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CARDIOLOGY (WW LAI, SECTION EDITOR)

Pulmonary Arterial Hypertension Associated with Congenital Heart Disease

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Abstract Pulmonary arterial hypertension (PAH) with increased pulmonary vascular resistance is a frequent complication of congenital heart disease, most commonly occurring with systemic-to-pulmonary shunt lesions. The natural disease progression involves pulmonary endothelial damage due to exposure to increased pulmonary blood flow and pressure, and in its most severe form results in Eisenmenger syndrome, in which there is shunt reversal and cyanosis. Because of anatomic and pathologic similarities of PAH in the congenital heart disease population compared with idiopathic PAH, there is an evolving role for the use of the newer targeted PAH therapies in these patients. While early closure of shunt lesions is the best preventive measure, the concept of a combined medical-surgical approach for these patients has emerged as well. An additional group of patients that may benefit from the use of targeted PAH therapies includes the rapidly growing subpopulation of patients who have undergone the Fontan operation due to single ventricle anatomy.

Keywords Pulmonary arterial hypertension · Congenital heart disease · Eisenmenger syndrome · Operability

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Abbreviations

APAH	Associated pulmonary arterial hypertension
ASD	Atrial septal defect
CHD	Congenital heart disease
ES	Eisenmenger syndrome
IPAH	Idiopathic pulmonary arterial hypertension
PAH	Pulmonary arterial hypertension
PAP	Pulmonary artery pressure
PBF	Pulmonary blood flow
PDA	Patent ductus arteriosus
PLE	Protein-losing enteropathy
PVD	Pulmonary vascular disease
PVR	Pulmonary vascular resistance
PVRI	Pulmonary vascular resistance indexed to body surface area
RV	Right ventricle
SVR	Systemic vascular resistance
VSD	Ventricular septal defect
WU	Wood units

Introduction

Pulmonary arterial hypertension (PAH) with increased pulmonary vascular resistance (PVR) is a frequent complication of congenital heart disease (CHD), known as associated pulmonary arterial hypertension (APAH)–CHD [1, 2]. This results from pulmonary vascular remodeling due to non-restrictive, shunt-related increases in pulmonary blood flow (PBF) and/or exposure to increased pulmonary artery pressure (PAP) and sheer stress [3]. The development of APAH–CHD is partly dependent on the type and size of the cardiac defect, and likely due to other predisposing environmental and genetic factors. Post-tricuspid

valve lesions, such as ventricular septal defect (VSD) and patent ductus arteriosus (PDA), are more prone to the development of PAH than pre-tricuspid valve lesions, such as atrial septal defect (ASD) [4]. According to the second natural history study of CHD, over 50 % of patients with large, unrestrictive VSDs will develop PAH and cyanosis due to a reversal of left-to-right shunting, known as Eisenmenger syndrome (ES) [4]. The risk of development of PAH in patients with this type of VSD is much greater compared to smaller, restrictive defects [5]. In contrast, the risk of development of PAH is somewhat less in patients with pre-tricuspid defects such as ASD, although it tends to be higher in sinus venosus ASD compared to the more common secundum ASD type [6, 7]. A significant number of adults with PAH have unrepaired ASDs, and this may partially be because ASD is more often undiagnosed during childhood than VSD, and also because of the prevalence of smaller ASDs as incidental findings in adults with PAH. A recent European survey of 1877 adults with CHD found that PAH was present in 34 and 28 % of patients with unrepaired ASD and VSD, respectively [8]. In patients with closed defects, PAH was present in 12 % of ASD and 13 % of VSD patients [8].

It is generally believed that in order to avoid the development of pulmonary vascular disease (PVD), non-restrictive post-tricuspid defects such as large VSDs and PDAs should be repaired prior to one or 2 years of age, while ASDs may be repaired later on in childhood. In addition, there are more complex cardiac defects that are associated with the early development of PAH. These include truncus arteriosus, transposition of the great vessels (especially in the presence of a VSD), and complete atrioventricular septal defect (especially in the setting of trisomy 21). If these defects are not repaired within the first few weeks to months of life, severe PVD will almost invariably develop [9•]. Early onset of PAH during infancy may also be seen in some patients with simple defects such as VSD and PDA. In such cases, the usual infant findings of pulmonary congestion, failure to thrive and congestive heart failure are notably absent, and in many of these patients it is believed that the normal neonatal fall in PVR never occurred. A comprehensive evaluation including cardiac catheterization may be required to determine operability in these patients.

In patients with CHD, it is especially important to clearly define the presence of both PAH and PVD. While non-invasive tools, such as an echocardiogram, can be quite helpful in the diagnosis and evaluation of pulmonary hypertension and CHD, the only way to definitively distinguish between subtypes of pulmonary hypertension is by performing a complete cardiac catheterization. It is first important to differentiate PAH from pulmonary venous hypertension, which is often present in patients with CHD affecting left-sided structures. There is more than one currently accepted hemodynamic definition of PAH; however, a representative definition includes a mean PAP $\geq$25 mmHg with normal left-sided filling pressures (left ventricular end-diastolic pressure or pulmonary capillary wedge pressure $\leq$15 mmHg), and an elevated PVR (PVR indexed to body surface area (PVRI) >3 Wood units (WU)xm^2) [10–12]. This is in contrast to patients with increased PAP in the setting of elevated left-sided filling pressures and normal PVR. Patients with a mixed picture may present with elevation of PAP, left-sided filling pressures, and also an increase in PVR. It is critical to distinguish between patients with PAH, pulmonary venous hypertension, and mixed disease, as the treatments for the various forms of disease not only vary but may be unsafe in differing clinical situations. In the case of pulmonary venous hypertension, with elevation of PAP and also pulmonary capillary wedge pressure, the use of pulmonary vasodilators may lead to pulmonary edema and worsening of the clinical situation.

Almost all patients with large, non-restrictive left-to-right shunts will have elevated PAP and fit the currently accepted definition of PAH; however, determination of the degree of PVD is of utmost importance. In the setting of a low PVR (PVRI $\leq$3 WUxm^2), patients can and should be treated with surgical closure of the shunt. On the opposite end of the spectrum are patients with shunt reversal, low PBF, and cyanosis in the setting of elevated PAP and high PVR, known as Eisenmenger physiology, or ES. In these patients, surgical closure would not be advisable in many cases, and these patients may benefit from some of the newer targeted PAH medical therapies [13–16•]. With advances made in PAH therapies, the concept of a combined medical-surgical approach has become feasible, as is the concept of partial repair in which a fenestration, most commonly in the atrium, is left by the surgeon to serve as a "pop-off valve" for the right ventricle (RV) [9•]. However, just because we "can" close a defect, does not mean that it is in the patient's best long-term interest. In operating on a patient with CHD and borderline PVR, who un-operated would progress to ES, we may in fact be converting the patient into a patient physiologically similar to idiopathic pulmonary arterial hypertension (IPAH), with poorer long-term outcome than ES. This determination of operability is one of the more challenging and more important aspects of the management of patients with APAH–CHD.

Anatomic and Physiologic Classification

Anatomic and physiologic classification is an important part of the evaluation of APAH–CHD, and has recently been updated [17]. Five anatomic features should be evaluated, including defect type and size, net directionality

of shunting, associated cardiac or extracardiac anomalies, and repair status (see Table 1). Location of the cardiac defect in relation to the tricuspid valve is important as patients with large, post-tricuspid defects are more likely to develop PVD than patients with pre-tricuspid defects. Directionality of the shunt can be determined by echocardiography, and can also be evaluated by exercise testing, during which abrupt systemic desaturation is indicative of right-to-left shunting and more advanced PVD. In cases of a PDA, it is important to obtain oxygen saturations both pre- and post-ductally as patients may only have desaturation in the lower extremities. The repair status of the defect is also important with respect to the physiologic classification of the patient, e.g., IPAH versus ES physiology.

Table 1 Anatomical classification of congenital systemic-to-pulmonary shunts. From Simonneau, et al., 2009 [17]

Type
Simple pre-tricuspid shunts
Atrial septal defect (ASD)
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 (PDA)
Combined shunts (describe combination and predominant defect)
Complex congenital heart disease
Complete atrioventricular sepal defect
Truncus arteriosus
Single ventricle physiology with unobstructed pulmonary blood flow
Transposition of the great arteries with VSD (without pulmonary stenosis) and/or PDA
Other
Dimension (specify for each defect if more than one)
Hemodynamic (specify ratio of pulmonary to systemic blood flow)
Restrictive (pressure gradient across the defect)
Non-restrictive
Anatomic
Small to moderate (ASD $\leq$2 cm and VSD $\leq$1 cm)
Large (ASD >2 cm and VSD >1 cm)
Direction of shunt
Predominantly systemic-to-pulmonary
Predominantly pulmonary-to-systemic
Bidirectional
Associated cardiac and extracardiac abnormalities
Repair status
Unoperated
Palliated (specify type of operation(s), age at surgery)
Repaired (specify type of operation(s), age at surgery)

There are four physiologic subtypes of patients with APAH–CHD, which are described in Table 2. The latter two categories, PAH in the setting of small defects and PAH after corrective cardiac surgery, are physiologically analogous to IPAH with respect to the lack of an adequate "pop-off valve" for the failing RV. These patients are at increased risk for more rapidly progressive RV failure and worse outcomes than those patients with adequate RV "pop-off valves", underscoring the importance of the determination of operability in patients with APAH–CHD. The medical approach in these patients does not differ from that of other forms of group 1 pulmonary hypertension, although there are less controlled data available for such patients. Management of patients within the first two categories, those with Eisenmenger physiology, and those with PAH in the setting of unrepaired moderate to large defects, is more challenging, and is the focus of the remainder of this article.

PAH Associated with Congenital Systemic to Pulmonary Shunts: Pre-Eisenmenger Syndrome

The clinical presentation of APAH–CHD spans a wide range. At either end of this spectrum, medical decision making with regard to surgical intervention is relatively straightforward. At one end, ES patients with severely elevated PVR and shunt reversal are not candidates for surgical repair and are managed medically. At the other end, the infant with a large, non-restrictive septal defect, increased PBF, and congestive heart failure is referred for early surgical repair, with little fear that PAP will remain elevated post-operatively. Within this group, there is a small percentage ($\sim$2 %) in which post-operative PAH is an issue, with about 0.75 % having pulmonary hypertensive crises [18]. In these patients, mortality remains relatively high at 20–30 % [18–20]. Within this group, there are not good pre-operative predictors of who will suffer this fate; however, "at risk" patients include those with a high degree of pulmonary vascular reactivity, extracardiac syndromes (especially trisomy 21), and elevated pulmonary venous or left atrial pressures [21]. There are also patients repaired appropriately that will develop post-operative PAH months or even years following surgery. Although environmental and genetic factors likely play a role in their development of PAH, it is not completely understood. These patients act physiologically like IPAH, and are treated similarly.

Patients with APAH–CHD in the second physiologic subgroup (see Table 2) with mildly to moderately elevated

Table 2 Clinical classification of congenital systemic-to-pulmonary shunts associated with PAH. From Simonneau, et al. 2009 [17]

Eisenmenger syndrome	Patients with unrepaired systemic-to-pulmonary shunts resulting from large, non-restrictive defects leading to a severe, progressive increase in PVR, bi-directional shunting, and ultimately reversed shunting with central cyanosis
PAH with moderate to large defects	PVR is mildly to moderately increased, systemic-to-pulmonary shunt is still present, and no cyanosis is present at rest
PAH with small defects	Smaller defects generally include VSD $\leq$1 cm and ASD $\leq$2 cm, and clinical picture is similar to IPAH
PAH following corrective cardiac surgery	CHD has been corrected, but PAH is present either immediately after surgery or recurs several months or years after surgery in the absence of significant residual shunts

PVR and moderate to large increases in PBF are the most challenging to manage. Whether PAH will improve or progress following surgical repair determines operability, and unfortunately there is no accepted protocol or algorithm for such situations. A vital tool at the disposal of the cardiologist for determining operability is the cardiac catheterization. Although no validated criteria exist for predicting postoperative morbidity and mortality, a complete set of hemodynamics should be obtained, along with acute vasodilator testing, and possible balloon occlusion of the defect.

Cardiac catheterization alone, however, cannot determine operability. Especially in infants and children under general anesthesia, catheterization data are often obtained under "ideal" resting conditions. While a patient at rest may seem to be operable, with a minor respiratory illness and hypoxic vasoconstriction, it may become evident that a shunt should not be closed, or at least not completely. A thorough medical history and physical examination, and exercise testing when possible, play important roles in the determination of operability. Important elements of the history include age, type of CHD, and time of and circumstances surrounding diagnosis. The importance of the type of CHD has been previously discussed, and in general, the earlier a shunt lesion is diagnosed, the more likely the patient is operable. In addition, a history of cyanosis and/or dyspnea with exertion is important. Signs of cyanosis such as blue lips or nail beds with exercise, clubbing, and erythrocytosis also help provide a complete picture to determine operability.

Ultimately, cardiac catheterization is the main determinant of operability in APAH–CHD. In IPAH patients, the most prognostic catheterization data are indices of right heart function, such as cardiac index and right atrial pressure [22]. PAP is generally less useful for assessing disease severity and prognosis as it may in fact decrease with worsening right heart failure due to the RVs inability to generate higher pressure. In shunt lesions, it is important to realize that by having a non-restrictive VSD or PDA, PAP will be at systemic levels regardless of the PVR. In order to evaluate the degree of PVD, it is important to examine PVR, the ratio of PVR to systemic vascular resistance (SVR), and the ratio of pulmonary to systemic blood flow. In pediatrics, by convention, PVR is indexed to body surface area (PVRI) to allow for a more direct comparison of hemodynamics between disparately sized patients [23].

During evaluation of a systemic-to-pulmonary shunt, baseline room air hemodynamics should include three oxygen saturation runs and pressure measurements in the superior vena cava, right atrium, RV, pulmonary artery, and pulmonary capillary wedge position. Once baseline data are collected, if there is no evidence of pulmonary venous hypertension and PVRI is >3 WUxm^2, acute vasodilator testing should be performed with inhaled nitric oxide or intravenous epoprostenol, and another full assessment should be performed. A separate assessment with 100 % oxygen may be performed as well. Data should be obtained in the absence of respiratory or metabolic acidosis, anemia, or agitation [9]. Catheterization in infants and small children can often be quite complex, causing difficulties in the interpretation of results [24, 25]. Several sources of error exist in the calculation of systemic and pulmonary blood flow by Fick method, and PVR and SVR, especially when oxygen consumption is assumed. Whenever possible, oxygen consumption should be measured directly during the procedure. While cardiac catheterization is a key element for decision-making, management decisions need to include the use of medical history, physical examination, and results of all invasive and non-invasive testing.

An extensive review of hemodynamic parameters in determining operability in APAH–CHD was recently published by Giglia and Humpl [26]. The authors acknowledged limitations to many of the studies reviewed, and were clear that any parameters be used as a guide within the context of the complete clinical picture. PVRI values in the range of 6–8 WUxm^2 or lower are generally considered operable [26], although good surgical outcomes are also reported at higher values. The ability to lower PVRI to 6 WUxm^2 or lower on vasodilator testing with inhaled nitric oxide $\pm$ oxygen has been associated with better outcomes as well [27–29]. Additionally, a > 10 % decrease in PVR and PVR/SVR ratio in response to acute vasodilator testing, with a final PVR/SVR ratio of <0.3 are predictive of better post-operative outcomes [30, 31]. Because of advances in targeted PAH therapies, there is an

evolving role for a combined medical-surgical approach to those patients that are either borderline operable, or in some cases initially inoperable [32–36]. It is reasonable to treat with targeted therapies for a period of months, and re-evaluate by catheterization, sometimes needing serial re-evaluations. One example of a treatment strategy in an ASD patient is illustrated in Fig. 1. If medical treatment of a patient with a shunt and moderate PVD is effective, PVR will lower and result in increased PBF. As a result, surgical measures may actually be necessary to protect the pulmonary vasculature from the development of further damage.

When recommending surgery on APAH–CHD patients, the entire medical team including cardiologists, surgeons, anesthesiologists, and intensivists should converse, and special perioperative care should take place due to the high incidence of postoperative complications in these patients. Partial closure by fenestrated ASD patch, or creation of an interatrial communication, should be considered to allow for an RV "pop-off" to maintain cardiac output in the event of a pulmonary hypertensive crisis, especially in the immediate postoperative period. Modification of the cardiopulmonary bypass procedure, modified ultrafiltration, careful postoperative exposure to blood products, especially platelets, and postoperative use of pulmonary vasodilators such as inhaled nitric oxide, intravenous epoprostenol, and oral or intravenous sildenafil may influence postoperative outcomes in these high-risk patients.

Eisenmenger Syndrome

In 1897, Viktor Eisenmenger first described a 32-year-old patient who died of massive hemoptysis and had a VSD on post-mortem examination. The term "Eisenmenger syndrome" was coined by Paul Hamilton Wood in 1958 to define the condition of increased PAP and PVR in relation to a VSD with resultant shunt reversal and cyanosis. Subsequently, ES has been used to describe any CHD or shunt between the great arteries with resultant increase in PVR and shunt reversal [5]. Advances in CHD diagnosis and cardiac surgery, especially during infancy and early childhood, have helped to increase the number of CHD patients surviving into adulthood, and decrease the number of patients with ES in the Western World. Only around 5 % of adults with CHD will develop PAH [37]. However, in developing countries where patients seek medical care later in life, ES still remains a significant problem, and the worldwide prevalence of PAH in adults with CHD has recently been estimated at between 1.6 and 12.5 million, with 25–50 % presenting with ES [38]. In Latin America, the prevalence of advanced APAH–CHD relative to IPAH at cardiovascular centers is between 2:1 and 3:1 [39].

Although life expectancy is reduced in ES, it is significantly better than IPAH, with many surviving into their third and fourth decades [40], and even some into their seventh decade [40, 41]. More than 40 % of subjects are expected to be alive 25 years after diagnosis [4, 42]. There is some bias in this data as many patients were from the era prior to targeted PAH therapies. As a result, many who died early of severe hypoxemia and RV failure due to advanced ES may not have been included. However, with advances in targeted therapies, the hope is for future improvements to these numbers, and a recent study predicts 5-year survival of 95.3 % in children with ES [43].

The signs and symptoms of ES are a result of chronically low oxygen saturation, erythrocytosis, and blood hyperviscosity. The symptoms often present in adolescence or early adulthood, and include dyspnea, fatigue, progressive exercise intolerance, cyanosis, palpitations and syncope. Of all CHD patients, ES patients have the most exercise intolerance, and this has been demonstrated to be a predictor of hospitalization and mortality [44]. On physical examination, central cyanosis with clubbing may be present, RV heave and a prominent second heart sound are likely auscultated, and hepatomegaly and peripheral edema may be appreciated in more advanced cases. Patients may be seen with serious complications such as cerebral abscess or stroke, pulmonary arterial thrombosis, massive hemoptysis due to rupture of thin-walled pulmonary vessels, bacterial endocarditis, or severe myocardial dysfunction with low cardiac output.

Conventional Therapies for Eisenmenger Syndrome

Historically, treatment options for ES patients had been limited to palliative therapies and heart–lung transplantation or lung transplantation with closure of simple shunt lesions. Currently, conventional management is used in combination with targeted PAH therapies in ES management. Commonly used conventional therapies include digoxin, diuretics, anticoagulation, and antiarrhythmics, although none of these has been shown to improve survival in ES. Although supporting evidence is not particularly strong, digoxin is generally used for right heart failure [45]. Diuretics are often employed in this situation as well; however, they should be used cautiously as they may reduce plasma volume in patients with erythrocytosis, and also lead to dehydration. Anticoagulation in ES patients is a debatable subject due to increased risks of pulmonary artery thrombosis as well as hemoptysis, stroke, and hemorrhage [45]. Although the benefit of anticoagulation in IPAH patients has been demonstrated [46, 47], no such data exist in ES patients, and, given the potential complications, the decision to anticoagulate should be made carefully on an individual case basis. Long-term use of

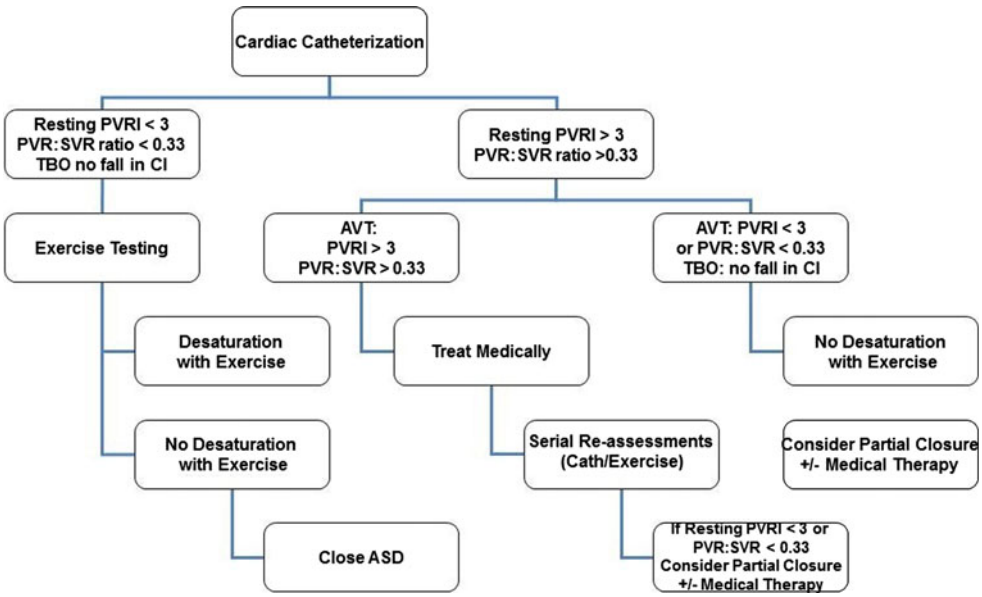

Fig. 1 APAH–CHD (ASD) clinical management algorithm: individualized case approach. From Rosenzweig and Barst [9•]. *ASD* atrial septal defect; *AVT* acute vasodilator testing; *PVRI* pulmonary vascular resistance indexed to body surface area; *PVR:SVR ratio* ratio of pulmonary vascular resistance to systemic vascular resistance; *TBO* temporary balloon occlusion

oxygen is often employed in ES patients, and while it may be associated with improvement in subjective status, no survival benefit has been reported [45, 48]. Maternal mortality in ES patients is reported at approximately 45 %, with death usually occurring during delivery or the first post-partum week due to hypovolemia, thromboembolism, or preeclampsia. In addition, spontaneous abortion rates are quite high, and for babies carried to term, there are high rates of intrauterine growth retardation and perinatal mortality. As a result, pregnancy is contraindicated in ES [49, 50].

Targeted Therapies for Eisenmenger syndrome

There are three main classes of targeted PAH therapies, and all are used in the treatment of ES patients. These include prostanoids, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors. As opposed to APAH–CHD with moderate PVD, ES patients are unlikely to experience a significant decrease in PVR that would be enough to reverse shunting and allow for possible surgical correction of CHD. The aim of targeted therapies in these cases is to improve exercise tolerance, hypoxemia, physical capacity, and ultimately survival.

Intravenous epoprostenol has been used in pediatric PAH [51], and specifically in APAH–CHD [32, 52], leading to improvements in functional capacity, hemodynamics, and survival. Treatment with epoprostenol requires use of a permanent central venous catheter, which can be problematic in the setting of right-to-left shunt due to the potential for thromboembolic events. In addition, systemic and local complications may include infections, sepsis and line breakage with drug interruption. Treprostinil, a similar and longer-acting prostanoid, can be delivered either intravenously, subcutaneously, or by inhalation, and offers potential advantages over epoprostenol. However, efficacy and safety has not been fully established in this patient population. Oral formulations of prostanoids are currently undergoing evaluation as well.

The first randomized, double-blinded, placebo-controlled study in ES patients was the BREATHE-5 trial investigating the efficacy and safety of the dual endothelin receptor antagonist bosentan in adult ES patients [14]. During the 16-week study, bosentan significantly reduced PVR, and improved PAP and exercise capacity compared to placebo [14], and longer-term data from the follow-up portion of the study demonstrated continued improvements in exercise capacity over an additional 24 weeks [15]. Safety findings were of particular importance given the potential for worsening of right-to-left shunting in the face of decreased SVR with vasodilator therapies. The study also demonstrated a worsening of PVR in the placebo group, underscoring the progressive nature of untreated ES. Smaller-scale, open-label studies in adults and pediatrics align with the BREATHE-5 trial. The selective endothelin receptor antagonist ambrisentan offers potential advantages over bosentan given its selectivity for the endothelin-A receptor, which demonstrates vasoconstrictor effects. Although less studied, ambrisentan has also been noted to be safe and efficacious in APAH–CHD and ES [36].

Oral sildenafil is the most widely used of the phosphodiesterase-5 inhibitors in the treatment of PAH, and has been used in pediatrics and APAH–CHD, with benefits on exercise capacity and hemodynamics [34, 53, 54]. A recent prospective, open-label, multicenter study on ES patients demonstrated safety and improved exercise capacity,

oxygen saturation, and hemodynamics after 12 months of therapy [13]. Sildenafil also comes in an intravenous form, often used postoperatively in the intensive care setting. The longer-acting, once-daily dosed tadalafil is less well-studied than sildenafil; however, a recent randomized, placebo-controlled, double-blinded, crossover study in ES patients also demonstrated safety and short-term improvements in exercise capacity, functional class, oxygen saturation, and hemodynamics after 6 weeks of therapy [55].

Thoracic Organ Transplantation

Heart–lung transplantation and lung transplantation in combination with repair of CHD are treatment options for advanced ES. Post-transplant bronchiolitis obliterans remains a serious postoperative complication, with effects on short- and long-term outcomes [56], and transplantation in ES patients is associated with high postoperative mortality [57]. However, short- and long-term survival rates following heart–lung transplant in ES patients are similar to non-ES patients [58]. Although thoracic organ transplantation does not improve long-term survival compared to conventional and targeted therapies in ES, it may be associated with improved exercise capacity and quality of life, and remains an option for ES patients in select cases.

The Fontan Circulation

Because of the passive flow of blood through the pulmonary vasculature, the Fontan circulation is exquisitely sensitive to changes in PVR. Postoperatively, even small increases can lead to low cardiac output syndrome, even in the setting of a technically successful operation [59]. Late complications include ventricular dysfunction and low cardiac output syndrome, protein-losing enteropathy (PLE), hypoxemia and exercise intolerance, and are all quite interrelated with PVR [60, 61].

The underlying mechanism for changes in PVR in Fontan patients is not entirely clear, and is likely multifactorial. Pulsatile PBF plays an important role in the recruitment of pulmonary capillaries [62], especially in the setting of increased cardiac output in response to exercise. In the absence of pulsatile PBF, recruitment is reduced, leading to increases in PVR [62, 63]. Pulsatile flow is also an important regulator of endothelium-derived vasomediators [64]. Dysregulation of this mechanism may lead to endothelial dysfunction, as well as an imbalance of vasodilators such as endothelium-derived nitric oxide and prostacyclin, and vasoconstrictors such as endothelin [64, 65].

Current medical management of Fontan failure aims mostly at treating manifestations such as ventricular dysfunction and PLE. Although there is a lack of reported benefit [66, 67], ACE inhibitors are used to treat ventricular dysfunction, while therapies such as subcutaneous heparin, oral budesonide, spironolactone and sildenafil are used in the treatment of PLE [43, 68–72]. Given the likely relationship of these manifestations of Fontan failure with increases in PVR, this presents an evolving role for targeted PAH therapies in an exponentially growing population of patients with complex CHD. In the immediate postoperative period, studies have demonstrated hemodynamic benefits derived from inhaled nitric oxide alone, or in combination with milrinone [73–75]. Although prostacyclins are rarely used in the perioperative period, epoprostenol has been shown to prevent the rebound effects of nitric oxide cessation [76]. Although not approved for use in this particular population, sildenafil is also beneficial in augmenting the cessation of inhaled and intravenous pulmonary vasodilators postoperatively [77, 78]. There is scant literature on the effects of targeted PAH therapies in failing Fontan patients; however, sildenafil appears beneficial in the treatment of PLE [43], plastic bronchitis [79], and after a single dose in Fontan patients has been noted to improve hemodynamic response to exercise [80]. Similarly, reports on bosentan use are limited to a case report on a patient with plastic bronchitis following Fontan, noting improvements in symptoms, exercise capacity and hemodynamics [81]. Because of the transaminase side effect associated with endothelin receptor antagonists and the potential for liver complications in Fontan failure patients, there is hesitancy to use bosentan in these patients. Post-marketing surveillance of bosentan found transaminase elevation to be less of a problem in patients with APAH–CHD than other types of PAH [82].

Since its development over three decades ago, the Fontan procedure has undergone several modifications and improvements, leading to an exponential increase in post-Fontan survivors. Although the physiology of Fontan failure is incompletely understood, elevations of PVR play a central role, and the maintenance of a low PVR remains a main goal of therapy. Given the lack of reported data on the use of targeted PAH therapies in this growing population, the development of trials for the treatment of patients with Fontan physiology will be a goal for pediatric and adult congenital cardiologists moving forward.

Conclusions

While PAH associated with CHD is classified with many other subgroups as group 1 pulmonary hypertension, this group is very heterogeneous in terms of anatomic, physiologic, and clinical features. Improvements in diagnosis and surgery for CHD, especially in infancy, have dramatically improved the short- and long-term outlook for

patients with APAH–CHD. Although advancements in noninvasive imaging, such as echocardiography, have helped in the evaluation of this patient population, the importance of cardiac catheterization cannot be overstated in helping with management. In addition, the newer targeted PAH therapies have clear short-term benefits in these patients, and their use in patients with borderline hemodynamics has paved the way for a combined medical-surgical approach to management. A sub-population of APAH–CHD that is growing rapidly includes those patients with Fontan physiology due to complex single ventricle anatomy, and work needs to be done to better understand the increases in PVR and potential use of targeted PAH therapies in these patients as well.

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