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Management of Heart Failure in Adult Congenital Heart Disease

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Keywords

Congenital heart disease; Heart failure; Systemic ventricle dysfunction; Single ventricle dysfunction; Fontan

INTRODUCTION

In the United States, children living with congenital heart disease (CHD) are outnumbered by adults with CHD (ACHD). Due to surgical and medical advances, it is now estimated that there are more than 1 million adults with CHD in the United States.[1,2] Advances in surgical technique, trans-catheter intervention, imaging modalities, and focus on high-quality multidisciplinary care teams has contributed to improved CHD survival. Recent studies have shown that the median age of patients with severe CHF has increased from 11 years in 1985 to 17 years in 2000, and the overall age at death increased from 37 years in 2002 to 57 years in 2007.[3] Improved survival to adult age and late adulthood translates to a population with both cardiac and extracardiac disease, and specialized care needs. In particular, heart failure (HF) is common in the adult patient with CHD. Adults with CHD experience more hospitalizations, episodes of decompensation, and ultimately have higher mortality than non-CHD cohorts.[4–6] Therefore, it is critical to understand the heterogenetic nature of HF in ACHD population, assessment and management across the spectrum of CHD, and treatment options, as well as current gaps in treatments available to this unique group.

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THE DISTINCT NATURE OF HEART FAILURE IN ADULT CONGENITAL HEART DISEASE

As CHD patients live to older age, the population becomes even more diverse because it includes patients who survived several percutaneous and surgical procedures in childhood, and adults who presented and were diagnosed later in life. Residual anatomic and hemodynamic lesions accompanied by acquired heart disease lead to an increasingly complex group of patients with varied presentation. HF, along with arrhythmia, sudden death, and late vascular complications are the most common late cardiac presentations in adults.[7]

Bolger and colleagues[8] described CHD as the original HF syndrome as "…characterized by a triad comprising cardiac abnormality, exercise limitation, and neurohormonal activation." The Heart Failure Society of America guidelines' define HF as "…a syndrome characterized by either or both pulmonary and systemic venous congestion or inadequate peripheral oxygen delivery, at rest of during stress caused by cardiac dysfunction."[9,10] In the CHD population, it is often difficult to stratify patients into common categories such as left-sided failure or right-sided failure. Standard functional class categorization is also difficult because it based on the premise that patients do not have structural abnormalities at baseline. For instance, the 2005 American College of Cardiology and American Heart Association guidelines recommend HF be divided into 4 subtypes: A, at risk for HF; B, structural heart disease without signs or symptoms; C, structural heart disease with previous or current symptoms; and D, refractory heart disease requiring advanced therapies.[11] One may wonder how CHD patients fit into this classification, which, despite updating in 2013, still did not account for the CHD patient with an underlying congenital cardiac defect. Guideline-level documents such as this are often not particularly helpful in the management of CHD patients because they amass data in the acquired HF population, which is often significantly different if not less well-studied than CHD patients.[9,12,13]

From an epidemiologic perspective, CHD patients do not fare as well as patients with HF from acquired forms of heart disease. Hospitalization rates in CHD patients with HF are higher (214 admissions/1000 adults) and the mean length of stay is longer (11.5 days in complex CHD vs 8 days in the acquired HF cohort).[14] The underlying anatomic defect and prior surgical interventions have been identified as independent risk factors for HF admission in CHD. When admitted for HF, CHD patients have a 5-fold higher risk of in-hospital mortality; death at 1 and 3 years post-HF admission was exceptionally high at 24% and 35%, respectively.[15]

Predictors of death due to HF include endocarditis, supraventricular tachycardia, ventricular tachyarrhythmia, conduction disturbances, pulmonary arterial hypertension, and myocardial infarction (hazard ratio 2–5; $P<.05$).[7] In 2 different European cohorts, HF has been shown to be the most common cause of mortality with the average age of death reported between 47 to 50 years of age.[7,16] As the CHD population continues to age, both outpatient and inpatient care for HF will continue to become among the most important aspects of managing these patients.[17–19]

ANATOMY DICTATES HEART FAILURE PHENOTYPE

HF in CHD is a broad topic that is often difficult to understand. It is easy to see why this may be the case, given the broad spectrum of CHD. Clinically, CHD is subdivided into categories based on the complexity of the structural lesions. Defects are classified as simple CHD, moderately complex CHD, or severely complex CHD. Published guidelines in the treatment of ACHD have indicated follow-up intervals for continued care based on the severity of underlying CHD[20] (Table 1). Prior interventions, including cardiac surgery, also play a role in the development of HF and late CVD risk; therefore, they are crucial to consider in caring for the ACHD patient. Given the heterogenous nature of CHD and palliative or surgical repair, the cause and presentation of HF in CHD is diverse. Some common themes in describing HF in this population include the side of the HF (subpulmonic ventricular vs subsystemic ventricular dysfunction),[21] cyanotic versus acyanotic HF, single ventricular failure, and pressure versus volume-mediated HF, among others.

ETIOLOGIC FACTORS OF CONGENITAL HEART DISEASE–HEART FAILURE

The mechanisms leading to HF in CHD are numerous and variable. Some potential causes include abnormal pressure or volume-loading of either the morphologic right ventricle (RV) or left ventricle, myocardial ischemia from either a supply demand mismatch or coronaries anomalies, ventricular hypertrophy, and constriction from prior sternotomy. Myocardial architecture must be considered in patients with CHD. Data suggest embryologic development of the right ventricular myocardium may be different from the left ventricle and more susceptible to dysfunction in lesions where the RV is the systemic ventricle.[9,22] Perfusion also seems to also be important as evidenced by the high prevalence of RV systolic function following the atrial switch operation in complete transposition.[23,24] Reduced right ventricular myocardial microvascular density of the septal wall is seen in complete transposition and in RV hypertrophy in tetralogy of Fallot patients. This seems to be related to a reduced myocardial perfusion reserve and impaired right ventricular systolic function.[25] It is likely that myocardial perfusion defects are a sensitive predictor of systemic ventricular impairment.[26] Similar to acquired heart disease, activation of natriuretic peptides, the sympathoadrenergic system, and the endothelin and renin angiotensin aldosterone system have been implicated to play an important role in CHD-HF.[27] Fibrosis and aberrant remodeling are also important deleterious processes important to HF in CHD.[28–30]

CLINICAL PRESENTATION AND EVALUATION

Presentation of HF in CHD can vary depending on anatomic and physiologic factors related to underlying anatomy and prior repair. Systolic function may not necessarily be the primary cause of HF in these patients. Typical HF symptoms, such as exertional dyspnea, fatigue, exercise intolerance, and signs of volume overload, although present may not always be dramatic. A comprehensive history and examination is critical in evaluation of this population. Special testing often involves imaging, such as transthoracic echocardiogram or cardiac MRI–computed tomography, to provide information about anatomic detail and function. Cardiopulmonary stress testing is an invaluable tool to assess functional capacity

and other vital information, such as chronotropic competence and oxygenation level with exercise. Patients with CHD exhibit lower than normal oxygen consumption per unit time (VO_2) in comparison with age-matched healthy cohorts[31,32] and, given that New York Heart Association status is not accurate in CHD, trends in peak Vo_2 and functional capacity are valuable. A rhythm monitor is also very important in CHD because arrhythmia and requirement for pacemaker are more common than in other forms of acquired heart disease.

MANAGEMENT OF HEART FAILURE IN CONGENITAL HEART DISEASE

In acquired HF, medical treatment is the cornerstone of management; however, the same therapy is not well-studied in CHD patients. Treatment typically focuses on correcting structural abnormalities and potentially reversing abnormalities. The management of arrhythmia is also critically important in the ACHD patient because it occurs in 15% of CHD patients and more than doubles the risk of HF.[33] Common late anatomic, physiologic, or arrhythmogenic problems, as well as available interventions in select moderate and severely complex ACHD patients, are reviewed in Table 2.

Medical Therapy

Traditional HF medications are not well-studied in the ACHD population (Table 3). Even with the lack of substantial data, there may be a role for these treatments because some of the mechanisms for HF overlap.[34] In general, one must consider all the indications for cardiac medications in these patients because there are often multiple reasons to use medications such as beta-blockers, diuretics, and angiotensin-converting enzyme inhibitors. Typically, patients with significant HF and ACHD are followed by both congenital heart specialists and HF specialists. This allows each team to provide expertise on the nature of CHD and recommended HF therapies, respectively. A reasonable approach to the clinical evaluation of some common ACHD-HF phenotypes is outlined in Fig. 1 with potential treatment considerations and strategies.

Mechanical Circulatory Support and Cardiac Transplantation

Advanced therapies for HF, which include the use of mechanical circulatory support (MCS), total artificial heart, and organ transplantation, are challenging in the CHD population owing to prior surgical repair, repeat sternotomy, nontraditional anatomy, elevated panel reactive antibodies, bleeding risk, hypercoagulability, and extracardiac disease secondary to CHD. Several studies have shown that up-front mortality is higher in the CHD population; however, long-term outcomes (>1 year posttransplant) are favorable.[35,36] The current organ allocation system is predicated on the sickest patients receiving listing preference. Unfortunately for many CHD patients, their anatomy may not be suitable for traditional measures for HF decompensation. In particular, this is true of the patient with a single functioning ventricle or Fontan that may have preserved systolic function but presents with congestive right-sided failure symptoms. There are only a handful of centers that have the resources and multidisciplinary teams required to care for these unique patients when MCS and transplant are considered.

SUMMARY

As the CHD population continues to age, managing late HF will continue to be an important part of long-term care. Important first steps in evaluating these patients are to consider prior anatomy and procedures, and to identify potentially reversible or treatable lesions. Device therapy, MCS, and transplant have a limited role in this population, and require evaluation by an experienced and specialized team.

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KEY POINTS:

- Children with congenital heart disease (CHD) are outnumbered by adults with CHD (ACHD).
- CHD–heart failure (HF) presentation differs based on anatomy and prior surgical repair.
- HF medical therapy is less well studied in CHD and needs to be considered in the context of CHD-related anatomy or physiology.
- The first step in evaluation of the adult CHD patient with HF is to examine the underlying anatomy for lesions with the possibility for intervention.
- Mechanical circulatory support and heart transplant in CHD is more complex secondary to anatomic limitations. These patients are at a disadvantage in the current allocation system.

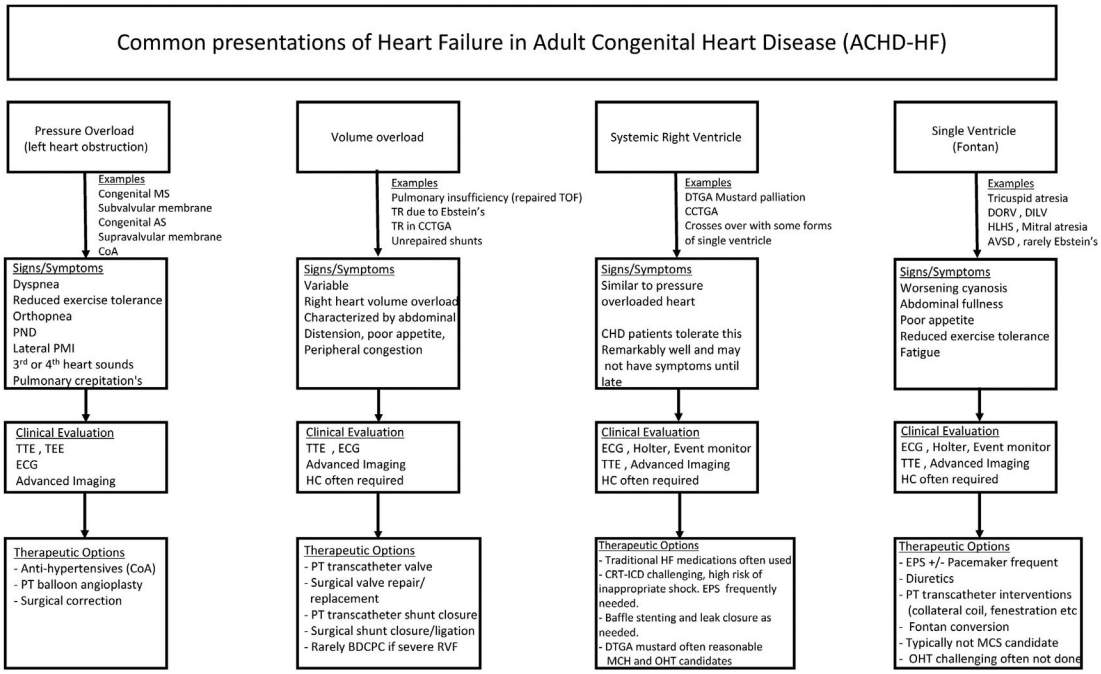

Fig 1.

Approach to managing HF in ACHD. Common presentations of ACHD-HF are outlined inclusive of example CHD lesions, signs, or symptoms; reasonable clinical evaluation or special testing; and potential therapeutic options. +/−, with or without; AS, aortic stenosis; AVSD, atrioventricular septal defect; BDCPC, bidirectional cavopulmonary connection; CCTGA, congenitally corrected transposition of the great arteries; CoA, coarctation of the aorta; CRT-ICD, cardiac resynchronization therapy–implantable cardiac defibrillator; DILV, double inlet left ventricle; DORV, double-outlet RV; DTGA, dextrotransposition of the great arteries; ECG, electrocardiogram; EPS, electrophysiology study; HC, hemodynamic catheterization; HLHS, hypoplastic left heart syndrome; MCS, mechanical circulatory support; MS, mitral stenosis; OHT, orthotopic heart transplant; PMI, point of maximum impulse; PND, paroxysmal nocturnal dyspnea; PT, percutaneous; RVF, RV failure; TEE, transesophageal echocardiogram; TOF, tetralogy of Fallot; TR, tricuspid regurgitation; TTE, transthoracic echocardiogram.

Table 1:

Complexity of adult congenital heart disease

Simple CHD	Moderate CHD	Severely Complex CHD
• Native disease ○ Isolated congenital aortic valve disease ○ Isolated congenital MV disease ○ Small ASD ○ Isolated small VSD ○ Mild PS ○ Small PDA	• Aorto-left ventricular fistulas • Anomalous pulmonary venous drainage • AVSD (partial or complete) • CoA • Ebstein anomaly • Infundibular RVOTO of significance • Ostium primum ASD	• Conduits • Cyanotic CHD (all forms) • Double-outlet ventricle • Eisenmenger syndrome • Fontan procedure • Mitral atresia • Single ventricle • Pulmonary atresia (all forms) • Transposition of the great arteries
• Repaired conditions (without residua) ○ Ligated or occluded PDA ○ Repaired VSD ○ Repaired secundum or sinus venosus ○ ASD	• PDA, not closed • Pulmonary valve regurgitation (moderate to severe) • Pulmonary valve stenosis (moderate to severe) • Sinus of Valsalva fistula or aneurysm • Sinus venosus ASD • Subvalvular AS or supra-AS • Tetralogy of Fallot • VSD with absent valves, AI, CoA, mitral disease, RVOTO, straddling TV or MV, sub-AS	• Tricuspid atresia • Truncus arteriosus, hemitruncus • Abnormalities of atrioventricular or ventriculoarterial connection NOS (ie, crisscross heart, isomerism, heterotaxy, ventricular inversion)

Abbreviations: AI, aortic insufficiency; AS, aortic stenosis; ASD, atrial septal defect; AVSD, atrioventricular septal defect; CoA, coarctation of the aorta; MV, mitral valve; NOS, not otherwise specified; PDA, patent ductus arteriosus; PS, pulmonic stenosis; RVOTO, right ventricular outflow tract obstruction; TV, tricuspid valve; VSD, ventricular septal defect.

Modified from Connelly MS, Webb GD, Somerville J, et al. Canadian consensus conference on adult congenital heart disease, 1996. Can J Cardiol 1998;14:395–452; with permission.

Table 2:

Common procedural and surgical interventions in moderate-severe adult congenital heart disease-heart failure patients

Late (Adult) Anatomic or Physiologic Problem		Intervention	
Tetralogy of Fallot	• PI • RV enlargement and dysfunction due to PI • RVOT obstruction, specifically if a conduit is present • High risk of VT and SCD	• Transcatheter pulmonary valve replacement • Balloon pulmonary valvuloplasty • Surgical pulmonary valve replacement or conduit replacement • EPS, VT ablation, ICD placement	
DTGA with atrial switch	• Baffle leak and/or stenosis in up to 25%[37, 38] • Baffle leak can impact ventricular volume and lead to volume-related HF, systemic desaturation, and paradoxic emboli • Atrial scarring leads to increased IART, and other atrial arrhythmias[39] • High risk of atrial arrhythmia degenerating to VT and SCD[40, 41] • High risk of chronotropic incompetence and need for pacemaker[42–44]	• Transcatheter baffle intervention (stent placement or occlusion of leak) • EPS with or without RFA, pacemaker, ICD placement	
CCTGA	• Tricuspid regurgitation may occur due to a dysplastic TV • Increased risks of heart block and need for pacemaker[20,45]	• Surgical pulmonary valve replacement • Surgical TV repair or replacement • EPS, pacemaker placement	
Ebstein anomaly	• Tricuspid regurgitation • RV enlargement and dysfunction • Atrial arrhythmias • Heart block • ASD often present	• Surgical TV repair or replacement • EPS, pacemaker placement • Transcatheter ASD closure	
Fontan palliation	• Fontan failure is common later in life • Up to 40% diagnosed with HF[46] • Residual fenestration or collateral formation → ↑ Fontan pressures → ↑ shunt → worsening hypoxia • Hemoptysis due to collateral formation • Fontan pathway leak • Branch pulmonary artery stenosis • High risk for atrial arrhythmias and heart block • Extracardiac disease: PLE, FALD, renal dysfunction, hematologic	• Transcatheter fenestration closure • Transcatheter collateral coiling • Transcatheter baffle puncture • Transcatheter pulmonary artery angioplasty and stenting • Surgical Fontan conversion • EPS with or without RFA, pacemaker placement	

Abbreviations: CCTGA, congenitally corrected transposition of the great arteries; DTGA, dextro-transposition of the great arteries; EPS, electrophysiology study; FALD, Fontan-associated liver disease; IART, intra-atrial reentrant tachycardia; ICD, implantable cardiac defibrillator; PI, pulmonic insufficiency; PLE, protein-losing enteropathy; RFA, radiofrequency ablation; SCD, sudden cardiac death; Side arrows, leads to; upward arrow, increased; VT, ventricular tachycardia.

Table 3:

Heart failure medication use in congenital heart disease patients

Diagnosis	Medications (Reference)	Important Findings
TGA, systemic RV	Beta blockers: Giardini et a I,[47] 2007; Shaddyetal,[48] 2007; Doughan et aI,[49] 2007; Bouallal et al,[50] 2010; Khairy et al,[41] 2017	• Positive RV remodeling[47] vs neutral or possible worsening function,[48] improved exercise duration,[47] improved NYHA functional class[49, 50] and QOL,[50] protective against appropriate shocks[41]
	ACE inhibitors: Therrien et al,[51] 2008; Hechteret al,[52] 2001; Robinson et al,[53] 2001; Tutarel etal,[54]2012	• No effect on RVEF, RVEDV and RVESV,[51] no improvement in exercise performance[52],[53] • Decreases NT-pro (BNP) levels[54]
	Angiotensin receptor blockers: Van der Bom et al,[55] 2013; Dore et al,[56] 2005; Lester et al, [57] 2001	• No effect on RVEF, QOL,[55] and exercise capacity[55,56] • During active treatment, systolic BP and degree of TR decreased and duration of exercise increased[57]
	Aldosterone receptor blockers: Dos etal, [58]2013	• Improvement of an altered baseline CTB profile suggesting reduction in myocardial fibrosis[58]
Tetralogy of Fa Not, subpulmonic RV	Beta blockers: Norozi et al,[59] 2007	• No effect on peak Vo_2 or ventricular function in patients with BNP >100 pg/mL and peak Vo_2 <25 mL/kg/min[59]
	ACE inhibitors: Babu-Narayan etal,[60]2012	• No improvement in RVEF[60]
	Angiotensin receptor blockers: Bokma etal (REDEFINE),[61] 2018	• No significant effect on RVEF, and secondary outcomes such as LVEF, peak aerobic exercise capacity, and NT-pro (BNP)[61]
Single ventricle circulation	Beta blockers: Ishibashi et al,[62] 2011	• Cardiothoracic ratio improved, dosage of furosemide reduced, and ejection fraction improved[62]
	ACE inhibitors: Hsu et al,[63] 2010; Kouatli etal,[64] 1997	• In infants, no improvement in somatic growth, ventricular function or HF severity; incidence of death and transplantation did not differ between groups[63] • No change in exercise capacity diastolic function, resting cardiac index, and SVR[64]
	Aldosterone receptor blockers: Mahle etal,[65] 2009	• Did not improve endothelial function or alter most serum cytokine levels[65]
	Phosphodiesterase inhibitors: Goldberg etal, [66] 2011 Endothelin receptor blockers: Hebert et al (TEMPO),[67] 2014; Schuuring etal,[68] 2013	• Increase in peak Vo_2 and improved exercise time and functional class[67] • No effect on peak Vo_2, NT-pro (BNP) level, and mental QOL[68] • Improved ventilator efficiency during peak and submaximal exercise but no effect on peakVo_2[66]

Abbreviations: ACE, angiotensin converting enzyme; APPROPRIATE, Ace Inhibitors for Potential Prevention of the Deleterious Effects of Pulmonary Regurgitation in Adults with Repaired Tetralogy of Fallot; BNP, brain natriuretic peptide; CTB, collagen turnover biomarker; LVEF, left ventricular ejection fraction; NT-pro (BNP), N-terminal pro (brain natriuretic peptide); NYHA, New York Heart Association; QOL, quality of life;

RVEDV, right ventricular end diastolic volume; RVEF, right ventricular ejection fraction; RVESV, right ventricular systolic; SVR, systemic vascular resistance; TGA, transposition of the great arteries (here includes DTGA with atrial switch and CCTGA); TR, tricuspid regurgitation.