lesions in the presence of pulmonary arterial hypertension. PAH-CHD, pulmonary arterial hypertension associated with congenital heart disease; PVR, pulmonary vascular resistance; PVRi, indexed pulmonary vascular resistance.

Criteria for Shunt Closure in Patients With Group B PAH-CHD		
PVR (WU)	PVRi (WU/m^2)	Candidate for Shunt Closure
<2.3	<4	Yes
2.3–4.6	4–8	Individualized decision
>4.6	>8	Likely not

With moderately increased PVR, the decision to repair should be individualized following careful assessment at a tertiary care center with expertise in PAH-CHD. Results of intervention in these patients have been mixed and residual PAH after closure appears to carry a very poor prognosis.[37] Finally, repair is contraindicated with severely increased PVR, as the defect is likely to be acting as a "relief valve" for the right-sided heart chambers (permitting right-to-left shunting to maintain cardiac output at the expense of cyanosis when the system is under duress). It is important to realize that the static condition of cardiac catheterization (particularly when a structural heart intervention is planned and sedation is administered) does not necessarily predict what happens when the patient attempts to be active or is under duress. Such situations are generally difficult to replicate in the catheterization laboratory setting.

Patients in group C (PAH with small/coincidental defects) and group D (PAH after corrective surgery) have PAH that appears to be very similar in pathophysiology to idiopathic PAH. Hence, repair is not generally indicated for these patients and some variation of the WHO Group 1 treatment algorithm should be applied.[38]

Several factors limit the feasibility of corrective cardiac surgery in the ACHD population, especially in patients who have undergone previous cardiac procedures. Extensive scar tissue from prior operations and the development of collateral vessels often complicate or even preclude reentry into the chest, as this can result in bleeding that is challenging to control. Furthermore, the proximity of the heart and other cardiovascular structures to the sternum requires extreme caution when accessing the chest cavity. Finally, cardiopulmonary bypass times in adults with CHD are significantly longer and these patients typically require larger amounts of blood products.[39] Novel surgical techniques utilizing smaller and alternative incisions as well as laparoscopic and robotic guidance have emerged as growing technologies to reduce operative risk. Furthermore the increased use of percutaneous technologies by interventionalists skilled in the field of CHD, either as an alternative or performed as hybrid procedures, with some lesions treated surgically and others with catheter-based options, have grown in popularity. Data has shown fewer procedural complications and shorter hospital stays with these techniques, while maintaining nearly equivalent long-term outcomes.[40,41] It is important to recognize that in some cases defects may be closed or even created in order to optimize pulmonary and systemic blood flow. In each case preprocedural assessment, careful discussion and consideration of the patient's wishes, as well as group discussion with input from cardiologists, cardiac surgeons and

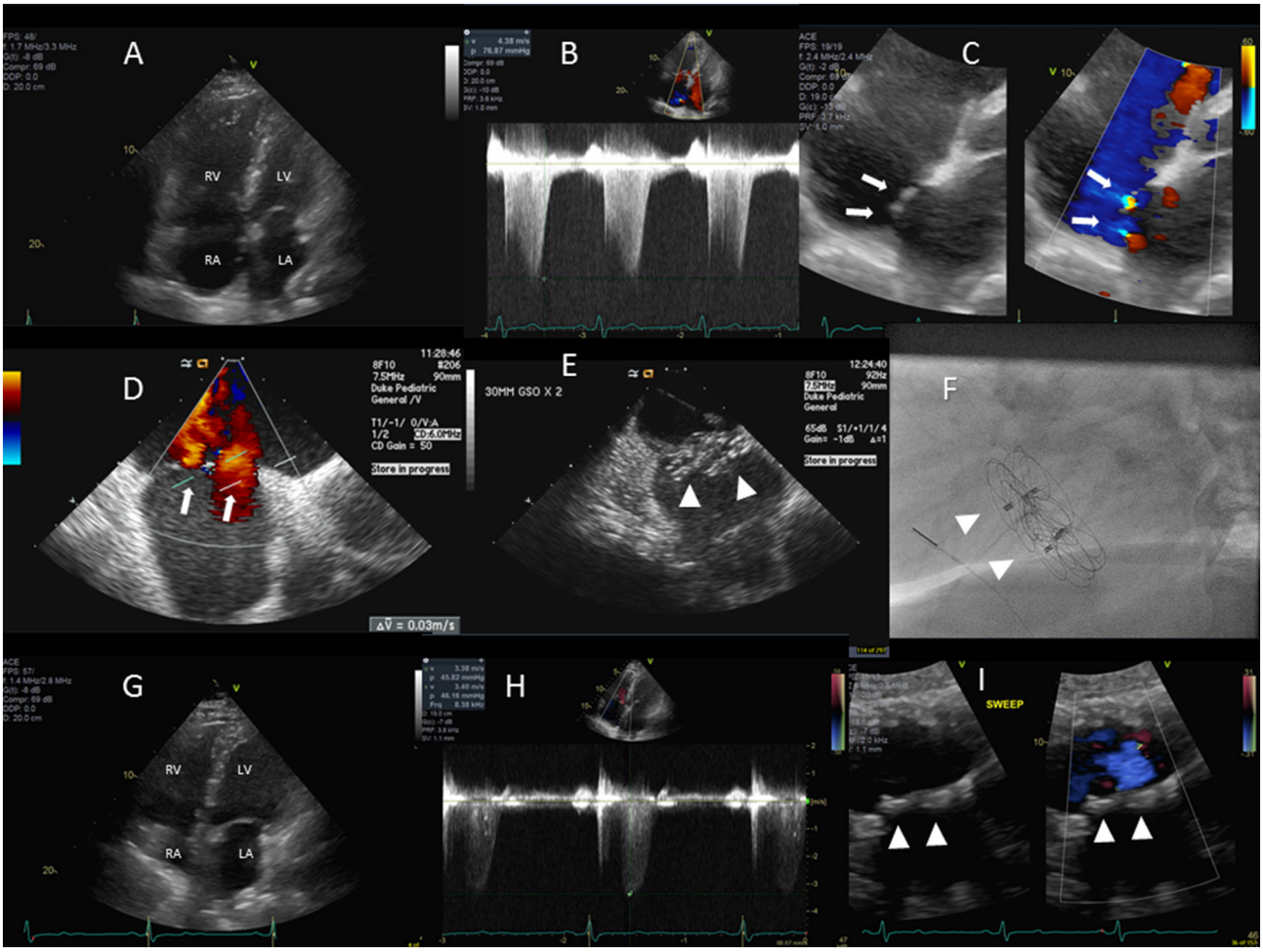

Fig 1. Imaging from a 65-year-old woman who had moderately severe pulmonary hypertension as a result of having two atrial septal defects (arrows). Transcatheter closure of the defects using 30 mm Gore Cardioform devices (arrowheads) resulted in a significant decrease in pulmonary artery pressure and right atrial and ventricular sizes by 1 year of follow-up. Please refer to the text for additional information. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

cardiac interventionalists increases the chances that the most appropriate management technique will be selected.

Advanced PAH-specific medical therapy

To date the majority of pivotal trials on PAH-specific therapies have recruited only a small number of patients with CHD, with most cases being fully repaired simple defects, as their pathophysiology most closely resembles idiopathic PAH. Whether these results can be generalized to the overall PAH-CHD population is uncertain, and thus a consensus for a unified therapeutic approach to advanced therapy in those patients remains lacking. Most medical treatment strategies in PAH-CHD are based upon expert opinion rather than clinical trials. However, there is growing evidence from randomized controlled trials and observational studies in patients with ES that suggests benefit with targeted medical therapies. Several small randomized and non-randomized trials (including the Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 [BREATHE-5] discussed below) have suggested hemodynamic and functional improvements with the use of targeted medical therapy. In a systematic review including a total of 1131 patients, the ten-year mortality in treatment-naïve ES patients was 30% to 40%, without any significant improvement over the last several decades.[42] In two sizable registries, however, ES patients receiving PAH therapies appeared to have significantly improved survival compared to treatment-naïve patients.[43–45]

To date, three main pathways involved in the pathophysiology of PAH have been the targets of PAH-specific therapy: the endothelin pathway, the nitric oxide pathway and the prostacyclin pathway. Oral, inhaled, subcutaneous and parenteral medications have been developed to target those pathways, namely, endothelin receptor antagonists (ERAs), phosphodiesterase-5 inhibitors (PDE-5i) and prostanoids. Newer agents include soluble guanylate cyclase stimulators (such as riociguat), which target the nitric oxide pathway and selective IP prostacyclin-receptor agonists (such as selexipag), which target the prostanoid pathway. Of the longer, outcome based clinical trials, the GRIPHON study randomized the largest population of PAH-CHD patients to date (110; all corrected shunts) to either selexipag or placebo and suggested similar clinical improvement compared with other Group 1 patients.[46]

Selection of therapeutic agents in PAH-CHD should be determined by WHO Function Class, proven drug efficacy and safety, hemodynamics and RV function, as well as patient preference, with a goal of maximizing patient compliance. Figs. 2 and 3 provide an evidence-based overview for the interventional and medical management of patients with PAH-CHD. Patients in WHO Function Class I are usually treated with supportive care only. Those with Class II or III symptoms can either be offered upfront combination oral therapy, most commonly an endothelin receptor antagonist (ERA) and a phosphodiesterase-5 inhibitor (PDE-5i), or sequential monotherapy.

Although data regarding combination therapy in PAH-CHD patients are generally lacking, a few small studies suggest significant clinical

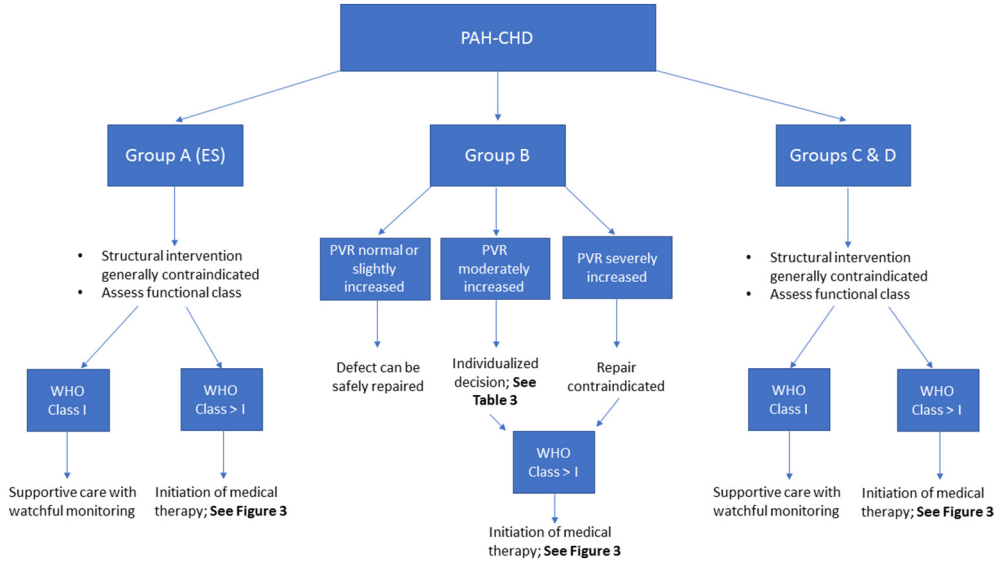

Fig 2. Generalized algorithm for approaching management of different types of PAH-CHD. ES, Eisenmenger syndrome; PAH-CHD, pulmonary arterial hypertension associated with congenital heart disease; PVR, pulmonary vascular resistance; WHO, World Health Organization.

improvement over monotherapy. In the Ambition (A study of first-line ambrisentan and tadalafil combination therapy in subjects with pulmonary arterial hypertension) Trial, Galié and colleagues found that treatment-naïve PAH patients started on upfront combination therapy with ambrisentan and tadalafil had a significantly lower risk of clinical-failure events compared to patients started on either drug alone.[47] However, only 9 out of the 500 patients enrolled in the trial had PAH-CHD, making it minimally applicable to this population of patients. In a recent study of 32 ES patients clinically deteriorating on bosentan, the addition of sildenafil resulted in a significant improvement in hemodynamics, clinical status and exercise tolerance.[48] Several other studies have also shown either clinical improvement or prevention of further deterioration in ES patients receiving combination therapy.[49,50]

Bosentan is the preferred therapeutic agent for ES patients with WHO class III symptoms in the latest European Society of Cardiology (ESC) and the European Respiratory Society (ERS) Guidelines. This recommendation is based upon BREATHE-5, the first randomized control trial (RCT) in ES, as well as its 40-week open-label extension study.[51,52] In this trial of 54 ES patients, bosentan treatment resulted in significant improvements in exercise capacity, hemodynamics and function class, regardless of the location of shunt lesion and without adversely affecting systemic arterial oxygen saturations.[53] Macitentan is the newest approved, dual receptor ERA. It was found to significantly reduce morbidity/mortality and increase exercise capacity in a large RCT that included 565 patients with PAH, almost 8% of which had repaired congenital shunts.[54] However, in the most recent RCT of 226 patients with ES (MAESTRO), macitentan did not significantly improve 6-MWT distance or WHO functional class compared to placebo.[55]

Fewer studies have been conducted to test the efficacy of PDE-5i's (such as sildenafil and tadalafil) in PAH-CHD. Overall these limited studies have shown improvement in exercise capacity, function class and hemodynamics.[56–58] Since the level of evidence for use of these medications is lower than that for ERAs, they are usually considered second-line agents. Riociguat has been studied in a RCT (PATENT-1) that included 35 PAH-CHD patients with repaired defects, representing 8% of

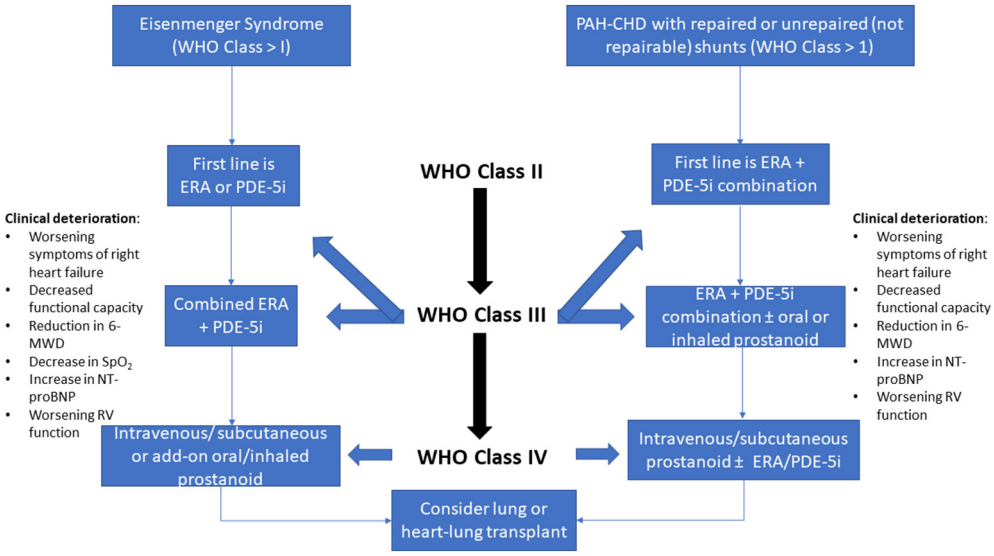

Fig 3. A simplified algorithm for approaching medical therapy in PAH-CHD. 6-MWD, six-minute walk distance; ERA, endothelin-receptor antagonist; ES, Eisenmenger syndrome; NT-proBNP, N-terminal pro-Brain Natriuretic Peptide; PAH-CHD, pulmonary arterial hypertension associated with congenital heart disease; PDE-5i, phosphodiesterase-5 inhibitor; RV, right ventricle; SpO2, peripheral capillary oxygen saturation; WHO, World Health Organization.

the study population. Riociguat appeared to improve exercise capacity, functional class and hemodynamics, N-terminal pro-BNP levels and the time to clinical worsening.[59] Importantly, riociguat should not be used in combination with PDE-5i's due to risk of profound hypotension or syncope.[60]

In patients with WHO class IV symptoms, intravenous epoprostenol is strongly recommended. Epoprostenol is a short-acting prostacyclin analog that has been tested in small cohorts of patients with ES and shown to result in improvements in hemodynamics and exercise capacity.[61,62] Other intravenous prostacyclins, such as the longer-acting treprostinil, can also be used as alternatives. The latter agent is particularly attractive in ES patients because of the additional availability of a subcutaneous manner of delivery. Long-term intravenous prostanoid administration increases the risk of paradoxical embolism and infectious complications in PAH-CHD patients with residual shunts, and therefore should be used with caution.

Finally, it is important to note that pulmonary vasodilator therapy is generally contraindicated in patients with elevated left-sided filling pressures, as these drugs may further increase pulmonary vascular congestion and consequent hypoxemia. Patients with interstitial lung disease, not an uncommon comorbidity in CHD, may also experience worsening hypoxia related to worsened VQ matching. Calcium channel blockers, historically given to PAH patients with positive vasoreactivity testing, are contraindicated for use in patients with ES, as systemic vasodilatation may result in systemic vascular resistance dropping more than PVR and consequently worsened hypoxemia from increasing right to left shunt.

Conclusion

The main goal of CHD management should remain timely recognition and repair of defects before irreversible damage to the pulmonary circulation occurs. PAH is still a common complication in ACHD, even in patients who have undergone successful repair; and its prevalence appears to be increasing in parallel with growth in the population of adults with CHD. Determining the optimal management for the heterogeneous group of PAH-CHD patients requires a thorough and sophisticated approach integrating tertiary-level resources and multicenter initiatives. Cumulative data now supports the introduction of advanced PAH-specific therapies, especially in patients with ES or repaired defects. Advanced therapy for the other types of PAH-CHD has been less thoroughly studied, and additional research is needed to better define this practice. Although ES has now been extensively studied, available therapies still remain mostly palliative and focused on improving quality of life; data evaluating survival outcomes are scarce and ES continues to be a highly debilitating disease with increased morbidity and mortality. Further understanding of the pathophysiology of this disease will undoubtedly open the door to better treatment options. Ensuring strict follow-up of these patients and having a high index of suspicion for clinical worsening, will undoubtedly lead to timelier medical interventions and improved outcomes for the CHD-PH population.

Statement of Conflict of Interest

Dr. Krasuski has served as a consultant for and has received research funding from Actelion Pharmaceuticals. He serves as an investigator for Edwards Lifesciences. He is a non-paid scientific advisory board member for Ventripoint. Dr. Fathallah reports no conflicts.

References

1. van der Linde D, Konings EE, Slager MA, et al. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. J Am Coll Cardiol 2011;58(21):2241-2247.
2. Warnes CA, Williams RG, Bashore TM, et al. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to develop guidelines on the management of adults with congenital heart disease). Circulation 2008;118(23):e714-e833.
3. Engelfriet PM, Duffels MG, Möller T, et al. Pulmonary arterial hypertension in adults born with a heart septal defect: the Euro Heart Survey on adult congenital heart disease. Heart 2007;93(6):682-687.
4. Duffels MG, Engelfriet PM, Berger RM, et al. Pulmonary arterial hypertension in congenital heart disease: an epidemiologic perspective from a Dutch registry. Int J Cardiol 2007;120(2):198-204.
5. van Riel AC, Schuuring MJ, van Hessen ID, et al. Contemporary prevalence of pulmonary arterial hypertension in adult congenital heart disease following the updated clinical classification. Int J Cardiol 2014;174(2):299-305.
6. McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on expert consensus documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. J Am Coll Cardiol 2009;53(17):1573-1619.
7. Beghetti M, Galiè N. Eisenmenger syndrome a clinical perspective in a new therapeutic era of pulmonary arterial hypertension. J Am Coll Cardiol 2009;53(9):733-740.
8. Lowe BS, Therrien J, Ionescu-Ittu R, Pilote L, Martucci G, Marelli AJ. Diagnosis of pulmonary hypertension in the congenital heart disease adult population impact on outcomes. J Am Coll Cardiol 2011;58(5):538-546.
9. Dimopoulos K, Diller GP, Koltsida E, et al. Prevalence, predictors, and prognostic value of renal dysfunction in adults with congenital heart disease. Circulation 2008;117(18):2320-2328.
10. Kempny A, Dimopoulos K, Alonso-Gonzalez R, et al. Six-minute walk test distance and resting oxygen saturations but not functional class predict outcome in adult patients with Eisenmenger syndrome. Int J Cardiol 2013;168(5):4784-4789.
11. Dimopoulos K, Wort SJ, Gatzoulis MA. Pulmonary hypertension related to congenital heart disease: a call for action. Eur Heart J 2014;35(11):691-700.
12. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the joint task force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Heart J 2016;37(1):67-119.
13. Alonso-Gonzalez R, Lopez-Guarch CJ, Subirana-Domenech MT, et al. Pulmonary hypertension and congenital heart disease: an insight from the REHAP National Registry. Int J Cardiol 2015;184:717-723.
14. Ramjug S, Hussain N, Hurdman J, et al. Pulmonary arterial hypertension associated with congenital heart disease: comparison of clinical and anatomic-pathophysiologic classification. J Heart Lung Transplant 2016;35(5):610-618.
15. Hopkins WE. The remarkable right ventricle of patients with Eisenmenger syndrome. Coron Artery Dis 2005;16(1):19-25.
16. Hopkins WE, Waggoner AD. Severe pulmonary hypertension without right ventricular failure: the unique hearts of patients with Eisenmenger syndrome. Am J Cardiol 2002;89(1):34-38.
17. Yoshibayashi M, Nishioka K, Nakao K, et al. Plasma endothelin concentrations in patients with pulmonary hypertension associated with congenital heart defects. Evidence for increased production of endothelin in pulmonary circulation. Circulation 1991;84(6):2280-2285.
18. Fuse S, Kamiya T. Plasma thromboxane B2 concentration in pulmonary hypertension associated with congenital heart disease. Circulation 1994;90(6):2952-2955.
19. Diller GP, Gatzoulis MA. Pulmonary vascular disease in adults with congenital heart disease. Circulation 2007;115(8):1039-1050.
20. Tuder RM, Cool CD, Geraci MW, et al. Prostacyclin synthase expression is decreased in lungs from patients with severe pulmonary hypertension. Am J Respir Crit Care Med 1999;159(6):1925-1932.
21. Post MC, Janssens S, Van de Werf F, Budts W. Responsiveness to inhaled nitric oxide is a predictor for mid-term survival in adult patients with congenital heart defects and pulmonary arterial hypertension. Eur Heart J 2004;25(18):1651-1656.
22. D'Alto M, Romeo E, Argiento P, et al. Pulmonary vasoreactivity predicts long-term outcome in patients with Eisenmenger syndrome receiving bosentan therapy. Heart 2010;96(18):1475-1479.
23. Nagaya N, Nishikimi T, Okano Y, et al. Plasma brain natriuretic peptide levels increase in proportion to the extent of right ventricular dysfunction in pulmonary hypertension. J Am Coll Cardiol 1998;31(1):202-208.
24. Giannakoulas G, Mouratoglou SA, Gatzoulis MA, Karvounis H. Blood biomarkers and their potential role in pulmonary arterial hypertension associated with congenital heart disease. A systematic review. Int J Cardiol 2014;174(3):618-623.
25. Kehmeier ES, Sommer MH, Galonska A, Zeus T, Verde P, Kelm M. Diagnostic value of the six-minute walk test (6MWT) in grown-up congenital heart disease (GUCH): comparison with clinical status and functional exercise capacity. Int J Cardiol 2016;203:90-97.
26. Haworth SG. Pulmonary hypertension in the young. Heart 2002;88(6):658-664.
27. Diller GP, Dimopoulos K, Broberg CS, et al. Presentation, survival prospects, and predictors of death in Eisenmenger syndrome: a combined retrospective and case-control study. Eur Heart J 2006;27(14):1737-1742.
28. Broberg CS, Bax BE, Okonko DO, et al. Blood viscosity and its relationship to iron deficiency, symptoms, and exercise capacity in adults with cyanotic congenital heart disease. J Am Coll Cardiol 2006;48(2):356-365.
29. Hoffmann A, Chockalingam P, Balint OH, et al. Cerebrovascular accidents in adult patients with congenital heart disease. Heart 2010;96(15):1223-1226.

30. Broberg CS, Ujita M, Prasad S, et al. Pulmonary arterial thrombosis in Eisenmenger syndrome is associated with biventricular dysfunction and decreased pulmonary flow velocity. J Am Coll Cardiol 2007;50(7):634-642.
31. Ladouceur M, Benoit L, Radojevic J, et al. Pregnancy outcomes in patients with pulmonary arterial hypertension associated with congenital heart disease. Heart 2017;103(4):287-292.
32. Sandoval J, Aguirre JS, Pulido T, et al. Nocturnal oxygen therapy in patients with the Eisenmenger syndrome. Am J Respir Crit Care Med 2001;164(9):1682-1687.
33. Habib G, Lancellotti P, Antunes MJ, et al. 2015 ESC guidelines for the management of infective endocarditis: the task force for the management of infective endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J 2015;36(44):3075-3128.
34. Lin MT, Chen YS, Huang SC, et al. Alternative approach for selected severe pulmonary hypertension of congenital heart defect without initial correction—palliative surgical treatment. Int J Cardiol 2011;151(3):313-317.
35. Burkhart HM, Dearani JA, Williams WG, et al. Late results of palliative atrial switch for transposition, ventricular septal defect, and pulmonary vascular obstructive disease. Ann Thorac Surg 2004;77(2):464-468. [discussion 468-469].
36. Beghetti M, Galiè N, Bonnet D. Can "inoperable" congenital heart defects become operable in patients with pulmonary arterial hypertension? Dream or reality? Congenit Heart Dis 2012;7(1):3-11.
37. Manes A, Palazzini M, Leci E, Bacchi Reggiani ML, Branzi A, Galiè N. Current era survival of patients with pulmonary arterial hypertension associated with congenital heart disease: a comparison between clinical subgroups. Eur Heart J 2014;35(11):716-724.
38. Rosenkranz S, Ghofrani HA, Beghetti M, et al. Riociguat for pulmonary arterial hypertension associated with congenital heart disease. Heart 2015;101(22):1792-1799.
39. Stellin G, Vida VL, Padalino MA, Rizzoli G, Association ECHS. Surgical outcome for congenital heart malformations in the adult age: a multicentric European study. Semin Thorac Cardiovasc Surg Pediatr Card Surg Ann 2004;7:95-101.
40. Vogel M, Berger F, Kramer A, Alexi-Meshkishvili V, Lange PE. Incidence of secondary pulmonary hypertension in adults with atrial septal or sinus venosus defects. Heart 1999;82(1):30-33.
41. Hoffman JI, Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol 2002;39(12):1890-1900.
42. Diller GP, Kempny A, Inuzuka R, et al. Survival prospects of treatment naïve patients with Eisenmenger: a systematic review of the literature and report of own experience. Heart 2014;100(17):1366-1372.
43. Kempny A, Hjortshøj CS, Gu H, et al. Predictors of death in contemporary adult patients with Eisenmenger syndrome: a multicenter study. Circulation 2017;135(15):1432-1440.
44. Diller GP, Körten MA, Bauer UM, et al. Current therapy and outcome of Eisenmenger syndrome: data of the German National Register for congenital heart defects. Eur Heart J 2016;37(18):1449-1455.
45. Dimopoulos K, Inuzuka R, Goletto S, et al. Improved survival among patients with Eisenmenger syndrome receiving advanced therapy for pulmonary arterial hypertension. Circulation 2010;121(1):20-25.
46. Sitbon O, Channick R, Chin KM, et al. Selexipag for the treatment of pulmonary arterial hypertension. N Engl J Med 2015;373(26):2522-2533.
47. Galiè N, Barberà JA, Frost AE, et al. Initial use of Ambrisentan plus Tadalafil in pulmonary arterial hypertension. N Engl J Med 2015;373(9):834-844.
48. D'Alto M, Romeo E, Argiento P, et al. Bosentan-sildenafil association in patients with congenital heart disease-related pulmonary arterial hypertension and Eisenmenger physiology. Int J Cardiol 2012;155(3):378-382.
49. Monfredi O, Heward E, Griffiths L, Condliffe R, Mahadevan VS. Effect of dual pulmonary vasodilator therapy in pulmonary arterial hypertension associated with congenital heart disease: a retrospective analysis. Open Heart 2016;3(1), e000399.
50. Diller GP, Alonso-Gonzalez R, Dimopoulos K, et al. Disease targeting therapies in patients with Eisenmenger syndrome: response to treatment and long-term efficiency. Int J Cardiol 2013;167(3):840-847.
51. Galiè N, Beghetti M, Gatzoulis MA, et al. Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. Circulation 2006;114(1):48-54.
52. Gatzoulis MA, Beghetti M, Galiè N, et al. Longer-term bosentan therapy improves functional capacity in Eisenmenger syndrome: results of the BREATHE-5 open-label extension study. Int J Cardiol 2008;127(1):27-32.
53. Berger RM, Beghetti M, Galiè N, et al. Atrial septal defects versus ventricular septal defects in BREATHE-5, a placebo-controlled study of pulmonary arterial hypertension related to Eisenmenger's syndrome: a subgroup analysis. Int J Cardiol 2010;144(3):373-378.
54. Pulido T, Adzerikho I, Channick RN, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. N Engl J Med 2013;369(9):809-818.
55. Galie N, Landzberg M, Beghetti M, et al. P5462Evaluation of macitentan in patients with Eisenmenger syndrome: results from the randomised controlled MAESTRO study. Eur Heart J 2017;38(1). (ehx493.P5462-ehx5493.P5462).
56. Mukhopadhyay S, Sharma M, Ramakrishnan S, et al. Phosphodiesterase-5 inhibitor in Eisenmenger syndrome: a preliminary observational study. Circulation 2006;114(17):1807-1810.
57. Chau EM, Fan KY, Chow WH. Effects of chronic sildenafil in patients with Eisenmenger syndrome versus idiopathic pulmonary arterial hypertension. Int J Cardiol 2007;120(3):301-305.
58. Mukhopadhyay S, Nathani S, Yusuf J, Shrimal D, Tyagi S. Clinical efficacy of phosphodiesterase-5 inhibitor Tadalafil in Eisenmenger syndrome—a randomized, placebo-controlled, double-blind crossover study. Congenit Heart Dis 2011;6(5):424-431.
59. Ghofrani HA, Galiè N, Grimminger F, et al. Riociguat for the treatment of pulmonary arterial hypertension. N Engl J Med 2013;369(4):330-340.
60. Galiè N, Müller K, Scalise AV, Grünig E. PATENT PLUS: a blinded, randomised and extension study of Riociguat plus sildenafil in pulmonary arterial hypertension. Eur Respir J 2015;45(5):1314-1322.
61. Rosenzweig EB, Kerstein D, Barst RJ. Long-term prostacyclin for pulmonary hypertension with associated congenital heart defects. Circulation 1999;99(14):1858-1865.
62. Fernandes SM, Newburger JW, Lang P, et al. Usefulness of epoprostenol therapy in the severely ill adolescent/adult with Eisenmenger physiology. Am J Cardiol 2003;91(5):632-635.