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Pulmonary Arterial Hypertension Associated with Congenital Heart Disease and Eisenmenger Syndrome: Current Practice in Pediatrics

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Abstract

Pulmonary arterial hypertension (PAH) is an uncommon but serious disease characterized by severe pulmonary vascular disease and significant morbidity and mortality. PAH associated with congenital heart disease (APAH-CHD) is one etiology of PAH that has innate characteristics delineating it from other forms of PAH. The patient with APAH-CHD presents with unique challenges consisting of not only pulmonary vascular disease but also the complexity of the cardiac lesion. Eisenmenger syndrome (ES) represents the severe end of the spectrum for disease in APAH-CHD. Over time, systemic-to-pulmonary shunting through cardiac defects increases pulmonary vascular resistance to levels significant enough to reverse shunting across the defect. Historically, ES patients have been reported to have better outcomes than IPAH despite similarities in pulmonary vascular disease. However, recent studies are challenging this notion. Nonetheless, APAH-CHD survival has improved with the advent of modern PAH targeted therapies. New therapeutic options have allowed us to reconsider the dogma of inoperability in APAH-CHD patients with unrepaired defects. Certainly advances have been made, however, investigators must continue to advance the field through controlled clinical trials in both adult and pediatric APAH-CHD patients.

Keywords

Pulmonary hypertension; Eisenmenger syndrome; pediatrics

Introduction

Nearly 1 in 100 children are born with congenital heart disease (CHD), making it one of the most common inborn birth defects worldwide[1]. The heterogeneity of the lesions included in CHD run the gamut from simple septal wall defects to complex cardiac lesions associated with single ventricle disease. Improvements in surgical correction or palliation concomitant with advancements in the ability to detect CHD lesions have allowed improved survival into

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adulthood[2,3]. Increasing survival may be beneficial. However, survival also carries the burden of associated complications, such as the development of pulmonary arterial hypertension (PAH), bringing new obstacles in the management of CHD.

PAH is defined by the World Health Organization (WHO) as pre-capillary pulmonary hypertension with a mean pulmonary artery pressure (mPAP) greater than or equal to 25 mm Hg and an additional requirement of a pulmonary capillary wedge pressure (PCWP) less than or equal to 15 mm Hg[4]. A diagnosis of PAH in children is often associated with a pulmonary vascular resistance (PVR) greater than 3 indexed Wood units[5]. CHD is the most common co-diagnosis in the pediatric population with PAH and is classified in Group 1 of the WHO classification system[6–9].

PAH associated with CHD (APAH-CHD) can be a consequence of a diversity of lesions, but it is most frequently the result of the presence of a systemic to pulmonary shunt between the two circulations. Over time, pulmonary vascular remodeling can occur through a number of mechanisms leading to reversible and irreversible vaso-occlusive lesions that result in elevated PVR. Advanced, irreversible, and severe PAH associated with CHD is known as Eisenmenger syndrome (ES). In ES, an unrepaired congenital heart defect-associated shunt reverses to right-to-left due to severe PAH. Although found more frequently in the adult CHD patient, the changes to the pulmonary vasculature occur as early as age 2, and thus to avoid ES, it requires early surveillance and intervention.

Dr. Victor Eisenmenger first described ES in 1897[10]. His patient presented with a history of cyanosis and dyspnea since infancy. He had significant clubbing, severe cyanosis, and heart sounds consistent with a ventricular septal defect (VSD). However, autopsy findings following sudden death with hemoptysis revealed severe pulmonary vascular disease with small vessel thrombo-occlusive findings. It was not until nearly 60 years later in 1958 that Eisenmenger's case gave rise to the term, Eisenmenger Syndrome. In a two-part lecture published in the British Medical Journal, Dr. Paul Wood ascribed not only Eisenmenger's case but also a cohort of 127 VSD and non-VSD cases as Eisenmenger's complex[11,12]. However, given the diversity of anatomical defects that could lead to Eisenmenger's complex, he assigned this physiology as Eisenmenger's syndrome. In addition, he assigned the first definition of ES as "pulmonary hypertension due to a high pulmonary vascular resistance with reversed or bidirectional shunt at aortopulmonary, ventricular, or atrial level". This definition still stands today.

ES encompasses the beautiful physiology of CHD, but it also represents some of the most severe consequences of untreated CHD. Therefore, it is crucial to educate all who partake in care of the pediatric patient. In this review, we describe not only ES but also other forms of APAH-CHD. We strived to educate the reader about the epidemiology, pathophysiology, early and late disease presentation, and the current management of ES and other APAH-CHD with a focus on the pediatric perspective of the disease. For a comprehensive look at the disease in adults or other forms of PAH, we encourage the reader to examine recent reviews[13–16].

Classification of APAH-CHD and Description of Associated Defects

Recently, at the 5th World Symposium on pulmonary hypertension (PH) in Nice, France, a classification of APAH-CHD was proposed (Table 1)[17]. Classified into 4 groups, APAH-CHD was grouped by both its anatomy and physiology. Group 1 represents patients with ES defined by systemic-to-pulmonary shunting of blood through large intra- and extracardiac defects that result in high PVR, PAH and in time, a reversed or bidirectional shunt. As previously discussed, this is one of the most severe forms of PAH, and the defect is considered inoperable.

Similar to Group 1 patients, Group 2 patients have large defects with only mild to moderately increased PVR, thereby, shunting continues systemic-to-pulmonary. Many of these patients may be considered operable, but it should be considered at a PH specialty center. Depending on the severity of PAH, these patients may also benefit from pre-surgical PAH targeted treatment.

In Group 3, patients have severe PAH with small, restrictive defects that allow little pressure relief for the RV. These patients are suspected to have additional underlying innate abnormalities of the pulmonary vascular bed of unknown etiology, rather than ES physiology. As such, they are often considered and treated as patients with idiopathic PAH (IPAH).

The final group, Group 4, includes patients who develop significant PAH following correction of their defect. PAH may develop early or late following the correction, and it is often difficult to treat. It has been proposed that there may be a genetic predisposition in these patients for developing PAH[14].

ES is associated with long-standing systemic-to-pulmonary shunts that induce changes in the pulmonary vasculature and increase PVR. A majority of the lesions causing ES consist of the more commonly occurring defects including large VSDs, atrioventricular septal defects (AVSDs), atrial septal defects (ASDs), and patent ductus arteriosus (PDA)[14]. However, a variety of other lesions can contribute to the pathology as noted by Dr. Paul Wood in his seminal work in 1958. At that time, he attributed 12 different lesions with ES[12]. These included PDA, aorto-pulmonary septal defect, persistent Truncus arteriosus, transposition of the great vessels with VSD, corrected transposition with VSD, single ventricle, VSD, AVSD, single atrium, ASD, and partial or total anomalous pulmonary venous return. In order to provide a more organized characterization of APAH-CHD lesions, the 4th World Symposium on pulmonary hypertension in Dana Point in 2009 created an anatomical and pathophysiological classification scheme (Table 2)[18].

Epidemiology

Epidemiological data on APAH-CHD and ES has been gleaned from natural history studies and recent studies utilizing PAH registries. The true number of both pediatric and adult APAH-CHD patient is not known as many patients are likely lost to follow up, especially upon completion of the repair[19]. Nonetheless, APAH-CHD prevalence differs between the adult and pediatric population.

Natural history studies estimate that 10% of all patients with CHD go on to develop PAH[20]. Data from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL), the PAH registry from France, the PAH registry from the Netherlands (CONCOR), the Scottish Morbidity record, and a group of tertiary European PH centers (Euro Heart Survey) reveal a prevalence of APAH-CHD in 10%, 11%, 4%, 23%, and 28% of all PAH cases, respectively,[21–25]. This slight variability likely reflects inclusion criteria differences and ability to recruit patients.

The more severe form of APAH-CHD, ES, carries a prevalence of 1.1%, 12.3%, and 7.6% according to the CONCOR registry, Euro Heart Survey, and REVEAL registry, respectively[22,23,26]. Importantly, data suggests that this number is on the decline, decreasing by 50% since the 1950s[27]. The numbers are often much higher when reported from single centers as certainly referral bias becomes an issue. Two studies illustrate this as ES is prevalent in 31% and 71% of adult APAH-CDH patients studied at two centers[28,29].

The prevalence of pediatric APAH-CHD is substantially higher than adults with APAH-CHD. The prevalence ranged from 24–75% in the Dutch pediatric PAH registry, French pediatric PAH registry, REVEAL, and the Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension (TOPP) registry[6,7,9,30]. Concerning the prevalence of early onset ES in children, data from the UK Pulmonary Hypertension Service for Children from 2001–2006 noted 31% of APAH-CHD cases were confirmed as ES[8].

Reporting on frequency of specific lesions varies for both pediatric and adult APAH-CHD. In the French pediatric PAH registry with a limited number of patients, the lesions reported in APAH-CHD included ASD, PDA, TGA, and Scimitar syndrome with a prevalence of 25%, 25%, 42%, and 8%, respectively[7]. Both the pediatric PAH registry from the Netherlands and the TOPP registry identified a systemic-to-pulmonary shunt-type defect in greater than 93% of pediatric patients with APAH-CHD[9,30]. Sub-analysis of the Dutch pediatric PAH registry illustrates a significant propensity for post-tricuspid shunts and very few patients with pre-tricuspid shunts in the pediatric population.

Similar lesions are seen in adult APAH-CHD patients. A natural history study on VSDs in adult patients reported up to 50% of patients with a large (>1.5 cm in diameter) defect and 3% with a smaller VSD developed ES[20]. ES was somewhat less commonly associated with large ASDs in a natural history from the 1960s where 13% of the patients developed ES. In the Euro Heart Survey, 12% of closed ASDs, 34% of open ASDs, 13% of closed VSDs, and 28% of open VSDs led to PAH in APAH-CHD patients[23]. The CONCOR registry in the Netherlands assigns PAH prevalence to even more specific lesions including ASDs (7–8%), VSDs (11%), AVSDs (41%), PDA (3%), truncus arteriosus (6%), aorto-pulmonary window (100%), double inlet left ventricle (7%), double outlet right ventricle (17%), and single ventricle (11%)[22]. Overall in this registry, VSDs are the predominant defect associated with ES (Group 1) and non-ES PAH (Groups 2–4), followed by ASDs and AVSDs.

Survival for ES and APAH-CHD has improved significantly since the 1950s[15]. This is especially true in the pediatric population. Prior to the era of modern PAH-targeted therapies, survival from PH was estimated at 66%, 52%, and 35% from 1-, 3-, and 5-year survival rates, respectively[31]. Data from multiple recent studies illustrate a significant improvement in survival for all forms of PAH with estimates at 73–96%, 63–88%, and 60–81% for 1-, 3-, and 5-year survival rates, respectively[6–9,32]. APAH-CHD-specific survival compared to that of IPAH in children in the initial analysis of the REVEAL registry showed no significant difference in survival (90% versus 85% 2-year survival, respectively). Furthermore, on examination of repaired versus unrepaired/partially repaired lesions, there was no difference in survival as well (865 versus 85% 2-year survival, respectively).

In the pediatric PAH registry in the Netherlands, children with APAH-CHD had better survival than children with IPAH (77%, 70%, and 66% versus 62%, 50%, and 46%, respectively)[9]. On further sub-analysis of APAH-CHD, differences became apparent. Pre-tricuspid shunts and APAH-CHD after shunt closure showed similar survival to IPAH; however, accelerated APAH-CHD and APAH-CHD without shunts showed much worse survival. Better survival was observed in APAH-PAH with a post-tricuspid shunt or with an abnormal pulmonary vasculature when compared to IPAH. The UK Pulmonary Hypertension Service for Children study performed a different sub-analysis on all forms of APAH. On examination of APAH-CHD only survival, ES-related APAH-CHD had the best survival rates and post-operative APAH-CHD had one of the worst survival rates with death in 23% of the children enrolled in the study[8].

Survival in adults with APAH-CHD has significantly improved as well since the advent of modern therapy. Prior to targeted drugs, the PAH registry designed the National Institutes of Health demonstrated an estimated median survival of 2.8 years for all primary pulmonary hypertension patients after a diagnosis was made[33]. The recent REVEAL registry provided a picture of improvement in survival for all PAH with 1-, 3-, 5-, and 7-year survival estimates of 85%, 68%, 57%, and 49%, respectively[34]. Although initial analysis of the REVEAL registry revealed no improvement in survival for APAH-CHD compared to other subgroups of PAH, a more recent analysis demonstrated that APAH-CHD had the highest 7-year survival estimate at 67%[34,35]. This was also observed in the French adult PAH registry in the at APAH-CHD survival was better than then either IPAH or connective tissue disease associated PAH (APAH-CTD)[36]

Recent studies have attempted to discern survival in ES and other forms of APAH-CHD, and they have shown conflicting results. Overall, patients with ES have a four-fold increase in mortality compared to the healthy population[37]. Despite this, studies report a trend towards improved survival compared to other forms of PAH[29,38]. At the same time, other studies such as the REVEAL registry report no difference in survival among ES and other subtypes of APAH-CHD[26]. In addition, a recent meta-analysis illustrated that most previous studies had not accounted for immortal time bias into their analyses[39]. After the authors analyzed the previous studies' data and accounting for immortal time bias, there was no evidence of increased survival in previous studies. As such, a recent study revealed that when reporting survival from diagnosis, there was improved survival in ES patients compared to other forms of PAH. But when comparing total life span, there were no differences. Therefore, it has been recommended to cautiously interpret previous outcomes data for ES.

Despite the incongruence in survival data amongst studies, comparison of outcomes of subtypes of APAH-CHD within a study can provide important epidemiological data. For instance, a large single center study examining APAH-CHD patients revealed improved survival in patients with ES compared to patients with other forms of APAH-CHD[29]. After analyzing subgroups in their study, patients with ES (Group 1) have similar survival to patients with significant systemic-to-pulmonary shunts (Group 2), but the two groups had significantly improved survival over patients with severe PAH due to small systemic-to-pulmonary shunts (Group 3) and patients with severe PAH following corrected defects (Group 4). Another study examined survival and lesion location in the ES patient[40]. Defined as either pre-tricuspid versus post-tricuspid, lesion location had no affect on survival in the total population of patients. However, on examination of patients greater than or equal to 48 years of age, pre-tricuspid shunts had significantly decreased survival.

Pathophysiology

The pathophysiology involved in aberrant pulmonary vascular remodeling in PAH associated with CHD arises early in disease. Protection of the pulmonary vascular bed is an innate function of the cardiopulmonary system initiated in fetal life. The low resistance of the placental circulation and high resistance of the pulmonary circulation, due in some part to hypoxia, ensures that a very low percentage of the cardiac output reaches the pulmonary vascular bed. Much of this is accomplished through shunting of blood through the foramen ovale and ductus arteriosus. Postnatal changes in the pulmonary vasculature occur immediately with the first breath. Theory suggests that an increase in alveolar distension providing mechanical forces and exposure to oxygen both play some part in the drop in PVR and, thus, increase in pulmonary blood flow[41]. An increase in pulmonary blood flow leads to an increase in left atrial filling and pressure, closing the foramen ovale. Over the next few days, exposure to oxygen and other vasoconstrictor factors closes the ductus arteriosus, further increasing pulmonary blood flow.

The equalization of ventricular pressures seen in fetal life continues postnatally in the setting of a large communication between the aorta and pulmonary artery or right and left ventricles. Thus, pulmonary arterial (PA) pressures will remain high with a significant delay in in the normal decrease in PVR. Normally, the pulmonary arteries remodel and thin postnatally, but in the presence of high PVR, there can be persistence in the thickness of the medial layer of pulmonary arteries. Eventually, the PA pressures fall and right ventricular (RV) compliance decreases. The resultant increased pulmonary blood flow can elicit shear stress and mechanical stretching of the pulmonary vessels. These events may lead to abnormal endothelial cell activation and set off a cascade of growth factors, vasoconstrictors, and extracellular matrix degradation. In addition, over time the medial layer can extend peripherally to the normally non-muscularized pulmonary arterioles, reducing the compliance of the vessel wall and thus further increasing PVR. Over time, these changes lead to significant PAH. Eventually, the right ventricular pressure becomes suprasystemic, and the shunting of blood through the defect reverses or becomes bidirectional.

While all defects associated ES share some common pathophysiological mechanisms, there are clearly differences as patients present with ES at various stages of life. Pre-tricuspid shunts such as atrial defects tend to present later in life while post-tricuspid shunts present as early as infancy in the case of some patients with AVSDs[27,40]. A recent study points out the physiological differences between pre-tricuspid and post-tricuspid shunts. Pre-tricuspid shunts such as an atrial septal defect have impaired RV function compared to post-tricuspid shunts[40]. Systemic PA pressures occur early in life in post-tricuspid shunts and expose a RV that still contains some characteristics of a more adaptive fetal-like RV[42]. Because pre-tricuspid shunt patients develop pulmonary vascular disease later in life, they may have lost any remnant of RV plasticity to develop adaptability to high PA pressures.

The underlying cellular mechanisms behind aberrant remodeling of the pulmonary vasculature in APAH-CHD are likely multifactorial. Data is limited in this specific type of PAH as modeling the disease can be difficult. However, large animal models such as the neonatal lamb model have provided some insight, and some knowledge can be extrapolated from other animal models for PH[43]. We will focus on only a few pathways that are currently being targeted for therapy. Otherwise, for a comprehensive review of mechanisms of PAH, we invite the reader to examine these reviews[44,45]

The endothelium is a source of both vasoconstrictor and vasodilator agents that are maintained in a delicate balance. Upon abnormal activation by insults such as shear stress, mechanical stretch, or hypoxia, the balance of vasoactive mediators can be disrupted. A decrease in the production of vasodilators such as nitric oxide-cyclic guanosine monophosphate (NO-cGMP) and prostacyclin (PGI_2) concomitant with an increase in the release of vasoconstrictors such as endothelin (ET-1), Rho GTPases , and thromboxane can lead to abnormal activation of cell signaling pathways causing aberrant vascular remodeling[44]. In the neonatal lamb systemic-to-pulmonary shunt model, there is not only increased ET-1 production but also diminished NO-cGMP signaling[46]. Similarly, phophodiesterase-5 (PDE5), an enzyme involved in the degradation cGMP, is upregulated in another animal model of flow-induced PH, which could be alleviated by the PDE5 inhibitor, sildenafil[47]. Furthermore, increased circulating levels of ET-1 and decreased levels of NO metabolites have been observed in some fashion in children with increased PA pressures or pulmonary blood flow and CHD[48–51].

In addition, endothelial injury can also lead to the production or inhibition of potent growth inhibitory or stimulator agents with specific effects on vascular smooth muscle. ET-1 itself is a potent mitogen form pulmonary arterial smooth muscle cells (PASMCs). Additional growth factors affected include angiopoietin-1 (Ang-1), and its dysregulation has been seen PAH[44]. The transforming growth factor-β (TGF-β) family has been implicated in the disease process as well. In addition to the discovery of mutations in the bone morphogenetic protein (BMP) receptor type 2 (*BMPR2*) in Familial PAH (FPAH), multiple family members appear to have unregulated PASMCs in flow-induced PH models[27,47]. There is also significant data on non-mitogenic factors produced by, or innate to, vascular smooth muscle cells and potentially involved in the pathogenesis of PAH. These include potassium and calcium ion channels, components involved in serotonin signaling, and molecules involved in RhoA/ROCK signaling.

Genetics

Currently, there exists little evidence of genetic susceptibility to APAH-CHD and no evidence for ES[52]. But we have yet to truly tap the vast genetic information including that of non-coding RNA. Nonetheless, over the last 15 years, there has been exciting genetic discoveries in the field of PAH, and we recommend the reader to turn to this recent review for more details on the genetics of PAH[53]. We will review some of the data below.

As far back as the 1950s, PH was recognized as a heritable disease[54]. Through the 1980s and 1990s, research continued on kindreds to determine genetic loci of susceptibility[55–57]. In 2000 and 2001, genetic studies on the rare, autosomal dominant FPAH identified mutations in the *BMPR2*[58–60]. Since this discovery, numerous studies have confirmed multiple mutations not only in *BMPR2* but also other members of the transforming growth factor-β (TGF-β) family including activin A receptor type II-like kinase 1 (*ACVRL1*), type II receptor endoglin (*ENG*), and the SMADs *SMAD1*, *SMAD4*, and *SMAD9*[61–63]. In addition, a recent study has revealed rare mutations in the BMP type1B receptor (*BMPR1B*) in childhood PAH[64]. Additional whole exome sequencing and genome-wide association studies have identified mutations in caveolin-1 (*CAV1*), potassium channel *KCNK3*, and cerebellin 2 (*CBLN2*)[65–67].

While any one of these mutations has been identified in a majority of adult PAH patients, they are found less frequently in childhood PAH, especially APAH-CHD[52]. Studies estimate less than 40% of childhood PAH cases contain known mutations[68–70]. It is unclear whether having a mutation affects outcomes as studies have shown both worse and better outcomes[69,71]. In addition, studies are limited in that genetic testing is performed infrequently in pediatric PAH.

Twelve to 13% of pediatric PAH diagnoses are associated with a chromosomal abnormality, and Trisomy 21 is the most well known syndrome associated with APAH-CHD[7,9,30,72]. Combined with potential intrinsic pulmonary vascular bed abnormalities and chronic upper airway obstruction, CHD, especially with systemic-to-pulmonary shunts, can potentially augment the propensity toward PAH[73]. Other syndromes possibly associated with APAH-CHD include Velocardiofacial, Noonan, CHARGE, and Scimitar syndromes[7,9,74].

Presentation

A combination of the findings observed in cyanotic CHD and PAH composes the clinical presentation of ES and other APAH-CHD patients. The presentation may differ between patients given the heterogeneity of CHD involved in the disease. Overall, the effects of APAH-CHD are multisystemic and require a thorough examination.

Generally, patients can present with dyspnea, chest pain, syncope, or sudden death. Exercise intolerance is common in patients with APAH-CHD with a majority of patients classified in New York Heart Association functional class II and higher[26]. These findings are not broadly assigned to both adults and children. The pediatric population with APAH-CHD tends to have longer 6 minute walk distances and lower NYHA function classification.

Although there is large discrepancy in the timeline of presentation, RV failure is a significant cardiac manifestation of the disease. As previously discussed, some lesions induce pulmonary vascular changes early and result in high PA pressures and condition the RV to maintain a fetal-like phenotype. Other cardiac manifestations include sudden cardiac death due to arrhythmias, and supraventricular arrhythmias have been shown to be an independent predictor of mortality[75].

Patients with CHD and PAH frequently exhibit signs and symptoms of chronic cyanosis. Long-standing cyanosis has effects on multiple organ systems and can be a source of significant morbidity and mortality. Hematological, neurological, renal, hepatic, and skeletal systems are affected by chronic cyanosis.

Secondary erythrocytosis is a consequence of chronic hypoxia mediated by the renal release of erythropoietin. While increased tissue oxygen delivery may be beneficial, there are secondary complications associated with the presence of increased red blood cell number. Hyperviscosity is not as common as previously thought[76]. And phlebotomy to remedy hyperviscosity may result in microcytic anemia due to iron deficiency. Iron deficiency itself has been associated with an increased risk for stroke[15]. In addition, erythrocytosis is thought to dilute the whole blood, potentially reducing clotting factors and may cause pulmonary thromboembolism. Furthermore, chronic cyanosis is associated with thrombocytopenia and platelet dysfunction and may result in bleeding abnormalities including hemoptysis[27].

Other systems affected in APAH-CHD include the renal, hepatic, skeletal, and immune systems. Renal dysfunction is apparent in APAH-CHD and in some patients manifests with abnormal renal fluid balance and hyperuricemia[15]. It has also been shown to be an independent risk factor for mortality in ES patients[77]. Gall stones, cholecystis, scoliosis are less common and less serious findings. On the other hand, shunting of blood from the pulmonary circulation and the effects of chronic hypoxia on the immune system and permeability of the blood brain barrier are proposed to create significant infectious complications including cerebral abscesses and endocarditis[15,75,77].

Diagnosis

Although not specific to APAH-CHD, comprehensive diagnostic algorithms have been published to guide the diagnosis and treatment of PAH patients[78,79]. The history followed by the physical examination is first insight into the diagnosis of APAH-CHD patients. This should be followed by comprehensive testing using laboratory studies, oximetry, imaging, exercise capacity testing, and potentially hemodynamic catheterization.

A New York Heart Association/WHO classification system is used to assess the functional capacity of a patient[78]. In summary, patient in class I have no physical activity limitations, class II have a slight limitation, class III have marked physical activity limitations but are comfortable at rest, and class IV have no ability to carry out any physical activity without symptoms and may have symptoms at rest. The classification system can be used to evaluate the severity of the illness, and it can be used to assess response to treatment.

Auscultation may reveal an accentuated pulmonary component or single second heart sound. Additional findings may include an early diastolic murmur of pulmonary regurgitation. In cases of severe PAH with tricuspid valve regurgitation, a high frequency pan-systolic murmur at the lower left sternal border may be heard and should be delineated from VSD murmurs by frequency. In addition, in the setting of Eisenmenger's physiology, a systolic murmur of a systemic-to-pulmonary shunt should disappear.

The physical exam should also include palpation of the chest for a RV heave, indicative of severe PAH. In the setting of severe disease, increased right atrial pressure may cause hepatic congestion manifested by hepatomegaly with a firm, tender liver edge. If the PH is severe enough, presystolic pulsations, corresponding to the right atrial V wave, may be palpated. Other findings that will be associated with long-standing cyanotic heart disease include clubbing or edema in the setting of heart failure.

Laboratory testing should include a comprehensive blood count and metabolic panel. In addition, arterial blood gas should be drawn to accurately determine blood oxygen levels. As previously discussed, iron deficiency can be found in ES patients. In addition, liver enzyme testing may provide details on the severity of the disease and effects on the liver, and electrolytes, urea, and creatinine levels can be used to assess fluid balance and renal function. Some may employ assessment of the coagulability state as pulmonary thromboembolic disease may occur. Another important marker is the brain natriuretic peptide (BNP) level, and it has been used in both the adult and pediatric populations to monitor the cardiac response to treatment[78,80]. Finally, if the diagnosis of APAH-CHD is unclear, specialized blood testing for other forms of PAH may be warranted.

Electrocardiography has some utility in the diagnosis and monitoring of APAH-CHD patients. Specific findings may help raise awareness of an underlying cardiac defect on initial evaluation of an undiagnosed patient. In addition, the underlying heart rhythm should be documented as arrhythmias are independent predictors of mortality in ES patients[75]. There are also findings of RV hypertrophy and strain in adult and pediatric PH marked by increased amplitudes of the R-wave and S-wave in leads V_1 and V_6, respectively. The amplitude of the P-wave in lead II can correlate with RA enlargement as well.

Multiple imaging modalities exist to help determine not only the severity of PAH but also potential underlying defects associated with CHD. Chest x-ray can be used to estimate not only chamber size but also enlarged central pulmonary arteries. Severe disease can exhibit diminished peripheral vascular markings on the x-ray, and underlying lung disease such as changes observed in chronic lung disease may be identified.

Non-invasive transthoracic echocardiography is an important tool for initial assessment and tracking progression or regression of the disease. In cases of adults or large children with poor acoustic windows, a transesophageal echocardiography is an alternative. Imaging protocols are frequently institution-dependent. However, certain aspects of PAH and its related effects on the heart should always be assessed. First, associated CHD should be ruled out, and if present, measurements of the size of the defects, directionality of shunts, and velocity of the shunts. Although not always present, measuring the tricuspid regurgitant

(TR) flow velocity using Doppler allows one to estimate RV systolic pressure using the modified Bernoulli equation. In instances of the absence of the TR jet, some institutions will employ a recent method used to estimate peak systolic PA pressure by using Doppler and measuring the acceleration time of the flow across the pulmonary valve. Measurements of RV function can be obtained by several methods including the Tei index (using tricuspid inflow and RV outflow Doppler, isovolumetric contraction time + isovolumetric relation time/ejection time) and the tricuspid annular plane systolic excursion (TAPSE), a reliable method to estimate longitudinal RV contraction in PH patients[81]. A comprehensive protocol may also include assessment of the ventricular wall dimensions and both ventricular and atrial chamber size, main and branch PA size and flow velocity, pulmonary valve regurgitation quantification, interventricular septal wall position and motion, and inferior vena cava diameter.

Additional imaging modalities used less often include magnetic resonance imaging (MRI) and chest computed tomography (CT) scans. The MRI can further quantify shunt location and size, more accurately detail pulmonary vessel size and flow, and evaluate RV performance. While the chest CT can give some dimensional analysis like MRI, it may be more useful for evaluating the lung parenchyma for other lung disease and intrapulmonary thrombi.

Hemodynamic assessment by cardiac catheterization and acute vasodilator testing are key components and the gold standard in the initial diagnosis of the patient with additional benefit for serial assessment of the disease. While patients with mild PAH may be initially excluded from catheterization given the risk, any requirement of escalation of therapy should warrant more careful hemodynamic assessment. Cardiac catheterization allows one to not only determine the severity of the PAH, but it can also be employed to evaluate the APAH-CHD patient for operability of open defects and evaluate the need for transplantation. Hemodynamic measurements indicated include blood gas analysis with venous and arterial oxygen saturations, both systemic and pulmonary artery pressures, PCWP or left atrial pressure and RA pressure, and calculation of pulmonary blood flow by either Fick's equation or with the use of a thermodilution catheter. Acute vasoreactivity testing is required, as it may help predict patient response to vasodilator therapy; however, APAH-CDH rarely responds to the use of calcium channel blockers. Testing should include administration of oxygen, nitric oxide and/or prostacyclins. Although there is an anesthetic and procedural risk with cardiac catheterization in all patients with PAH, the risk of serious events appears to be lower in the modern era where most catheterizations are occurring at specialized centers. A single center study recently published revealed an overall complication rate of 5.7%, major complication rate of only 1.2% with only a 0.2% catheterization-related mortality rate[82].

Exercise testing consists of a 6-minute walk distance (6MWD), and following assessment of the severity of PAH, a more rigorous cardiopulmonary exercise test may be warranted. The 6MWD, a sub-maximal and highly reproducible test, can be used to determine exercise capacity and exercise related desaturation. There are currently standards for both children and adults, and 6MWD has been used frequently as a clinical outcomes indicator in clinical trials[78].

Current Management

Treatment of both APAH-CHD consists of supportive therapies in addition to PAH targeted drug treatment. Targeted drug treatment is based on a number of clinical trials performed mainly in adults. Some trials have been specific to APAH-CHD and/or ES, but a portion of the treatment strategies comes from data extrapolated from general PAH studies. Pediatric-specific clinical trial data is quite limited and is mostly based on adult trials. Some trials have been completed in children, and yet controversy continues. This review will summarize some of the larger trials, and we refer the reader to these recent reviews for a more comprehensive analysis of clinical trials and treatment strategies[13,16,83].

Surgical correction is not indicated in patients with severe pulmonary vascular disease in the setting of CHD. This would include patients with ES (Group 1), Group 3 patients with severe IPAH-like disease, and Group 4 patients with repaired/partially repaired CHD and severe PAH. Data on operability of patients with pulmonary vascular disease due to large systemic-to-pulmonary shunts is limited to retrospective cohort and case studies. A recent examination proposed arguments for and against a treat-and-repair approach, especially to defects involving septal defects[84]. One retrospective study of 76 patients with a large PDA, 11 of whom had ES or irreversible PAH, reported that the defects could be safely closed, and intermediate follow up revealed that no patient had worsening of disease by echocardiography[85]. However, no long-term follow up has been reported from any cohort. Therefore, the approach to addressing closure of any defect should be cautious, and guidelines have been proposed (Table 3)[17].

Supportive therapy plays an important role in the management of APAH-CHD patients. Living with chronic disease is both physically and mentally challenging. Appropriate support from family, friends and support groups should be advocated. Despite their limitations, APAH-CHD patients should be encouraged to take part in activities, but they should know their limitations. APAH-CHD patients may even benefit from supervised exercise training programs as demonstrated in a non-randomized, prospective study[86].

Other strategies for the management of APAH-CHD involve prevention and treatment of symptoms and complications. All patients and their families should be educated on the importance of regular immunizations. As per AHA guidelines, most APAH-CHD patients should receive antibiotics for endocarditis prophylaxis. Given the prevalence of iron deficiency anemia, vigilance and treatment should be required. Likewise, if present, hyperviscosity syndrome should be treated. Symptoms of pulmonary over circulation and ventricular failure may be addressed with the use of diuretics. While historical evidence indicates that anticoagulation is associated with a survival benefit in IPAH patients, data is inconclusive on its use in APAH-CHD and warrants careful consideration in each patient[87]. Oxygen therapy should be reserved for select patients with exercise induced cyanosis, but studies examining nocturnal use did not shown any benefit[88].

There is established evidence that PAH-specific therapeutic drugs have efficacy in APAH-CHD patients. Current directed therapy is targeted towards three pathways involved in vasoactive responses in the pulmonary vasculature. They include the endothelin pathway (endothelin receptor antagonists, ERAs), NO-cGMP pathway (PDE5 inhibitors and soluble guanylate cyclase stimulators, and prostacyclin pathway (prostaglandins). In the following discussion, we will focus on APAH-CHD-directed studies and PAH studies with significant numbers of APAH-CHD patients included.

ERAs, including bosentan, ambrisentan, and macitentan, target the receptors for ET-1, inhibiting its vasoconstrictor effects on the pulmonary vasculature. The class first demonstrated efficacy in ES patient in small, open-label studies. Bosentan, an oral dual receptor antagonist, was evaluated in a multicenter, double-blind, randomized, placebo-controlled study called Bosentan Randomized Trial of Endothelin Antagonist Therapy-5 (BREATHE-5). Compared to placebo, patients treated with bosentan had both hemodynamic (−472 dyn·sec/cm^5 difference in PVRi), exercise capacity (−53.1 m difference in 6MWD), and NYHA functional class improvements[89]. An extension study of this trial revealed that the improvements in exercise capacity were maintained at 40 weeks[90], and these results appear to be independent of shunt location[91]. Whether these benefits are maintained over several years is unclear as 6MWD may return to baseline after 2 years[92,93]. The efficacy of bosentan in the pediatric population has been studied in multiple retrospective studies. A 101 patient study in the UK included a significant number of APAH-CHD patients and revealed that bosentan improved WHO functional class and 6MWD with favorable survival estimates[94]. Other ERAs such as ambrisentan and macitentan have not been as well studied in the APAH-CHD population, and controlled trials in both adult and pediatric APAH-CHD populations are needed.

The NO pathway is targeted in several ways. PDE5 inhibitors target the enzyme responsible for degradation of cGMP, secondary messenger for NO. In addition, a newer drug, riociguat, is a soluble guanylate cyclase stimulator that has shown promise in adult PAH[95]. Its activity increases the amount cGMP synthesized in addition to other effects. Although there are no prospective, randomized clinical trials for PDE5 inhibitors specifically for the APAH-CHD population, its benefits have been demonstrated in the several randomized PAH studies that included APAH-CHD patients[96,97]. Observational studies have shown benefits for both sildenafil and tadalafil in ES patients, reducing PVR and mean PA pressures and increasing oxygen saturations and 6MWD[98,99]. PDE5 inhibitor treatment in children, in general, has been embroiled in controversy in recent years. Initially, small open-label studies revealed that PDE5 inhibitors improved pulmonary hemodynamics, exercise capacity and oxygen saturations[100]. The randomized, double-blind, placebo-controlled study, STARTS-1 (Sildenafil in Treatment-Naïve Children, Aged 1–17 Years, With Pulmonary Arterial Hypertension) initially suggested some efficacy for improvements in peak oxygen consumption, functional class, and hemodynamics using medium- and high-dose sildenafil[101]. However, in the STARTS-2 extension trial, increased mortality was reported in the high dose sildenafil group compared to the lower dose groups[102]. Overall, the study appeared to demonstrate favorable survival for children, especially those with APAH-CHD. Despite approval for sildenafil at a medium dose by the European Medicines Agency, the U.S. Food and Drug Administration has recommended against its use in the pediatric population. Of note, the authors of the study pointed out that of the 37 patients who died, 28 had IPAH/FPAH, baseline WHO functional class III/IV, and worse baseline hemodynamics.

Studies on combination therapy for adult and pediatric APAH-CHD patients are limited. In a randomized, double-blind, cross-over study of 21 ES patients, bosentan alone improved 6MWD and, PVR, and pulmonary blood flow, but the addition of sildenafil to bosentan did not improve 6MWD[103]. However, an observational study of 32 APAH-CHD patients on bosentan who underwent a right heart catheterization for clinical worsening had significant improvement in functional class, 6MWD, pro-BNP, SpO2, and hemodynamics after the addition of sildenafil[104].

Prostacyclin and its analogues, epoprostenol, treprostinil, and iloprost, are potent vasodilators. Although large, randomized, controlled clinical trials examining prostacyclins are not available for adults or children with APAH-CHD, small, retrospective or observational studies have validated its efficiency in the treatment of APAH-CHD. In a small prospective, uncontrolled study on pediatric and adult APAH-CHD patients, IV prostacyclin (PGI_2) after one year of treatment improved mean PA pressure, PVR, cardiac index, NYHA functional class, and exercise capacity[105]. Prostacyclin analogues have also shown efficacy. Epoprostenol improved NYHA functional class, 6MWD, systemic arterial oxygen saturation, and PVR after 3 months of therapy in a small, retrospective study on severely ill ES patients[106]. Long-term therapy with continuous infusions of prostacyclins can carry significant risks for infection and other complications[107]. However, other formulations such as inhaled, oral, or subcutaneously administered prostacyclins have met with varying efficacy. In the randomized, double-blind, placebo-controlled trial using oral beraprost, the efficacy at 12 weeks was limited to IPAH/FPAH patients. The improvement in 6MWD was not seen in APAH, but the study authors point out that this was a heterogeneous population with only 30% of APAH composed of patients with CHD. On the other hand, inhaled iloprost appears to improve exercise capacity and quality of life but had no effects on hemodynamics after 24 weeks of treatment in a prospective, uncontrolled study[108]. Given that new formulations for these potent vasodilators are quite new, future controlled studies should shed more light on the efficacy of these agents in adults and children with APAH-CHD.

Conclusion

PAH in patients with CHD carry unique characteristics that differentiate them from other PAH patients. Treatment of pulmonary vascular disease in these patient require additional discussion on the treatment of their associated simple to complex cardiac defects. This provides difficulty in establishing standardized care for these patients and will likely require a more individualized approach to the care of APAH-CHD patients. Nonetheless, the prospects of targeted PAH therapy are exciting, and the treat-and-repair approach looks promising for some patients. The advent of modern therapy has improved survival and quality of life for not only PAH patients but also patients with APAH-CHD. However, discrepancies still exist and should warrant continued investigations and trials into the treatment of both adults and children living with APAH-CHD.

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Table 1

Nice 2013 World Symposium on Pulmonary Hypertension's Clinical Classification of Congenital Systemic-to-Pulmonary Shunts Associated with Pulmonary Arterial Hypertension

A. Eisenmenger syndrome	Includes all large intra- and extra-cardiac defects which begin as systemic-to-pulmonary shunts and progress with time to severe elevation of pulmonary vascular resistance (PVR) and to reversal (pulmonary-to-systemic) or bidirectional shunting; cyanosis, secondary erythrocytosis and multiple organ involvement are usually present.
B. Left-to-right shunts	• Correctable • Noncorrectable Include moderate to large defects; PVR is mildly to moderately increased systemic-to-pulmonary shunting is still prevalent, whereas cyanosis is not a feature
C. PAH with coincidental CHD	Marked elevation in PVR in the presence of small cardiac defects, which themselves do not account for the development of elevated PVR; the clinical picture is very similar to idiopathic PAH. To close the defects is contraindicated.
D. Post-operative PAH	Congenital heart disease is repaired but PAH either persists immediately after surgery or recurs/develops months or years after surgery in the absence of significant postoperative hemodynamic lesions. The clinical phenotype is often aggressive.

PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; CHD, congenital heart disease. Reproduced from[17] with permission.

Table 2

Dana Point 4th World Symposium on Pulmonary Hypertension’s Anatomic-Pathophysiologic Classification of Congenital Systemic-to-Pulmonary Shunts Associated With Pulmonary Arterial Hypertension

1 Type
1.1 Simple pre-tricuspid shunts
1.1.1 Atrial septal defect (ASD)
1.1.1.1 Ostium secundum
1.1.1.2 Sinus venosus
1.1.1.3 Ostium primum
1.1.2 Total or partial unobstructed anomalous pulmonary venous return
1.2 Simple post-tricuspid shunts
1.2.1 Ventricular septal defect (VSD)
1.2.2 Patent ductus arteriosus
1.3 Combined shunts (describe combination and define predominant defect)
1.4 Complex congenital heart disease
1.4.1 Complete atrioventricular septal defect
1.4.2 Truncus arteriosus
1.4.3 Single ventricle physiology with unobstructed pulmonary blood flow
1.4.4 Transposition of the great arteries with VSD (without pulmonary stenosis) and/or patent ductus arteriosus
1.4.5 Other
2 Dimension (specify for each defect if >1 congenital heart defect)
2.1 Hemodynamic Qp/Qs (ratio of pulmonary blood flow to systemic blood flow)
2.1.1 Restrictive (pressure gradient across the defect)
2.1.2 Nonrestrictive
2.2 Anatomic
2.2.1 Small to moderate (ASD $\le$2.0 cm and VSD $\le$1.0 cm)
2.2.2 Large (ASD >2.0 cm and VSD >1.0 cm)
3 Direction of shunt
3.1 Predominantly systemic-to-pulmonary
3.2 Predominantly pulmonary-to-systemic
3.3 Bidirectional
4 Associated cardiac and extracardiac abnormalities
5 Repair status
5.1 Unoperated
5.2 Palliated (specify type of operation[s], age at surgery)
5.3 Repaired (specify type of operation[s], age at surgery)

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Table 3

Nice 2013 World Symposium on Pulmonary Hypertension’s Criteria for Closing Cardiac Shunts in PAH Patients Associated With Congenital Heart Defects*

PVRi, Wood units/m^2	**PVR, Wood units**	**Correctable†**
<4	<2.3	Yes
>8	>4.6	No
4–8	2.3–4.6	Individual patient evaluation in tertiary centers

PVR, pulmonary vascular resistance; PVRi, pulmonary vascular resistance index.

*Criteria: the long-term impact of defect closure in the presence of pulmonary arterial hypertension (PAH) with increased PVR is largely unknown. There are a lack of data in this controversial area, and caution must be exercised.

†Correctable with surgery or intravascular nonsurgical procedure.

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