



Heart failure in adults with congenital heart disease: a narrative review

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Abstract: The number of adults with congenital heart disease (ACHD) has increased over the last decades due to advancements in medical care, including interventional and surgical therapies. We are therefore more frequently challenged by the long-term consequences of palliative or corrective surgery carried out during childhood. Although patients with ACHD may develop conditions related to general cardiovascular risk factors, such as coronary artery disease, the most common complications leading to morbidity and mortality are arrhythmias, heart failure and thromboembolic events. For the management of arrhythmias, current recommendations regarding ablation and device therapy must be considered, whilst also taking into account the anatomical limitations of their congenital heart defect or surgical pathways. Heart failure treatment in acute and chronic settings must also consider the particular anatomy present, including the nature of the systemic ventricle. Treatments strategies for ACHD are typically extrapolated from the respective guidelines in non-ACHD patients, despite a lack of evidence to support this strategy. Right heart failure can be especially challenging to manage in conditions where either a systemic right ventricle or shunt lesions resulting in volume and/or pressure loading of the right ventricle are present. All physicians and cardiologists in particular should be acquainted with the most common diseases in ACHD, their complications and management regime, especially with regards to heart failure as this is a common reason for acute presentation in the emergency department.

Keywords: Congenital heart disease; heart failure; management; systemic ventricle

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Introduction

The number of patients with adults with congenital heart disease (ACHD) is constantly increasing due to advances in the medical and surgical treatment options improving the outcome of children with complex congenital heart disease (1-4) (*Figure 1* regarding epidemiology of ACHD patients). Current guidelines and other evidence suggest that treatment should be performed by trained physicians (1,2,4) with appropriate infrastructure for the specialised care for these patients (5-7).

The number of patients with ACHD has increased by about 50% compared with the number of children with congenital heart defects since the beginning of the new millennium (8-11). Currently adult patients account for about two thirds of all patients with congenital heart disease (12) and this change in demographics is resulting in a mortality shift from infancy to adulthood (5,13). Patients with complex cardiac disease after palliative or corrective surgery can present with the surgical sequelae of heart defects (2,4-6,14-16). The most common defects resulting in emergency hospitalisation of the patient are the univentricular heart, followed by tetralogy of Fallot, common arterial trunk, and discordant connections such as transposition of the great arteries following Senning or Mustard operations and congenitally corrected transposition of the great arteries (5,6,14-16). Frequent reasons for admittance to the emergency department are arrhythmias, as well as heart failure (HF), thromboembolic complications resulting in stroke or pulmonary embolism and non-cardiac causes (2,4-6,16).

This manuscript aims to describe the most common diseases in detail to elucidate diagnostic, treatment and management strategies for patients with ACHD.

Objectives

This review summarizes the aetiology, diagnostic process and treatment of heart failure in ACHD patients. In addition, the most recent guidelines were included, accomplishing the goal of a better treatment algorithm. Further a focus of the review is to give examples of special situations which are often encountered in ACHD patients presenting with heart failure like treatment with cardiac resynchronization therapy or potential treatment with a ventricular assist device. We present the following article in accordance with the NARRATIVE REVIEW reporting checklist (available at [http://dx.doi.org/10.21037/cdt-20-](http://dx.doi.org/10.21037/cdt-20-632)

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Methods

Literature search

A literature search was performed in PubMed covering publications up to April 2020. The following combinations of keywords were used: heart failure and CHD, morbidity and mortality in ACHD, guidelines heart failure and ACHD, guidelines diagnostic and treatment of patients with congenital heart disease. These search terms had to be identified anywhere in the text in the articles. The authors as well did choose literature depicting the current guidelines or multicenter trials, however most of the literature are of observational studies and guidelines for patients with ACHD have the evidence level of expert opinion.

Both qualitative and quantitative studies were considered to elucidate the use of the different aspects regarding congenital heart disease, anticoagulation and combination of both. The search was restricted to original research, humans, and papers published in English at any date. All abstracts were reviewed to assess whether the article met the inclusion criteria. After this selection process, a manual search of the reference lists of all eligible articles was performed. Two authors (i.e., EZ and CS) assessed independently the methodological quality of the qualitative and quantitative studies prior to their inclusion in the review.

Epidemiology of heart failure (HF) in ACHD

Patients with ACHD and complex cardiac anatomy are prone to develop HF over the course of their lives, especially those with a univentricular circulation. Signs of HF have been reported in about 22% of adults with transposition of the great arteries (TGA) following an atrial switch (Senning or Mustard operation), 32% of adults with congenitally corrected transposition (ccTGA) and 40% of adults following Fontan completion (17,18). In patients with ACHD, HF is responsible for about 20% of mortality, often during early adulthood (19). Current clinical guidelines may not be directly applicable to this complex cohort of patients due to a lack of evidence (18,20,21). For the treatment of patients with ACHD who develop HF, it is important to assess if there are any residual hemodynamic lesions such as a shunt or atrioventricular valve regurgitation (22,23).

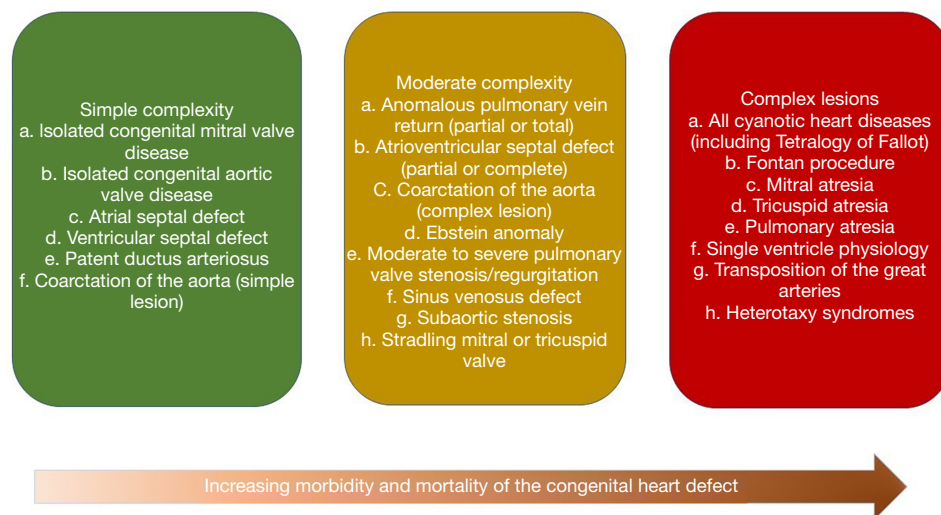


Figure 1 Complexity of congenital heart disease with prevalence of the disease. Prevalence of complex lesions is increasing due to a better survival in patients with moderate or complex congenital heart disease.

Limitation of exercise capacity in patients with ACHD and heart failure

Patients with ACHD often do not present with the same symptoms as other patients with HF (17,18,20,24) as they have already adapted to living with impaired physical exercise tolerance. It is therefore important to gain objective evidence from cardiopulmonary exercise testing to detect a decline in physical exercise tolerance in order to identify patients who may benefit from therapeutic interventions and those at risk of an adverse outcome (25,26). Many patients with congenital heart defects will have impaired peak oxygen consumption, this is due to multiple factors including inadequate cardiac reserve, poor heart rate response to exercise, raised pulmonary pressures upon exercise, poor pre-conditioning, or even due to restrictions recommended by physicians.

Comorbidities and anatomic variations predisposing to heart failure

Systemic right ventricle

In patients with TGA following an atrial switch, hypoplastic left heart syndrome following the Norwood operation, and uncorrected ccTGA, the morphologic right ventricle is in the systemic circulation. The morphologic right ventricle is a thin-walled structure with only two muscle layers, compared with three layers in the morphologic left ventricle, and is heavily dependent on loading conditions,

especially changes in afterload (18,20,22,23); it is therefore unable to sustain the pressure generation required to pump blood around the systemic circulation and over time is predisposed to fail. Additionally for the development of heart failure the presence of a trileaflet tricuspid valve rather than a bileaflet mitral valve is significant. These patients frequently develop tricuspid regurgitation which exacerbates heart failure symptoms, especially in Ebstein-like tricuspid dysplasia, which is the most common cardiac abnormality related to ccTGA (22,23,27).

Pulmonary vascular disease

Evaluation of the pulmonary circulation is of paramount importance in patients presenting with subpulmonary RV failure and those with a Fontan circulation (17,22,23). Pulmonary arterial hypertension (PAH) is common in ACHD as a result of anatomic heterogeneity and requires careful characterisation to target specific medical treatments addressing PAH, whilst misclassification can be deleterious for patients assessed for heart transplantation (17,22). Most patients with ACHD and PAH have WHO (World Health Organization) group 1 PAH, with a pulmonary vascular resistance (PVR) of ≥ 3 Wood units. Some may have pulmonary hypertension WHO class 2 with an increased pulmonary wedge pressure, whilst others, especially those with TGA or ccTGA, may have components of both pre- and postcapillary pulmonary hypertension which are most commonly related to WHO

class 2 or 5 (17,28). Postcapillary pulmonary hypertension can arise due to a failing systemic right ventricle in case of ccTGA or TGA after atrial switch procedure and precapillary pulmonary arterial hypertension can be associated with shunt lesions or abnormalities of the pulmonary vasculature (4,17).

Meticulous assessment of the hemodynamic status is crucial to determine whether a patient would require from lung transplantation in addition to heart transplantation (17). In patients with ACHD, development of pulmonary hypertension is associated with a 2-fold increase in all-cause mortality (17).

Shunts, collaterals and baffles

During the assessment of patients with complex CHD, it is important to consider the presence or persistence of shunts and collaterals as these may cause additional volume and/or pressure load. Pre-tricuspid shunt lesions, e.g., atrial septal defect, result in volume loading on the pulmonary circulation whilst post-tricuspid shunt lesions, e.g., ventricular septal defect and patent ductus arteriosus, cause volume loading of the left ventricle that may lead to a decline in left heart function. In a Fontan circulation, a spontaneous or surgically created fenestration may cause right-to-left shunting with arterial desaturation (22). Patients with TGA after atrial switch procedure show an impaired capacitance and conduit function of the baffles (29) and so a fast heart rate, such as during atrial fibrillation with a fast ventricular response, is not well tolerated, with reduced diastolic ventricular filling causing decreased cardiac output, that may even lead to cardiogenic shock (22,29). The baffles in patients with Fontan circulation are prone to narrowing or developing stenosis resulting in filling disorders of the single ventricle (4).

Heart failure management in ACHD and specific considerations

The number of patients with ACHD presenting to the emergency department with heart failure symptoms increases with the age and survival of the patients (9-11,18). Concerning the treatment strategy it has implications whether the anatomy of the patients is related to a morphologic left or right ventricle in the systemic circulation, whether the sub-pulmonary right ventricle is impaired, or whether the patient has a Fontan circulation

(18,30,31). HF in patients with ACHD is often complicated by comorbidities resulting from the initial palliative or corrective surgical procedure. Frequently impaired renal function or haematological disorders with increased haematocrit due to chronic systemic cyanosis can be observed. In patients with a Fontan circulation, chronically elevated pressure in the systemic venous pathways and hepatic veins leads to hepatic enlargement, progressive fibrosis and even cirrhosis and in some cases hepatocellular carcinoma (18).

Diagnosis of HF in patients with ACHD

Knowledge of the underlying congenital heart defect as well as the history of previous surgeries and interventions is crucial for the diagnosis of HF in ACHD. The change in symptoms might be subtle, a common first symptom being the onset of arrhythmia (18). Besides the need for a regular work-up with ECG and imaging including advanced imaging modalities like cardiac magnetic resonance imaging or computer tomography, two cornerstones for diagnosis are laboratory testing including N-terminal pro-B-type natriuretic peptide (NT-proBNP) and cardiopulmonary exercise testing (CPET). Two challenges for diagnosis are the symptomatic patients with normal systemic ventricular function and the asymptomatic patient with impaired function of the systemic right ventricle. In these two constellations a decrease of peak oxygen consumption by 25% in CPET or two-fold increase of NT-proBNP during 6 months of follow-up are indicators to start treatment (18).

An important difference to other current HF guidelines is the threshold of the ejection fraction being <40% before medical treatment is recommended (18). ACHD patients with heart failure and an anatomical left ventricle as systemic ventricle with a reduced ejection fraction <40% are treated with the same medication as recommended in non-ACHD patients (18). Most commonly renin-angiotensin-aldosterone-system blockers are used in addition to beta-blockers, mineralocorticoid receptor antagonists and diuretics or digoxin. If the failing ventricle is an anatomic right ventricle the medication is only used in symptomatic patients (18). Patients with a single ventricle are handled the same way. These patients are treated with the suggested medication if the ventricle is an anatomic left ventricle irrespective of symptoms and in case of an anatomic right single ventricle only if the patient is symptomatic (18).

Treatment of HF in ACHD

Patients with impaired function of the systemic left ventricle are often treated according to the ESC guidelines on HF (18,21). Most commonly the treatment includes therapy with an ACE-inhibitor, AT-1 receptor blocker or beta-blocker, as well as diuretics for symptomatic relief.

In patients with a systemic morphologic right ventricle, HF is likely to develop over time since the anatomy and geometry of the right ventricle are not adapted to generate the needed perfusion pressure for the systemic circulation (18,30). Whilst clear evidence for recommendations is lacking, asymptomatic patients with a failing systemic right ventricle are often treated with beta-blockers. However, symptomatic patients are treated analogous to patients with a failing morphologic left ventricle (18). If the sub-pulmonary morphologic left or right ventricle is compromised, no treatment is recommended in asymptomatic patients, but in the presence of symptoms, a combination of diuretics can provide symptomatic relief (18).

For patients with a functionally univentricular heart who have been palliated with a Fontan circulation, the presence of HF symptoms in conjunction with impaired ventricular function indicates the need for treatment and symptom relief, with no difference in approach to those with a systemic morphologic left or right ventricle (18). The largest benefits have been reported from reducing pulmonary vascular resistance with specific therapy such as phosphodiesterase inhibitors, or reducing afterload with beta blockers, whilst diuretics are only recommended if fluid overload is present (18).

Treatment of acute heart failure in patients with ACHD

Currently there are no specific guidelines for the treatment of patients with ACHD and acute heart failure (AHF), hence treatment recommendations are based on those for the general heart failure population, with a specific focus on comorbidities or anatomic variations present. Patients with ACHD and advanced HF may also be considered for ECMO therapy or ventricular assist device therapy as a bridge to destination therapy, if available and appropriate (18,21-23).

Heart failure therapy in patients with ACHD needs to take into account the individual anatomic circumstances and frequent comorbidities complicating therapy for an individual patient. Optimal outcomes are achieved when these patients are managed by specialist ACHD teams

(17,24).

Device treatment with intra-cardiac cardioverter defibrillator (ICD) in patients with ACHD and heart failure

Evidence for the use of an ICD in patients with ACHD is limited and is frequently based on expert opinion as the most commonly derived data on ICD use in ACHD is from observational studies (4,32-34). In general, the indications as outlined in the current ESC guidelines regarding ICD indications for secondary prevention can be extrapolated to ACHD (32-34). Patients with repaired tetralogy of Fallot, TGA following atrial switch, and uncorrected ccTGA are reported to have a high incidence of ventricular arrhythmias and are often candidates for ICD implantation in the context of secondary prevention (32-34). Regarding primary prevention, guidelines concur that patients with ACHD fulfilling the current ICD criteria with a left ventricular ejection fraction <35%, biventricular physiology, optimally treated heart failure, and NYHA symptom class II or III, are candidates for ICD implantation (32-34). However, appropriate selection of candidates remains challenging, weighing the benefits against the potential risks of infection or venous obstruction due to intravascular lead placement (32-34) as well as the potential technical challenges posed in patients with complex anatomy.

Cardiac resynchronization therapy (CRT) in patients with ACHD

The efficacy of CRT varies in patients with ACHD according to the underlying disease and anatomic substrate and whether a systemic morphologic left, right or functionally univentricular heart is present (32,34). Whilst reported data in ACHD is mostly derived from observational studies, CRT has a class I indication in patients with a systemic morphologic left ventricle and who fulfil the same indication criteria for CRT as non-ACHD patients (34,35). However, even if the systemic ventricle is a morphologic right ventricle, CRT can be considered if the ejection fraction is <35%, the ventricle is dilated, the patient displays NYHA class II to IV (ambulatory) symptoms, and a complete right bundle branch block with a QRS complex ≥ 150 msec is present (34,35). An additional important potential indication for CRT in patients with ACHD is the presence of a pacing threshold >40% during exchange of a pre-existing device or if a high pacing threshold is

anticipated (34,35). Reports of patients with ACHD who are potential candidates for heart transplantation improving their functional status after CRT implantation to the extent that they can be removed from the transplant waiting list, suggests that CRT indications should be reviewed in the ACHD population (34,35).

Ventricular assist devices: special considerations in patients with ACHD

Considering the rising number of patients with ACHD and the increase in HF in this population, there is a need to evaluate additional treatment options. Among the novel therapies developed for HF, durable mechanical circulatory support in the form of ventricular assist devices (VADs) can function as a bridge to transplantation. These devices have been shown to decrease mortality in end-stage HF among non-transplant candidates and appear to offer a similar benefit to transplant candidates who are deteriorating whilst awaiting transplantation (21,36). For VAD implantation, patients should be considered according to whether they have a systemic morphologic left or right ventricle or a functionally univentricular heart. In the largest study to date, more patients with ACHD required biventricular ventricular assist or a total artificial heart than non-ACHD patients, and they more often had concomitant dysfunction of the subpulmonary ventricle (either morphologic left or right ventricle) and pulmonary hypertension than their non-ACHD counterparts (36). Patients with ACHD had higher rates of mortality and adverse events than non-ACHD patients in the study, but the increased mortality rate was attributable solely to the higher use of biventricular ventricular assist devices and total artificial hearts. Conversely, the two groups who had VAD implantation to support the systemic ventricle alone, demonstrated similar survival regardless of cardiac anatomy (36).

Heart transplantation in patients with ACHD

In advanced HF, listing for heart transplantation is the ultimate option for disease management (21). However, patients with ACHD frequently have numerous adverse features including pulmonary arterial hypertension and other advanced organ involvement, such as liver disease in patients with Fontan circulation, resulting in a high waiting list mortality (17,37). Patients removed from the waiting list have an especially poor prognosis as they cannot be bridged to transplantation with a VAD or have severe HF with

multi-organ failure most commonly involving the liver and/or kidneys (37,38). During transplant assessment in patients with ACHD, a comprehensive anatomic and hemodynamic assessment is warranted to identify potentially correctable residual lesions from the original congenital heart defect and subsequent surgical or catheter procedures (17). Patients with moderate or complex congenital heart disease are closely screened and potential candidates for transplantation can be identified early, before multi-organ involvement prohibits potential listing. Until the definition of clear guidelines for the management of these patients, they should be screened especially carefully at a centre familiar with transplantation in congenital heart disease (4,18).

Summary

Heart failure is one of the most common causes of death in the increasing number of patients with ACHD. These patients frequently have impaired function of the cardiovascular system, but often do not present early because they have adapted to living with impaired function from childhood. Thus rigorous follow-up of patients with ACHD is necessary, especially for those who have had palliative surgery or with underlying complex lesions. Current guidelines support the use of imaging, cardiopulmonary exercise testing and biomarkers as key investigations in disease progression monitoring. Treatment is based on the extrapolation of current knowledge from acquired heart disease in patients with systemic left ventricular dysfunction, even though the stabilising or beneficial effect of these medications is yet to be demonstrated in patients with ACHD. In advanced heart failure, hemodynamic assessment is essential to identify patients who may be candidates for heart transplantation. In those who are not suitable for listing for transplantation or with precluding comorbidities, a durable ventricular assist device should be considered whilst taking into account that only patients with singular VAD for the systemic ventricle had an outcome comparable to non-ACHD patients. Whilst heart failure is frequently encountered in patients with ACHD and several treatment options are available, it is essential that they are managed by a team specialising in ACHD.

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to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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