Heart Failure in Adult Congenital Heart Disease

Luke J. Burchill, MBBS, PhD[a,b,*], Melissa G.Y. Lee, MBBS, PhD[a,c,d], Vidang P. Nguyen, MD[e], Karen K. Stout, MD[f]

KEYWORDS

• Cardiac defects • Cardiopulmonary exercise testing • Congenital heart disease • Fontan procedure • Heart failure • Right ventricle • Tetralogy of Fallot • Ventricular remodeling

KEY POINTS

- The burden of heart failure in adult congenital heart disease (ACHD) continues to grow and remains a formidable complication with high morbidity and mortality.
- Risk stratification and prognostication of heart failure in ACHD is challenging for many reasons including but not limited to the significant clinical heterogeneity within the ACHD population.
- Multi-modality investigations are indicated in all ACHD patients with suspected heart failure.
- Treatment of ACHD-related heart failure is guided by heart failure classification with early referral for advanced heart failure assessment.

CASE STUDY

Mr D is a 47-year-old man with D-transposition of the great arteries treated with a Mustard repair at age 2 years and transcatheter stenting of a superior vena cava baffle stenosis at age 35 years. He now presents to clinic with New York Heart Association (NYHA) functional class III symptoms, including fatigue, breathlessness with minimal exertion, weight gain, and poor sleep. Examination confirms a comfortable looking gentleman in no acute distress. He has a midline sternotomy scar and a body mass index of 30 kg/m^2 with 7-kg weight gain in the preceding 6 months. Blood pressure is 120/70 mm Hg, regular pulse at 70 beats per minute, and oxygen saturations 98% on room air. Jugular venous pulsation is 7 cm above the sternal angle. He has a 3/6 pansystolic murmur at the left lower sternal edge. Lung fields are clear to auscultation. His liver edge is palpable 3 cm below the right costal margin, and he has mild pitting edema of both legs extending to the knees. Electrocardiogram and Holter monitor show sinus node dysfunction with intact atrioventricular conduction. Transthoracic echocardiogram demonstrates a hypertrophied and dilated systemic right ventricle with moderately reduced ejection fraction (35%–40%) and moderately severe regurgitation of the tricuspid (systemic atrioventricular) valve, both rated as mild and stable 1 year earlier. There is no evidence of residual baffle stenosis or leak. The following questions arise: (1) What investigations are indicated in cases where adult congenital heart disease (ACHD)-related heart failure (HF) is suspected? (2) How do we classify ACHD-related HF and evaluate prognosis? (3) Which evidence-based treatments should be considered in this case?

[a] Department of Cardiology, The Royal Melbourne Hospital, Grattan Street, Parkville, Melbourne, VIC 3050, Australia; [b] Department of Medicine, The University of Melbourne, Melbourne, Australia; [c] Heart Research, Clinical Sciences, Murdoch Children's Research Institute, Melbourne, Australia; [d] Department of Paediatrics, The University of Melbourne, Melbourne, Australia; [e] Department of Cardiology, Cedars-Sinai Heart Institute, 127 S San Vicente Boulevard a3600, Los Angeles, CA 90048, USA; [f] Division of Cardiology, Department of Medicine, University of Washington, Seattle, WA 98195, USA
* Corresponding author. Department of Cardiology, The Royal Melbourne Hospital, Grattan Street, Parkville, Melbourne, VIC 3050, Australia.
E-mail address: blj@unimelb.edu.au

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INTRODUCTION

ACHD-related HF has often defied description or understanding leading to uncertainty surrounding the best approach to treatment. In recent years, research and clinical guidelines for ACHD-related HF have started to address these knowledge gaps leading to greater consensus on how to best assess and treat those presenting with ACHD-related HF. Even so, fundamental questions about ACHD-related HF remain. In this article we examine recent contributions to the field with a focus on ACHD-related HF research that translates into clinical practice.

HOW COMMON IS ADULT CONGENITAL HEART DISEASE–RELATED HEART FAILURE?

HF is a leading cause of mortality and morbidity in ACHD accounting for 21% to 40% of all ACHD deaths in large cohort and registry studies.[1–4] In a large study of 6969 ACHD patients, HF mortality increased exponentially over two decades while other causes of death remained relatively unchanged.[3] Among ACHD subgroups, HF is consistently reported as the leading cause of death in patients with moderate or complex congenital heart disease (CHD),[1,3,5–7] particularly in patients with Eisenmenger syndrome, systemic right ventricle, and single ventricle with Fontan palliation. ACHD-related morbidity also continues to rise with time. Population-based studies have demonstrated a dramatic increase in hospitalizations for ACHD-related HF in recent years.[8–10] Burchill and colleagues[8] analyzed data from approximately 8 million adult HF admissions in the United States between 1998 and 2011 and demonstrated a 91% increase in ACHD-versus a 21% increase in non-ACHD-related HF. ACHD-related HF hospitalizations resulted in significantly higher costs and procedural burden compared with non-ACHD HF hospitalizations.[8] Despite advances in care for the ACHD population, long-term survival and freedom from hospitalization remains significantly compromised by HF, particularly in those with more complex types of CHD.

DEVELOPING A COMMON LANGUAGE FOR CLASSIFYING AND REPORTING ADULT CONGENITAL HEART DISEASE–RELATED HEART FAILURE

The lack of a uniform definition for ACHD-related HF poses challenges not only for epidemiologic studies but also for developing clinical care and treatment guidelines. There is also a limited capacity to develop quality care indicators by which to track, compare, and harmonize ACHD-related HF care. Many, if not all, patients with ACHD meet criteria for having or being at increased risk of ACHD-related HF. The 2016 American Heart Association (AHA) Scientific Statement regarding Chronic HF in CHD defined CHD-related HF as a "syndrome characterized by either or both pulmonary and systemic venous congestion and/or inadequate peripheral oxygen delivery, at rest or during stress, caused by cardiac dysfunction…."[11] Most people born with complex congenital heart defects meet this definition for CHD-related HF at birth. Many have surgeries to repair their heart defects; however, they are not cured and late-onset complications are common. The ACHD AP classification system, first described in 2019, is intended to capture the complexity of ACHD anatomy and physiology, which are not always correlated.[12] Although not strictly for HF, the AP system offers a more integrated approach for classifying the severity of ACHD. Anatomic complexity is graded as I (simple), II (moderate), or III (great) and physiologic state is graded as stage A to D according to NYHA functional class, arrhythmia history, ventricular and valvular function, and the presence of end-organ dysfunction (see Table 4 of the 2018 AHA/American College of Cardiology [ACC] ACHD guidelines[12]). By making explicit the anatomic and physiologic variables at play, the AP classification system facilitates a more integrated and holistic approach to treatment.

NYHA classification is embedded within the ACHD AP classification system. It is worth noting that NYHA functional class alone has been found to predict disease severity and mid- to long-term ACHD mortality.[13] However, large cohort studies have shown that reduced exercise capacity and oxygen delivery (on cardiopulmonary testing [CPET]) is not uncommon in NYHA functional class I ACHD patients.[14,15] Thus, a combination of subjective (NYHA functional class) and objective (CPET) evaluation is important for identifying patients with asymptomatic ACHD-related HF.

Clinical stages of HF can also be classified using the ACC/AHA staging system (**Table 1**).[16] Largely for patients with acquired (ie, non-congenital forms) HF, the system purposefully guides clinicians on how to escalate treatment as HF progresses. Stage A patients are considered at risk of HF caused by comorbid conditions (e.g. hypertension, diabetes) and/or family history of HF. Stage B patients are those with existing structural heart disease or left ventricular systolic dysfunction. As such, most patients with ACHD fall into stage B and are considered pre-HF. Many patients with ACHD meet criteria for stage C because of the presence of clinical HF symptoms and a smaller

Table 1
Clinical stages and treatment of heart failure

ACC/AHA HF Classification System	Treatment Recommendations
Stage A Pre-HF. Family history of HF or increased HF risk based on the presence of the following medical conditions: Hypertension Diabetes CAD Metabolic syndrome History of alcohol abuse History of rheumatic fever Family history of cardiomyopathy Medications associated with cardiomyopathy	Regular exercise Stop smoking Low-sodium diet Treatment of hypertension Treatment of high cholesterol Abstinence of alcohol or recreational drugs Consideration of: ACE-I or an ARB for patients with CAD, diabetes, or hypertension β-Blocker for hypertension
Stage B Pre-HF. Left (systemic) ventricular systolic dysfunction on cardiac imaging (ie, echocardiogram or cardiac MRI) but without HF symptoms	Treatments as listed in stage A plus: Consideration of ACE-I/ARB β-Blocker if EF <40% or a history of MI Aldosterone antagonist if history of MI, diabetes, and EF ≤35% Exclusion of significant CAD, valvular or residual CHD requiring intervention
Stage C Diagnosis of HF with current or prior symptoms of HF	Treatments listed in stage A and B plus: Diuretics Daily weight Fluid restriction Consideration of device therapy, CRT, and/or ICD in selected patients
Stage D Advanced HF symptoms unresponsive to treatment	Treatments listed in stages A to C plus evaluation of candidacy for: High-risk heart surgery in a specialized CHD center Heart transplant Mechanical circulatory support Palliative care

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CAD, coronary artery disease; CHD, congenital heart disease; CRT, cardiac resynchronization therapy; EF, ejection fraction; HF, heart failure; ICD, implantable cardiac defibrillator; MI, myocardial infarction; MRI, magnetic resonance imaging.

Adapted from Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;62:e147-239.

subset of ACHD patients are classified as stage D based on advanced HF symptoms not responsive to treatment. Stage D HF describes advanced progression of HF characterized by structural abnormalities of the heart and severe resting symptoms despite optimal medical, surgical, and device therapy. The ACC/AHA classification system guides clinicians on which HF treatments to consider across each stage of HF.[16] Despite the lack of evidence for standard HF treatments in ACHD, certain treatments (β-blockers, renin-angiotensin aldosterone system antagonists, device therapies) may be justified according to ventricular function, blood pressure, hemodynamic profile (ie, systemic vascular resistance and ventricular afterload determined at the time of cardiac catheterization), and comorbidities (e.g. hypertension, diabetes, kidney impairment). It is important to ensure there are no other contributors to HF for which treatment would improve symptoms or ventricular function. Considerations include physiologic abnormalities such as valve dysfunction and residual shunts, or anatomic abnormalities such as coarctation of the aorta which increase afterload. Rhythm abnormalities are common in ACHD and also need to be assessed, because tachyarrhythmias or bradycardia can contribute to HF symptoms.

CLINICAL PRESENTATION OF ADULT CONGENITAL HEART DISEASE–RELATED HEART FAILURE

Many patients with ACHD have adapted to their underlying condition and consider reduced functional capacity to be their baseline.[14,15] A significant number of ACHD patients subjectively report having no limitations despite objective (CPET) evidence to the contrary. As such, worsening of NYHA functional class in patients with ACHD is significant and should prompt further evaluation, particularly given the association between NYHA functional class and worse clinical outcomes in this population.[17]

The clinical presentation of ACHD-related HF is highly variable and atypical. It is difficult to distinguish whether the symptoms are a cause or a manifestation of HF. Examples include atrial arrhythmias in patients with atrial switch for transposition of the great arteries or ventricular arrhythmia in patients with tetralogy of Fallot. In fact, in patients with tetralogy of Fallot, ventricular arrhythmia has been associated with myocardial fibrosis, elevated left ventricular end-diastolic pressure, and diastolic dysfunction on echocardiographic parameters.[18–20] These are all examples of the significant overlap between HF and arrhythmia in ACHD.

Other HF manifestations are idiosyncratic and manifest in patients with a Fontan circulation. These distinctive manifestations may include abdominal pain and diarrhea with protein-losing enteropathy and dyspnea with plastic bronchitis. Although the development of protein-losing enteropathy and plastic bronchitis is rare affecting up to 11%[21,22] and less than 5%[23,24] of patients with a Fontan circulation, respectively, these complications are extremely debilitating and carry high rates of hospitalization and mortality.[25,26] Because of the variety in manifestations, clinicians should have a low degree of suspicion for initiating investigation for ACHD-related HF, even in patients reporting subtle changes in functional capacity or other HF symptoms.

PROGNOSTICATION IN ADULT CONGENITAL HEART DISEASE–RELATED HEART FAILURE

Risk stratification and prognostication of HF in ACHD is challenging for many reasons. Significant clinical heterogeneity within the ACHD population makes it difficult to translate research findings from one subgroup to another. For reasons that are unclear, there is also significant variation in the clinical trajectory of HF, even among patients with the same CHD subtype and surgical repair.

Ventricular Dysfunction

ACHD HF may not be directly related to ventricular dysfunction and is reflected in the weaker association between ventricular dysfunction and B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) in ACHD compared with HF in acquired heart disease. Importantly, the risk of ventricular dysfunction varies according to CHD lesion complexity. Patients with a systemic right ventricle, such as those who have undergone an atrial switch procedure for transposition of the great arteries,[27,28] are at high risk of systemic ventricular systolic dysfunction. In contrast, patients with single ventricle physiology may manifest clinical features of systemic venous congestion as a reflection of the inherent limitations of the Fontan circulation rather than a direct reflection of ventricular systolic dysfunction.[29] Regardless, the finding of ventricular dysfunction is prognostically important and at least moderate ventricular dysfunction indicates a higher risk of sudden cardiac death in the ACHD population[30] and in subgroups including those with a systemic right ventricle[27,31–33] and in patients with repaired tetralogy of Fallot.[34]

Cardiopulmonary Exercise Testing

CPET includes assessment of exercise capacity and ventilatory gas exchange during exercise and is widely used in the follow-up of patients with ACHD.[35] It is essential that results obtained during CPET are referenced against patients with the same underlying ACHD lesion subtype because of inherent differences in baseline exercise tolerance between different subgroups.[14,15] A summary of CPET measurements and thresholds for predicting mortality and/or adverse outcomes by ACHD subtype is presented in **Table 2**. Peak oxygen consumption (V_{O_2} max) is of prognostic importance because lower peak V_{O_2} has been independently associated with hospitalization and mortality in mixed ACHD patient cohorts[14] and within certain ACHD subtypes.[15] A recent systematic literature review reported peak V_{O_2} to be an inconsistent predictor for mortality in the Fontan population.[36] Peak V_{O_2} has also been proposed for the assessment of perioperative risk and early mortality in patients with tetralogy of Fallot undergoing surgical pulmonary valve replacement.[37] Although peak V_{O_2} is widely used at the time of ACHD and HF assessment, CPET provides further important information. This includes measures of ventilatory efficiency, exercise oscillatory ventilation (EOV), heart rate reserve, and peak exercise blood pressure. Ventilatory efficiency is expressed as the minute

Table 2
CPET thresholds for predicting mortality and/or adverse outcomes by ACHD subtypes

ACHD Subtype	Outcome
Tetralogy of Fallot	Peak Vo_2 predictor of early mortality after surgical pulmonary valve replacement[37] VE/VCO_2 slope >31 predictor of all-cause mortality[38]
Systemic right ventricle	VE/VCO_2 slope $\geq$35.4 and peak Vo_2% $\leq$52.3% associated with an increased 4-y risk of death/hospitalization (cohort of d-TGA with Mustard/Senning repairs)[39] Lower peak exercise SBP, especially <180 mm Hg, associated with adverse clinical events (d-TGA with Mustard/Senning repairs and cc-TGA)[44]
Ebstein anomaly	Peak Vo_2 (<60% of predicted) and heart rate reserve (<25 bpm) predictors of death/hospitalization/cardiac surgery[43]
Fontan physiology	Peak Vo_2 inconsistent predictor for mortality in systematic literature review[36] Available cutoffs suggestive to be predictive of mortality: Peak Vo_2 <21.0 mL/kg/min[69] Peak Vo_2 <16.6 mL/kg/min[40] VE/VCO_2 slope >33.5[40] Peak heart rate <122.5 bpm[40] Change in peak Vo_2 ($-$3% points/y) and change in peak heart rate ($-$4% points/y) predictor of 5-y risk of cardiovascular adverse events[70] Presence of EOV associated with higher risk of death or transplant[45]

Abbreviations: EOV, exercise oscillatory ventilation; SBP, systolic blood pressure; TGA, transposition of the great arteries; VCO_2, volume of exhaled carbon dioxide; VE, minute ventilation; Vo_2, maximal oxygen uptake.

ventilation carbon dioxide production relationship (VE/VCO_2 slope). An elevated VE/VCO_2 slope greater than 30 is a powerful prognostic marker of HF. An elevated VE/VCO_2 slope is inversely related to cardiac output at peak exercise and is at least partly explained by a decrease in pulmonary perfusion. ACHD patient studies have demonstrated VE/VCO_2 slope to be independently predictive of hospitalization and/or mortality.[38–40] In fact, the combined use of VE/VCO_2 and peak Vo_2 has been demonstrated to have a higher predictive value than the use of either measurement alone.[39] Measures of heart rate and blood pressure response to exercise can also be assessed by CPET. Failure to achieve at least 80% of the heart rate reserve (the difference between the resting and maximum heart rate) is widely viewed as a cutoff for chronotropic incompetence or the inability of the heart to respond to exercise.[41] Chronotropic incompetence is seen in up to two-thirds of patients with ACHD and has been associated with NYHA functional class, hospitalization, and mortality.[42] In patients with Ebstein anomaly, heart rate reserve has been demonstrated to be a significant predictor of adverse outcomes.[43] In addition, lower peak exercise systolic blood pressure, especially less than 180 mm Hg, has been associated with clinical events in patients with systemic right ventricle.[44] Although all CPET measurements require maximal effort tests for accuracy, EOV is assessed on submaximal CPET tests. EOV signifies regular oscillations in minute ventilation during exercise and is thought to be caused by abnormal respiratory autoregulation. EOV is a common phenomenon in patients with Fontan physiology affecting more than a third of patients and has been demonstrated to be an independent predictor of mortality or transplantation in the Fontan population.[45]

Natriuretic Peptides

Although BNP and NT-proBNP are often elevated at baseline in asymptomatic patients with ACHD, there is growing evidence that these biomarkers may be helpful for evaluating disease severity. Studies exploring NT-proBNP and survival outcome have demonstrated worse survival in patients with higher versus lower NT-proBNP.[46,47] Among 595 ACHD outpatients followed for a median of 42 months, those in the highest quartile of NT-proBNP values (>33.3 pmol/L) had event- and heart-failure-free survival of only 35% and 72% at 50 months, respectively, compared with 87% and 99% in patients in the lowest NT-proBNP quartile (<6.8 pmol/L).[47] A normal NT-proBNP (<14 pmol/L) had a high negative predictive value thereby making it a useful screening

tool for ruling out HF and death.[47] The risk of an adverse event could be further categorized with the addition of additional biomarkers, namely high-sensitivity troponin-T and growth-differentiation factor 15.[47] Patients who had elevated levels of all three biomarkers were at highest risk of cardiovascular events.[47] In another prospective study, red cell distribution width was associated with adverse cardiovascular outcome in patients with ACHD independent of NT-proBNP.[48]

Heart Failure Prediction Models

There are scarce studies exploring prediction models for HF in ACHD. One of the earliest HF prediction models used in ACHD is the Seattle HF Model. The Seattle HF Model combines age, sex, weight, cardiac medication use, NYHA functional class, systolic blood pressure, systemic ejection fraction, laboratory values, and presence of a device to predict mean, 1-, 2-, and 3-year survival.[49] Seattle HF Model is used to identify patients at risk for adverse events in the ACHD population but the predicted mortality risks have been shown not to be representative of actual ACHD survival.[50] Baggen and colleagues[51] published a prediction model for a composite end point of mortality, HF, or arrhythmia in 602 patients with moderate or complex ACHD and were able to distinguish between high- and low-risk patients by incorporating similar clinical variables including age, body mass index, congenital lesion, NYHA functional class, cardiac medication use, reinterventions, and NT-proBNP. The prediction model was then externally validated in a different ACHD population of 402 patients and was able to discriminate between patients with and without an adverse outcome within 4 years of follow-up.[51] A systematic review exploring risk factors for adverse outcomes in ACHD-related HF[17] confirmed the literature for risk factors and prediction models in ACHD-related HF is scant. Not surprisingly, CHD lesion characteristics, NYHA functional class, and BNP were predictive of adverse outcome in ACHD-related HF.[17] Further research that includes large populations with well-defined clinical HF phenotypes is needed before prediction models are used to reliably guide ACHD HF care in daily clinical practice.

INVASIVE HEMODYNAMIC EVALUATION

Because of the unique and highly complex anatomy of patients with CHD, invasive cardiac catheterization is an integral part in the diagnosis and management. Information that is gathered from an invasive catheterization includes filling pressures; measures of vascular resistance; shunt fraction; and angiographic assessment of arterial and venous anatomy, anastomoses, and collateral vessels.

Pulmonary hypertension is common in patients with ACHD with and without HF. Pulmonary arterial hypertension is defined as mean pulmonary artery pressure by right heart catheterization greater than or equal to 25 mm Hg, pulmonary capillary wedge pressure less than or equal to 15 mm Hg, and pulmonary vascular resistance (PVR) greater than or equal to 3 Wood units. To calculate PVR one must first determine the transpulmonary gradient, the difference between the mean pulmonary artery pressure and the pulmonary capillary wedge pressure. By dividing transpulmonary gradient by cardiac output one can estimate the PVR. A common pitfall in patients with ACHD is to rely on automatically derived estimates of PVR without accounting for intracardiac shunting or careful consideration of the accuracy of cardiac output and the methods being used to derive it.

Cardiac output is most commonly determined by two methods: the Fick calculation and thermodilution. The Fick calculation is based on the principles that oxygen content diffuses through an area at a rate that depends on the difference in concentration between two points. However, in the presence of intracardiac shunting the flow for the pulmonary circuit (Qp) and the flow of the systemic circuit (Qs) must be calculated. The Qp assesses the difference between the pulmonary venous and arterial blood and Qs assess the difference between the systemic and mixed venous blood. The degree of shunting is typically expressed as the ratio between the Qp and Qs. A shunt is considered hemodynamically significant when Op/Qs ratio is greater than 1.5:1.[11] However, a normal Qp/Qs ratio does not rule out the presence of shunting because bidirectional blood flow can make this value look normal. When shunt closure is being considered, it is important to first determine the PVR. Although a patient may be hypoxic from right-to-left shunting, those with a PVR greater than 6 Wood units are not suitable for shunt closure because it may predispose them to right ventricular failure caused by the lack of a “pop off.” Certain tools, such as automatic cardiac flow monitors, are less likely to be accurate in the CHD population.[52]

Invasive hemodynamic assessment is informative in patients with a Fontan circulation presenting with features of systemic venous congestion or other HF symptoms. Failing Fontan physiology is characterized by high central filling pressures and low cardiac output.[53] The lack of a contractile

subpulmonic ventricle leads to a reliance on preload and passively pulmonary flow to propel blood to the systemic ventricle. Any increase in PVR leads to a decline in cardiac output. Longstanding nonpulsatile flow in the pulmonary bed leads to endothelial dysfunction and nitric oxide dysregulation, which increases the risk of developing pulmonary vascular disease.[54] Chronically reduced preload also leads to remodeling and diastolic dysfunction of the systemic ventricle. With the lack of validated noninvasive testing, routine cardiac catheterization remains necessary in the assessment of PVR and cardiac output in patients with Fontan physiology.[55] Although echocardiography is important in the surveillance of cardiac structure and function, Doppler cardiac output has only been shown to have a moderate correlate with the Fick cardiac output.[56]

ADVANCED HEART FAILURE TREATMENT

A growing number of patients with ACHD are presenting with advanced stage D HF.[7,57] With the lack of evidence-based methods of prognostic surveillance, clinical deterioration is rapid and unexpected. Because of patient complexity, the unpredictable clinical course of ACHD-related and the need for extensive multidisciplinary review and discussion, early referral for advanced HF is recommended.[11,58] The clinical flow of patients with CHD presenting with HF is provided in Fig. 1. This should occur before the development of irreversible end-organ dysfunction.

In addition to requiring more time for invasive hemodynamic assessment, imaging, and subspecialist review, patients with ACHD and families often need more time to align their expectations with those of the advanced HF team. Many patients with ACHD report being told they would not survive beyond childhood or following a major surgery. The sense that they have already "defied the odds," can feed into an altered perception of risk and mortality. Additionally, the transition from a pediatric to an adult medicine care team restarts the process of establishing trust between providers, the patient, and their family. Difficult conversations frequently arise at the time of

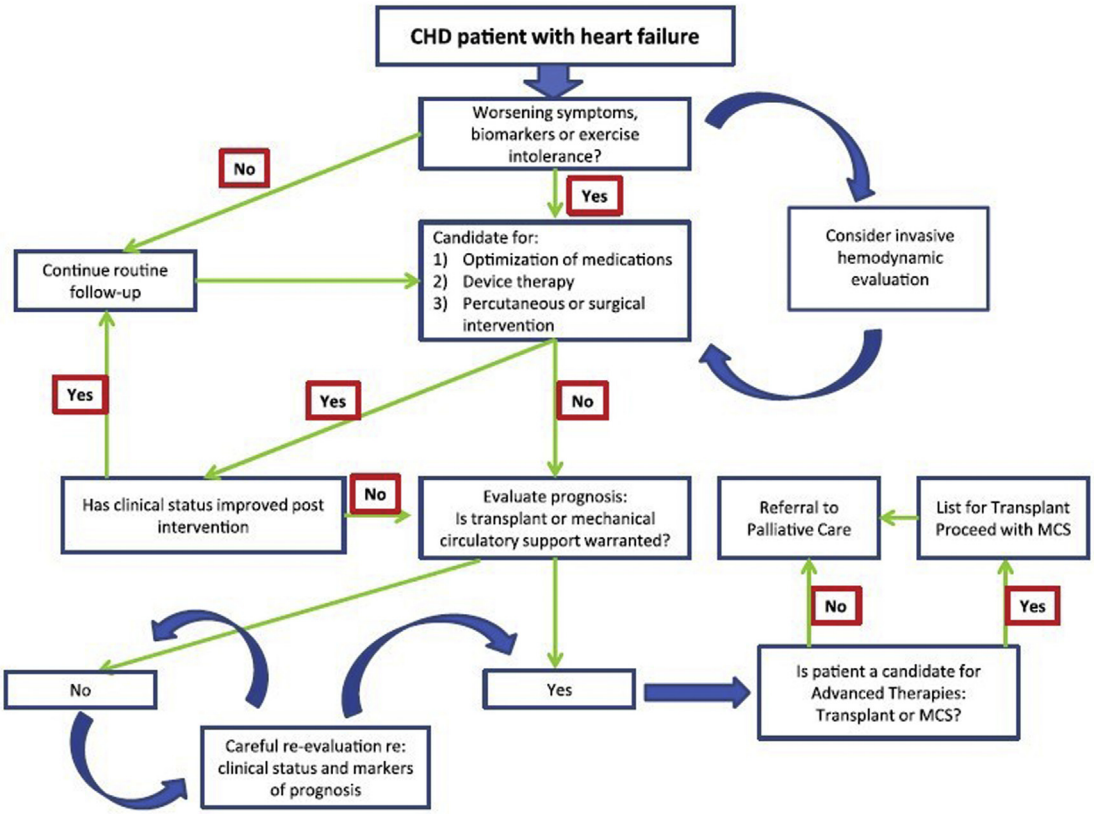

Fig. 1. Clinical flow of patients with CHD presenting with symptomatic and advanced HF. CHD, congenital heart disease; MCS, mechanical circulatory support. (*Reprinted with permission from* Ross HJ, Law Y, Book WM, Broberg CS, Burchill L, Cecchin F, et al. Transplantation and Mechanical Circulatory Support in Congenital Heart Disease: A Scientific Statement from the American Heart Association. Circulation. 2016;133:802-20 ©2016 American Heart Association, Inc.)

advanced HF assessment including whether to pursue high-risk interventions or proceed with advanced HF treatment options, such as mechanical circulatory support (MCS) or transplantation. Time is needed to introduce to patients and families the option of palliative and symptom-driven care as an alternative to high-risk treatments.

Heart transplantation remains the treatment of choice for eligible patients with severe advanced HF including those with end-stage ACHD-related HF. Suggested indications for heart transplantation in CHD are given in **Box 1**. Over time, the proportion of heart transplantations performed in patients with ACHD has increased.[58–60] Between 1999 and 2010 the prevalence of heart transplantation among patients with ACHD increased 41%.[61] Between 2015 and 2018, more than 200 adult patients with CHD were transplanted in the United States[59] with approximately 40% having univentricular anatomy.[60] Patients with ACHD are a high-risk group for transplant because they have undergone multiple prior sternotomies, have a significantly higher risk of allosensitization, may have occult pulmonary hypertension, and often have end-organ dysfunction including renal and liver disease.[62] Consequently, CHD is an independent risk factor for increased 1-year post-transplant mortality.[63,64] Risk factors for early mortality include long ischemic time, high PVR, redo transplantation, and Fontan physiology.[61,65,66] For those who survive the high-risk early postoperative period, survival is actually superior to those without CHD with a median survival of more than 20 years compared with 14 years in those with ischemic heart disease.[67] This may be caused by the lower incidence of cardiovascular comorbidities, such as diabetes and atherosclerotic disease, in this younger population.

The use of MCS devices for patients with advanced stage HF has also increased over time.[60] Given the anatomic complexity of ACHD, this group of patients may not experience similar benefits from durable MCS as patients without ACHD. This is in large part caused by a greater need for biventricular support[68] but other factors also increase mortality risk. Using the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) database to compare patients with and without ACHD undergoing MCS, VanderPluym and colleagues[68] found patients with ACHD had significantly higher mortality post-MCS exclusively during the first 5 months after implant and a lower probability of receiving a transplant. Risk factors for early mortality were biventricular or total artificial heart device implant and age greater than 50 years.[68] However, outcomes in patients with ACHD who are suitable for left ventricular assist device (LVAD) support

Box 1
Suggested indications for heart transplantation in ACHD

Patients with stage D HF refractory to medical therapy who will not benefit significantly from surgical, interventional, or electrophysiologic intervention

Patients with CHD with associated near-sudden death or life-threatening arrhythmias refractory to all therapeutic modalities

Patients with stage C HF associated with reactive pulmonary hypertension and a potential risk of developing fixed, irreversible elevation of pulmonary vascular resistance that could preclude orthotopic heart transplantation in the future

Stage C HF associated with systemic ventricular dysfunction in pediatric patients with previously repaired or palliated CHD when HF is associated with significant growth failure attributable to the heart disease

Pediatric patients with CHD with normal ventricular function when the following anatomic and physiologic conditions are present and not amenable to surgical intervention:

- Severe stenosis (stenoses) or atresia in proximal coronary arteries
- Moderate-to-severe stenosis or insufficiency of the atrioventricular or systemic semilunar valves
- Symptomatic arterial oxygen desaturation (cyanosis) that is not considered amenable to surgical correction
- Persistent protein-losing enteropathy despite optimal medical-surgical therapy

Abbreviations: CHD, congenital heart disease; HF, heart failure.

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seem to be comparable with patients without ACHD. The finding of equivalent survival among patients with ACHD treated with LVAD support, regardless of ventricular morphology, suggests LVAD is an option for those with end-stage HF, biventricular anatomy, and predominant systemic ventricular systolic dysfunction. Careful surgical planning is warranted because most modern day LVADs were designed for a morphologic left (systemic) ventricle.

In contrast, little is known about the use of temporary MCS, such as the intra-aortic balloon pump and Impella (Abiomed, Danvers, MA), in patients with ACHD who present with cardiogenic shock. With the unique anatomic challenges and lack of evidence to their use, most centers refrain from using short-term mechanical support. This proves to be a disadvantage in patients considered for heart transplantation in the United States, where listing status is based on the degree of hemodynamic support needed with higher priority given to those with temporary MCS devices (status 1 and 2). The new allocation system changes by United Network of Organ Sharing in 2018 addressed this disadvantage by giving higher priority to patients with CHD (status 4). However, the added challenges of allosensitization, elevated surgical risk from prior sternotomies, and need for CHD expertise at the transplant center makes the path to heart transplantation arduous and difficult for patients and providers alike. The key to success is an early referral to an advanced HF team so that a multidisciplinary care team can address many of these risk factors early.

RETURN TO CASE STUDY

Returning to Mr D, the 47-year-old man with D-transposition of the great arteries treated with a Mustard repair at age 2 years and transcatheter stenting of a superior vena cava baffle stenosis now presenting with NYHA functional class III symptoms with fatigue, dyspnea, and poor sleep, with clinical features of volume overload.

What Investigations Are Indicated When Adult Congenital Heart Disease–Related Heart Failure Is Suspected?

The following investigations are indicated in all patients with ACHD presenting with suspected HF: electrocardiogram, transthoracic echocardiogram, chest radiograph, and blood tests assessing for modifiable factors that may aggravate HF and/or indicate end-organ damage. Measurement of NT-proBNP or BNP and cardiopulmonary exercise testing (including respiratory function tests) further assist in guiding disease severity and prognostication. Modifiable factors that are evaluated with blood tests include anemia, iron deficiency, thyroid dysfunction, infection, ischemia, and vitamin deficiencies (ie, vitamin D, thiamine) when indicated. Blood tests for end-organ dysfunction includes kidney and liver function tests. Elevated NT-proBNP or BNP confirms significant ventricular dysfunction, provides prognostic information,[46,47] and may be helpful in tracking response to treatment in some patients with HF. In this case, Mr D had evidence of end-organ dysfunction with mild kidney impairment (glomerular filtration rate 70 mL/min/1.73 m^2) and a congestive hepatopathy with normal bilirubin but mildly elevated glutamyl transpeptidase, and alkaline phosphatase. NT-proBNP was moderately elevated at 400 pg/mL (normal <125 pg/mL). Mr D underwent a sleep study that confirmed moderate to severe obstructive sleep apnea. On CPET, Mr D exercised for 10 minutes, 11 seconds with anaerobic threshold achieved early. Blood pressure response and oxygen saturations were normal throughout. Peak oxygen uptake (V_{O_2}) was reduced at 19 mL/kg/min (52% predicted) with a blunted peak heart rate response (127 bpm [65% predicted]) indicating chronotropic incompetence. The O_2 pulse response was blunted and plateaued at 69% predicted indicating reduced stroke volume response to exercise. The VE/VCO_2 slope was abnormal at 33.

How Do We Classify Adult Congenital Heart Disease–Related Heart Failure?

To promote consistent classification and communication, we support the use of the ACHD AP classification system and the ACC/AHA classification systems (**Fig. 2**). Using our case study as an example, Mr D would be classified as ACHD AP classification IIIC and ACC/AHA HF classification stage C. Alignment between the staging systems is evident and the use of both systems enables consistent communication with ACHD and HF specialists.

Which Evidence-Based Treatments Should Be Considered in This Case?

HF classification guides treatment of ACHD-related HF. As previously discussed (see section on developing a common language for classifying and reporting ACHD-related HF and **Table 1**), all patients with ACC/AHA HF classification stage C HF should be given lifestyle and dietary advice with commencement of diuretics for fluid retention and consideration of afterload reducing angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers and β-blockaders.

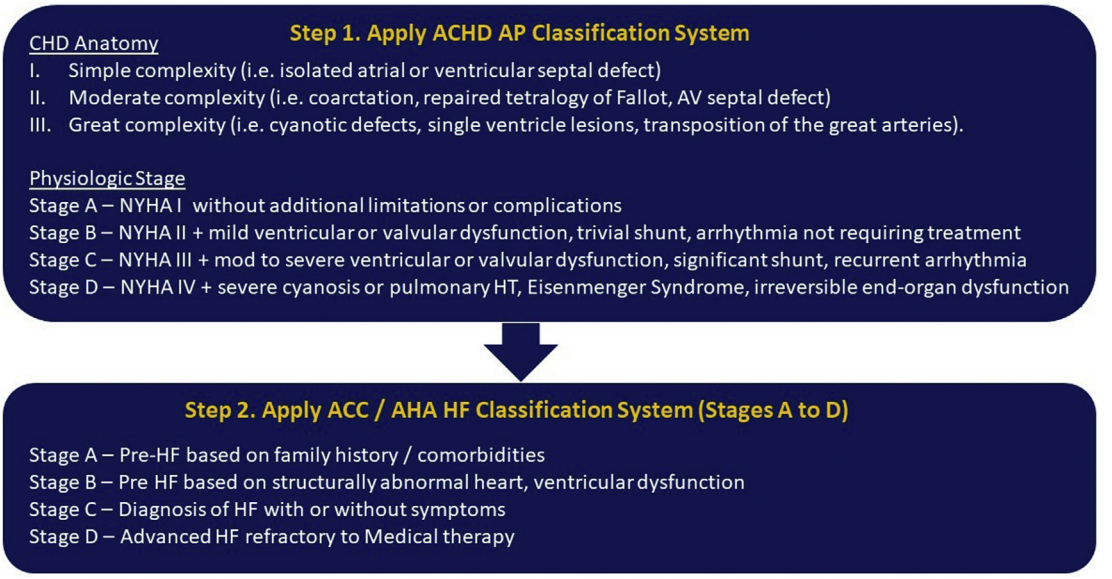

Fig. 2. Two-step application of the ACHD AP and ACC/AHA HF classification systems is recommended when evaluating patients with ACHD-related HF. AV, atrioventricular; CHD, congenital heart disease; HT, hypertension; NYHA, New York Heart Association.

Aldosterone antagonists may also be considered. Mr D was enrolled in cardiac rehabilitation and provided with a written HF action plan that included recommendations for physical activity, daily weights, and fluid and salt restriction. Oral frusemide 40 mg daily and oral ramipril 2.5 mg daily were commenced with initial weekly followed by monthly and then 3-monthly review of kidney function. A low-dose long-acting β-blocker was trialed but ceased because of worsening chronotropic incompetence and fatigue. He has been scheduled for a full heart study to exclude pulmonary hypertension and to guide optimization of medical therapy. Progression to refractory stage D HF will prompt early referral for advanced HF assessment and review of treatment options including MCS, heart transplantation, advanced care planning, and palliative care.

SUMMARY

As the population of patients with ACHD ages and grows, so too does the burden of ACHD-related HF. Despite the advances in medical and surgical therapies over the last decades, ACHD-related HF remains a formidable complication with high morbidity and mortality. There are ongoing challenges in determining the true burden of ACHD-related HF because of a lack of consensus definition of HF and an absence of population-based registries with clearly defined ACHD and HF cohorts. This challenge is further compounded by inherent differences in the natural course and outcomes of ACHD-related HF within and across its subtypes. In recent years, research and clinical guidelines for ACHD-related HF have started to address these knowledge gaps leading to greater consensus on how to best assess and treat those presenting with ACHD-related HF. High-quality studies focused on ACHD-related HF are required to better identify predictors of HF and to improve surveillance and management of this challenging condition.

DISCLOSURE

The authors have nothing to disclose.

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