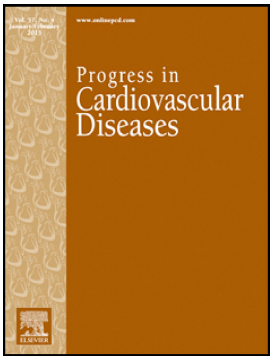

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Management of Heart Failure in Adult Congenital Heart Disease

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Abstract

Heart failure (HF) in the adult with congenital heart disease (ACHD) is associated with high morbidity and mortality and has been implicated as the leading cause of death in this patient population. The diagnosis of HF in ACHD involves a combination of clinical suspicion from subjective patient history, anatomic imaging, functional diagnostic studies, and rhythm evaluation. Once diagnosed, the approach to management of HF in this population varies widely and by lesion. Unfortunately, there is a paucity of literature available delineating the optimal management of these patients, making clinical decision-making extremely challenging. In this review, we aim to summarize available evidence to help guide the diagnosis and management of HF in ACHD.

Key Words: Heart Failure, Congenital Heart Disease, Fontan, Systemic right ventricle

Abbreviations:

ACE-I – angiotensin converting enzyme inhibitor

ACC - American College of Cardiology

AHA - American Heart Association

ACHD – adult congenital heart disease

ANP - atrial natriuretic peptide

ARB – angiotensin receptor blocker

BNP - brain natriuretic peptide

ccTGA – congenitally corrected transposition of the great arteries

CHF – congestive heart failure

CPET – cardiopulmonary exercise testing

CRT – cardiac resynchronization therapy

CT – computed tomography

CMR – cardiac magnetic resonance imaging

D-TGA – dextro-transposition of the great arteries

ETRA – endothelin receptor antagonist

ET-1 - Endothelin- 1

ESC - European Society of Cardiology

GDMT – guideline directed medical therapy

HF – heart failure

HFSA - Heart Failure Society of America

hsTnT - highly sensitive troponin T

LV - left ventricle or ventricular

MCS – mechanical circulatory support

NT-proBNP - N-Terminal pro-BNP

NYHA – New York Heart Association

PDE-5i – phosphodiesterase – 5 inhibitor

PH – pulmonary hypertension

PI – pulmonary insufficiency

PS – pulmonary stenosis

QoL-quality of life

RV – right ventricle or ventricular

TOF – Tetralogy of Fallot

Introduction

An estimated two-thirds of people with congenital heart disease are adults. This population continues to grow now that nearly 90% of infants born with congenital heart disease survive into adulthood[1,2]. With this aging population, the development of heart failure (HF) has become one of the most challenging sequelae of palliated congenital heart disease, often implicated as the leading cause of death in adults with congenital heart disease (ACHD)[3–7]. In a study by Zomer et al. using the Dutch CONCOR Registry, HF admissions occurred in 2.5% of the ACHD population and was associated with a 5-fold higher risk of mortality during a 21-year follow-up compared to ACHD patients who had no previous history of HF admissions[8].

The alarmingly high morbidity and mortality associated with HF in ACHD demands attention and current knowledge on its continuously evolving management. In this article, we provide a broad overview of available evidence to help guide the diagnosis and management of HF in ACHD.

Diagnosis of HF in ACHD

HF is characterized by pulmonary or systemic venous congestion and inadequate peripheral oxygen delivery that results from structural or functional cardiac diorders[9]. The diagnosis of HF in ACHD relies on a combination of clinical suspicion that arises from reported symptoms, anatomic imaging, functional studies, and rhythm evaluation.

Symptoms of HF in ACHD are typically related to underlying cardiac anatomy and can vary widely given the heterogeneity of ACHD lesions, outlined in Table 1. However, sub-normal peak VO2 during cardiopulmonary exercise testing (CPET) has been demonstrated in reportedly asymptomatic ACHD, which highlights the fact that even the absence of typical HF symptoms can be misleading in these particular patients[10].

Cardiac imaging plays an important role in diagnosing and guiding management of HF in ACHD. Echocardiography is one of the most utilized imaging modalities and can be used to monitor disease progression and provide assessment of intracardiac anatomy and overall cardiac function at rest and during exercise. ACHD imaging guidelines are readily available for echocardiographic evaluation of right ventricular (RV) volumes and RV function[11,12]. However, the limitations of echocardiography are often reached when attempting to evaluate structures outside the heart, and imaging quality is suboptimal in patients with poor acoustic windows. In these cases, computed tomography (CT) and cardiac magnetic resonance imaging (CMR) can be utilized, which allow for comprehensive imaging of the entire thorax. CMR does not expose patients to radiation and has found favor among both ACHD specialists as well as patients who were often exposed to radiation with prior imaging techniques. CMR has the comprehensive ability to provide quantitative assessment of blood flow, valvular regurgitation, chamber volumes, ventricular function, and has also been used as a tool in monitoring response to different therapeutic modalities[13]. Additionally, stress MRI is gaining popularity in ACHD, as it allows both anatomic and functional cardiac assessment during pharmacologic stress testing. Guidelines on the use of CMR in ACHD have been published by the European Society of Cardiology (ESC) and recommend that CMR services are available in centers that specialize in ACHD care[14]. As an alternative to CMR, cardiac CT can be used in the presence of epicardial pacing leads, implantable cardiac defibrillator leads, and other contraindications to the use of CMR. CT is also able to provide anatomic data and has superior image resolution when compared to CMR. Despite being limited by temporal resolution, CT can also be used to quantify ventricular volumes and assess ventricular function[15].

In addition, in the evaluation of functional status, CPET is often considered the gold standard for quantitative assessment of functional capacity in ACHD. Results from CPET have been found to correlate with New York Heart Association (NYHA) functional class, and the association between decreased functional capacity and anaerobic threshold with a slower maximal heart rate during CPET has been

demonstrated in individuals with ACHD compared to those without this condition[10,16]. Moreover, one study has shown that in patients with repaired Tetralogy of Fallot, CPET can highlight limitations in cardiac reserve and a diminished ability to increase cardiac output[17].

Asymptomatic ACHD have been found to have elevated levels of atrial natriuretic peptide (ANP), Brain-type natriuretic peptide (BNP), N-terminal pro-BNP (NT-proBNP), endothelin-1 (ET-1), norepinephrine, renin, and aldosterone at baseline compared to healthy individuals. The relationship between the degree of cardiac biomarker elevations and NYHA functional class and systemic ventricular function has been shown in several ACHD studies[18,19]. BNP has been traditionally used as a marker for systemic ventricular dilation in acquired heart disease. However, in ACHD, abnormal BNP levels are not always correlated with ventricular function, likely related to the heterogeneity of the variable cardiac diagnoses. Similar to acquired HF, BNP can be a marker of systolic function in the systemic RV, but in Tetralogy of Fallot, elevated BNP has been shown to correlate more so with severity of pulmonary regurgitation and RV end diastolic dimension[19]. The degree of NT-proBNP elevation also varies between ACHD lesions and has been found to be lowest in patients with coarctation of the aorta and highest in patients with Fontan circulation or a systemic RV[20]. NT-proBNP is useful with predicting functional status in ACHD, as increasing levels have been shown to correlate with decreasing exercise capacity and peak oxygen uptake during CPET[20].

Similar to BNP, cardiac troponin-T and highly sensitive troponin T (hsTnT) are expressed during cardiomyocyte injury and is extensively used the in the setting of acute coronary syndrome, hypertension, hypertrophic cardiomyopathy, and HF. Although elevated hsTnT is found in nearly 10% of stable ACHD patients, it is most frequently encountered in individuals with a systemic RV or elevated pulmonary artery pressure[21]. Previous studies involving ACHD have demonstrated an association between degree of hsTnT elevation and NYHA functional class, systemic systolic dysfunction, and the presence of non-sinus rhythm[21]. It has also proven to be a useful prognostic tool in ACHD with

pulmonary arterial hypertension, where elevated hsTnT has been associated with higher mortality rate compared to those with normal hsTnT levels[22].

A relatively newer cardiac biomarker, GDF-15, is a member of the transforming growth factor-beta family and has been found to be expressed in patients with hypertrophic and dilated cardiomyopathy. Elevated levels have been associated with a higher risk of cardiovascular disease (CVD) events and mortality, independent of left ventricular (LV) function, NYHA functional class, and levels of NT-proBNP and hsTnT[23,24,25]. Although a relationship between GDF-15 and ventricular dysfunction has not been found in ACHD, it has been associated with elevated pulmonary artery pressure, and decreased functional status and exercise capacity[26]. When GDF-15 levels are interpreted in concert with NT-proBNP and hsTnT, elevations in all three biomarkers can identify ACHD patients at highest risk for CVD events[27].

Medical HF Management – Lesion Specific

Guidelines published by the American College of Cardiology (ACC)/ American Heart Association (AHA)/Heart Failure Society of America (HFSA) and the European Society of Cardiology (ESC) on the management of HF in acquired heart disease are readily available. These recommendations emphasize the use of neurohormonal blockade with angiotensin converting enzyme inhibitors (ACE-i), angiotensin receptor blockers (ARB), and beta-blockers, which have proven morbidity and mortality benefits in HF[28,29].

Most recently, studies involving Sacubitril/Valsartan, a combination angiotensin receptor-neprilysin inhibitor, has resulted in favorable outcomes in quality of life and reduction in HF-associated hospitalizations and mortality in patients with HF with reduced ejection fraction (HFrEF) when compared to Enalapril[30–33]. Sacubitril/Valsartan has also been shown to be associated with a reduced rate of eGFR decrease when compared to Enalapril[34]. As a result of these promising findings, the ACC/AHA/HFSA HF

guidelines were updated in 2017 to include replacement of ACE-I or ARBs with Sacubitril/Valsartan as a Class I indication in symptomatic NYHA class II or III patients with systolic HF[35].

Although there may not be true ACC/AHA guidelines for the management of HF in ACHD, there were two major articles published in 2016 regarding HF in ACHD, an extremely comprehensive AHA Scientific Statement from Stout et al. in *Circulation*[36] and a position paper from the ESC by Budts et al[37]. Both of these articles provide excellent references, including extensive pathophysiology, diagnostic, and therapeutic options.

It is noteworthy that management of this complex ACHD population has largely been extrapolated from literature that is based on adults with acquired heart disease. General recommendations for risk factor modification with management of hypertension, lipids, and diabetes mellitus, weight reduction, and avoidance of tobacco and cardiotoxic agents can also be considered as beneficial in ACHD. However, given the heterogeneity of ACHD and the lack of large randomized controlled trials, caution should be taken to avoid generalizing available guidelines to this patient population[36].

Systolic Dysfunction in the Systemic LV

Aside from coronary artery disease, systolic dysfunction of the systemic LV in ACHD results from either volume loading lesions (aortic regurgitation, mitral regurgitation, patent ductus arteriosus, and ventricular septal defect) or pressure loading lesions such as subvalvar, valvar, and supravalvar aortic stenosis, and coarctation of the aorta.

Diagnostic testing with echocardiogram, CMR, or cardiac CT is helpful to diagnose and characterize lesions amendable to percutaneous or surgical correction. Guideline-directed medical therapy (GDMT) for HF can be beneficial to reducing morbidity and mortality in this patient population, and it is reasonable to apply the ACC/AHA HF guidelines to this group of patients[28,29].

Systolic Dysfunction in the Systemic RV

The RV is pyramidal-shaped and has a thin free wall. Predominantly composed of transverse fibers and longitudinally oriented subendocardial myofibers, the majority of RV ejection fraction results from longitudinal shortening. The RV architecture is ideal for responding to changes in volume load in the low-pressure, highly-compliant pulmonary system. In contrast to the RV, the LV is cylindrical and has a thick free wall. The left ventricular myofibers are arranged in helical fashion resulting in shortening, thickening, and twisting of the LV body along the long axis during ventricular systole[38,39]. These characteristics allow the LV to effectively function in the setting of a high pressure, low-compliance systemic circulation.

The systemic RV in a biventricular heart is seen with congenitally-corrected transposition of the great arteries (ccTGA) and Dextro-TGA (D-TGA) status-post the Mustard or Senning atrial switch operations. In the sub-aortic position, RV failure has been shown to develop in 67% of patients with ccTGA by the age of 45 years and in 12% of patients with D-TGA 12 years after undergoing the atrial switch procedure[40,41]. HF is the leading cause of death, occurring in up to 66% of patients with systemic RV[3].

Unfortunately, the effectiveness of GDMT in reducing morbidity or mortality in systemic RV failure has not been demonstrated. Although ACE-I has been shown to be safe for use in ACHD, no significant improvements in exercise peak VO2, tricuspid regurgitation, RV size, or RV systolic function have ever been demonstrated in these patients, despite some studies noting trends toward improved peak VO2 and a reduction in levels of NT-proBNP[42–44]. Studies involving ARBs have demonstrated a lack of benefit and no improvements in exercise capacity or NT-proBNP levels in the setting of a systemic RV[45].

Increased catecholamine levels have been demonstrated in patients with systemic RV, and elevation in concentrations of epinephrine and norepinephrine correlate with increased cardiothoracic ratio and RV diastolic dimensions[46]. Results of small studies have been promising, demonstrating improvements in quality of life (QoL) and NYHA functional class after initiation of beta-blockers in patients with a systemic RV, although the use of beta-blockers is limited by the inherently increased risk of sinus node dysfunction or atrioventricular nodal block[47]. In one study, patients with D-TGA and cardiac pacemakers who were on higher maintenance doses of beta-blockers demonstrated a significant improvement in NYHA functional class compared to those without cardiac pacemakers, suggesting potential dose-related benefits, although no significant improvements in RV size and systolic function were demonstrated[48].

Tachycardia-mediated cardiomyopathy is an important cause of systemic RV failure. In patients who have undergone atrial switch procedure for D-TGA, the incidence of arrhythmia increases over time, from nearly 78% arrhythmia-free survival at 10 years to only 36% at 25 years post procedure[49]. Therefore, it is important to be vigilant and assess for arrhythmias over the entire lifespan of these patients.

Systolic Dysfunction of the Subpulmonic RV

Although most commonly noted in patients with Tetralogy of Fallot (ToF), systolic dysfunction of the subpulmonic RV can develop in a variety of other cardiac lesions from right-sided volume and/or pressure loading. In addition to chronic pulmonary insufficiency (PI) seen in previously repaired TOF, volume loading of the RV can also occur with Ebstein anomaly and other lesions that result in left to right shunting such as anomalous pulmonary venous return, atrial septal defect, and rare cases of extra cardiac arteriovenous malformations. On the other hand, pulmonary stenosis (PS) and pulmonary

hypertension (PH) are the most common pressure-loading lesions that have the potential to result in subpulmonic RV failure.

Surgical or percutaneous intervention aimed at correcting these volume/pressure loading conditions (that is, PS or PI) offer the best chance of improving ventricular function, but the timing of such interventions is often debated. Pharmacologic therapy with pulmonary vasodilators (such as phosphodiesterase-5 inhibitors (PDE-5i), endothelin-receptor antagonists (ETRA), or prostacyclin analogs) form the basis of PH management, and diuretics can be effective for symptom management in the setting of significant RV volume loading [50]. The REDEFINE trial[51], a multicenter prospective randomized double-blind study did not demonstrate improvements in ventricular function, exercise capacity, NT-proBNP levels, or symptoms of right-sided HF with the use of Losartan compared to placebo in individuals with ToF. Similarly, there is a lack of evidence showing any benefits with the use of ACE-I and beta blockers in right-sided HF.

Fontan Failure

Fontan failure, either with depressed ejection fraction or with normal ejection fraction manifests in a wide variety of ways, summarized in Table 1. Chronic volume loading of the single ventricle, sudden volume offloading after Fontan, a personal history of multiple operations requiring cardiopulmonary bypass, long-standing cyanosis, and the absence of a sub-pulmonic pumping chamber may all contribute to the development of HF (often referred to as Fontan failure or the “failing Fontan” syndrome) in these hemodynamically-complex patients. It is still unclear why Fontan failure develops in some patients but not in others, despite similar anatomy and Fontan-type. The most common indications for hospital admission in Fontans have been found to be arrhythmia (22%), HF (20%), and cardiac surgery (16%) in a Mayo Clinic study, with the highest in-hospital mortalities seen in patients hospitalized for cardiac surgery (11%) and HF (8%)[52]. In the setting of suspected Fontan failure, complete

anatomic and functional assessment, in addition to cardiac catheterization in many cases, should be performed to evaluate for any correctable hemodynamically significant lesions including ventricular inflow or outflow obstruction, valve regurgitation, or anatomic obstruction to the Fontan circuit.

In the absence of a sub-pulmonary pumping chamber, the Fontan circulation is dependent on low pulmonary vascular resistance (PVR) and researchers are actively investigating ways to lower PVR in these patients. Of note, the Pediatric Heart Network is nearly finished with a RCT of udenafil (a PDE-5i) in Fontans, the first large trial of PDE-5i in Fontans. Several smaller studies evaluating the utility of sildenafil (another PDE-5i), have shown an increase in peak pulmonary blood flow, peak VO2, cardiac index, and stroke volume during exercise[53,54]. Additionally, increased ventricular end diastolic volume and decreased ventricular end-systolic volume on echocardiography and improvement in oxygen saturations (from a mean of 88% to a mean of 90%) have been shown after initiation of sildenafil[55]. Similar results have emerged in studies using bosentan (an ETRA), including improvements in functional class, exercise peak VO2, and increased CPET test time without the significant adverse effect of hepatotoxicity[56]. More recently studies involving newer generation pulmonary vasodilators in Fontans have been initiated.

Unfortunately, trials of neuro-hormonal blockade in Fontan failure have not shown much benefit. In a study of ACE-I use in failing Fontans, no improvements in cardiac index, exercise capacity, or diastolic filling patterns were demonstrated[57]. After initiation of beta-blockade in children and adolescents with failing Fontans, decreased requirements for diuretics were demonstrated in addition to increasing mean ventricular ejection fraction by 5%[58]. However, there are no large trials that show benefit from neuro-hormonal blockade in adult Fontan failure.

Adjunctive HF Therapies

Although HF management is primarily targeted at reducing associated morbidity and mortality, improving QoL and functional capacity are also important outcomes to strive for in HF in ACHD. Correction of iron deficiency, cardiopulmonary rehabilitation, and cardiac resynchronization therapy (CRT) are all valuable treatment options with evidence-based benefits.

Iron deficiency is associated with reduced QoL and increased morbidity and mortality in HF from acquired heart disease[59,60]. In congenital heart disease, iron replacement for individuals with iron deficiency has been associated with subjective improvements in QoL, reduction of HF symptoms, and increase in activity levels, in addition to quantitative improvements during 6-minute walk testing[61]. In children with congenital heart disease, treatment of iron deficiency with iron replacement has been shown to be safe and beneficial resulting in no increase in blood viscosity despite increase in hemoglobin/hematocrit, as well as improvement in oxygen saturations and decrease in symptoms of headache and visual changes[62].

Cardiopulmonary rehabilitation is another option that has proven benefit for symptomatic HF. The safety of cardiopulmonary rehabilitation in NYHA functional class III or IV HF was demonstrated in the HF-ACTION trial, which also showed a decrease in HF hospitalizations and all-cause mortality [63]. These findings were confirmed in a meta -analysis of 19 randomized controlled trials investigating the impact of exercise-based interventions in CHF patients, which showed reduction in HF hospitalizations and improvements in QoL[64]. Although historically, activity restrictions were generally placed on HF congenital heart disease patients, there is now growing evidence suggesting the safety of cardiopulmonary rehabilitation and exercise training in congenital heart disease[65]. Similar to studies involving adults with CHF and acquired heart disease, cardiac rehabilitation has been shown to improve QoL in ACHD as well[66]. Current literature suggests additional benefits including increased endurance capacity and exercise peak VO2, reduction of NT-proBNP levels, and improved event free survival in adults with HF and ACHD[67,68].

Additionally, CRT is an established treatment option utilized in adults with electrical dyssynchrony and symptomatic HF that is refractory to pharmacotherapy. It is based on the importance that ventricular interdependence plays in the pathophysiology of chronic HF. Results of CRT in HF from acquired heart disease have demonstrated significant improvements in LV function, exercise endurance, and QoL[69,70]. In ACHD, although it is still rarely performed, CRT has been found to improve BNP levels and NYHA function class. These findings are seen most notably in patients with a systemic LV and single ventricle physiology, but benefits when used in the setting of a systemic RV have not been demonstrated to the same extent[71,72].

Mechanical Circulatory Support (MCS) and Heart Transplantation(HT)

In many cases, implantation of MCS remains the only option in the management of end-stage HF in congenital heart disease. The use of MCS in ACHD is still relatively new, and few data on the type and optimal timing of MCS exist. The implantation of MCS in patients with ACHD can be technically challenging given often smaller patient size and less favorable anatomy, and currently there are no ideal options available for durable MCS in the failing Fontan with normal ejection fraction. Additionally, patients with ACHD are noted to have significantly higher mortality within the initial 5 months post-implantation of MCS and a lower probability of receiving a HT when compared to patients without ACHD[73]. MCS as a bridge to HT in ACHD has been associated with worse functional status, increased infection rate, and an increased need for ventilator support post-HT when compared to ACHD patients who did not require MCS[74]. Certainly, the higher morbidity and mortality seen in ACHD patients who require MCS suggests an overall sicker cohort with likely more advanced disease. As a result, there has been a growing trend towards earlier referrals for advanced HF evaluation and subsequent implantation of MCS in less critically-ill ACHD patients[75].

HT is feasible in the setting of ACHD. However, the complex intrathoracic anatomy frequently seen in ACHD is often a challenge and/or an exclusion by the medical review board at many HT centers. Multiple organ involvement due to long standing cyanosis and abnormal hemodynamics present additional risks to HT and are most often seen in patients with single ventricle physiology. Many of these patients face long wait times, high wait-list morbidity, and may require MCS as a bridge-to-HT. Despite these challenges, the largest study to date by Burchill et al[76], involving over 1800 ACHD post-HT patients, demonstrated better long-term survival at 10 and 15 years in patients with ACHD compared to non-ACHD (57% and 53% vs 53% and 37%, respectively).

Conclusion

The ACHD population continues to age, uncovering the natural (and unnatural) history of palliated ACHD. HF is the leading cause of morbidity and mortality in ACHD, but comprehensive guidelines on the management of HF in these patients have not yet been established. Caution should be taken when applying the adult HF guidelines to ACHD patients, since extensive data do not yet exist to verify the benefit of proven strategies to treat HF in these complex ACHD patients. Nonetheless, we should hope that evidence continues to grow and support new medical and surgical options in the diagnosis and management of HF in ACHD.

Conflicts of interest: Dr. Franklin is a consultant for Actelion US and Bayer.

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Table 1: Most Commonly Presenting Signs and Symptoms of Heart Failure in Congenital Heart Disease

	Contributing Cardiac Lesions	**Clinical Presentation/ Symptoms**
Failure of the Systemic Left Ventricle	*Volume Loading:* Aortic Regurgitation Mitral Regurgitation Ventricular Septal Defect Patent Ductus Arteriosus *Pressure Loading:* Sub aortic Stenosis Valvar Aortic Stenosis Supra valvar aortic stenosis Coarctation of the aorta	Pulmonary Edema, Dependent Edema, Persistent cough, Orthopnea, Decline in functional capacity
Failure of the Systemic Right Ventricle	Congenitally Corrected Transposition of the Great Arteries D-Transposition of the Great Arteries	Pulmonary edema, dependent edema, persistent cough, orthopnea, decline in functional status, chronotropic incompetence, atrial and ventricular tachyarrhythmia
Failure of the Sub-pulmonic Right ventricle	*Volume Loading:* Pulmonary regurgitation (i.e.: repaired Tetralogy of Fallot) Ebstein Anomaly Atrial Septal Defect Anomalous Pulmonary Venous Return Extra cardiac arteriovenous malformation *Pressure Loading:* Sub pulmonary Stenosis Valvar Pulmonary Stenosis Supra Valvar Pulmonary Stenosis Pulmonary hypertension/ Eisenmenger	Peripheral edema, exertional dyspnea, atrial and ventricular tachyarrhythmia *Erythrocytosis, progressive cyanosis/desaturation during exertion
Fontan Failure	Fontan Failure with Reduced Ejection Fraction (FFrEF) Fontan Failure with Preserved Ejection Fraction (FFpEF)	Protein losing enteropathy (diarrhea, hypoalbuminemia, electrolyte abnormalities), plastic bronchitis (expectoration of bronchial casts), Portal hypertension (ascites, abdominal distension), peripheral edema, Thrombus/pulmonary embolism/stroke, cyanosis, atrial and ventricular tachyarrhythmia

*symptoms pertaining to pulmonary hypertension/Eisenmenger