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Review Article

Medical Therapy for Heart Failure in Adult Congenital Heart Disease Patients

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ABSTRACT

There is an increasing recognition of heart failure among adults with congenital heart disease as a result of the advancements in medical, interventional, and surgical care. The long-term consequences of palliative therapy in infancy, childhood, and adulthood are incompletely understood. Medical therapy, including pharmacologic and device therapies, have been used for the treatment of heart failure. This review summarizes care strategies that have been applied within the spectrum of adults with congenital heart disease, including failing systemic ventricles, single ventricles, and Eisenmenger physiology.

ABBREVIATIONS

ACEI, angiotensin-converting enzyme inhibitor; ACHD, adult congenital heart disease; ARB, angiotenin receptor blocker; AV, atrioventricular valve; BNP, brain natriuretic peptide; CRT, cardiac resynchronization therapy; ECG, electrocardiogram; ERA, endothelin receptor antagonist; FC, functional class; GDMT, goal-directed medical therapy; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; LV, left ventricle; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PLE, protein-losing enteropathy; PVR, pulmonary vascular resistance; RV, right ventricle.

Introduction

Improved medical and surgical therapies have allowed generations of children born with congenital heart disease to age into the adult population. With this, there are now more than an estimated 1 million adults with congenital heart disease (ACHD) living in North America.[1] However, most interventions performed are palliative and not curative, increasing the susceptibility of patients to develop heart failure (HF) later in life. Mechanisms for HF include intrinsic abnormalities of the myocardium, hemodynamic derangements, and defective conduction. In turn, these can result in activation of neurohormonal systems, including endothelin, renin-aldosterone, natriuretic, and sympatho-adrenergic pathways.[2] Importantly, HF has become the leading cause of death for ACHD patients.[3]

The prevalence of HF can increase with the complexity of native anatomy, making those born with transposition of the great arteries or single ventricles, for example, more at risk. ACHD patients with uncorrected defects, those who underwent palliative intervention in childhood but developed HF, and those with single ventricles and failing Fontan physiology may be most at risk.[4] The heterogeneity of congenital cardiac defects, surgical palliations, catheter-based interventions, and intrinsic aberrations of the myocardium, coronary artery anatomy, and conduction pathways can pose great challenges for providers caring for this specific population. Thorough review of patients' prior medical histories is critical. Advanced knowledge of specific pathophysiologies and surgical and interventional procedures is required to deliver appropriate treatment in order to prevent, ameliorate, or offset HF symptoms in ACHD patients. This review aims to present the mechanisms of HF and medical therapies for the treatment of acute and chronic HF in ACHD patients.

Mechanisms

Anatomy dictates the HF phenotype. Recent guidelines distinguish classifications of anatomical complexity based on simple, moderate, and

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complex lesions. Simple lesions, such as isolated mild pulmonic stenosis or small atrial septal defect, are associated with a biventricular circulation with the left ventricle (LV) as the subaortic ventricle. Moderate lesions, such as anomalous pulmonary venous connection, ostium primum atrial septal defect, and supravalvular aortic stenosis, are also associated with a biventricular circulation with the LV as the subaortic ventricle but are at higher risk for the development of HF due to intrinsic abnormalities, postprocedure hemodynamic effects, and/or residual lesions. Complex lesions, such as double-outlet right ventricle (RV), transposition of the great arteries, and pulmonary atresia, can result in single or biventricular circulation, with the subaortic ventricle being either the morphologic LV or RV.[5]

Potential causes of HF include abnormal pressure or volume load of the morphologic RV or LV, ischemia of the myocardium from anatomic anomalies or supply/demand mismatch, mixed valvular disease, ventricular hypertrophy, ventricular-ventricular interaction, arrhythmias, and constriction of the pericardium from prior sternotomy.[6,7] Additionally, systemic or pulmonary hypertension, cyanosis, and/or chronotropic incompetence may contribute to HF pathophysiology.[8] Recurrence of stenosis, regurgitation, and shunting can add to HF risk.[9] Genetic or developmental factors that have yet to be identified may also be influencing HF risk and presentation.[10] The effects of aging, medical comorbidities, lifestyle, and acquired heart disease may compound HF risk and/or contribute to the severity of symptoms.[11] Exercise capacity can be limited due to inadequate cardiac reserve, raised pulmonary pressures upon exercise, deconditioning or poor preconditioning, and exercise restrictions enforced by providers.[12] Development of cardiac cachexia, frailty, cardiorenal syndrome, hepatic dysfunction, right HF, and pulmonary hypertension are indicative of a poor prognosis overall.[4] ACHD patients with concomitant chronic kidney disease admitted for decompensated HF have a tripled risk of death, transplantation, or ventricular assist device implantation.[13] Furthermore, those patients lost to follow-up care may miss the period where residual cardiac abnormalities or associated comorbidities could be addressed electively and potentially more safely than those presenting at the time of decompensated HF.[14]

ACHD patients present with HF symptoms due to their underlying anatomy and physiology. Failure may be related to the systemic LV, the systemic RV, the subpulmonic RV, or worsening Fontan physiology.[15]

The systemic LV is susceptible to dysfunction due to abnormal pressure and/or volume overload, ventricular hypertrophy as a maladaptive remodeling response, myocardial ischemia, and effects of cyanosis, prior cardiopulmonary bypass, and/or ventriculotomy.[16] These may result in fibrosis, altering systolic and diastolic function.[16]

The architecture of the morphologic RV differs from that of the left as the myocardial fibers transition from outward horizontal to deep longitudinal with some fibers shared with the LV at the anterior interventricular sulcus, resulting in a longitudinal contraction with a peristaltic wave.[17–19] Additionally, LV contraction pulls the free wall of the RV in the direction of the septum, which concurrently protrudes into the RV as well and allows for volume change without significant energy expenditure.[20,21] Thus, the RV can respond well to volume changes in the low-pressure, highly-compliant pulmonary system, but this architecture changes when placed in the systemic position, requiring maladaptive changes to support circulation.[15] The systemic RV must dilate and increase wall thickness and muscle contractility while its geometry becomes similar to the systemic LV with contraction changing toward circumferential and away from longitudinal shortening.[20,22,23] The septum then shifts leftward and contracts toward the center of the RV, reversing the normal contractile pattern.[24] This can then result in diminished myocardial work and decreased global function.[24]

The subpulmonic RV is affected by RV diastolic afterload, diastolic pressure gradient between the RV and main pulmonary artery, intrinsic RV compliance, and capacitance of the pulmonary arteries.[25,26] Prior history of repair of defects such as double outlet RV, truncus arteriosus, tetralogy of Fallot, pulmonary atresia, pulmonary stenosis, pretricuspid valve shunt, or intrinsic congenital heart disease-related pulmonary arterial hypertension can result in a subpulmonic RV susceptible to failure.[27]

Fontan failure itself can manifest in different phenotypes associated with underlying pathology, including HF with reduced ejection fraction (HFrEF), HF with preserved ejection fraction (HFpEF), HF with normal pressures, and HF due to lymphatic abnormalities.[28] Extracardiac shunts and collaterals can contribute to additional volume and/or pressure-loading conditions. Prior interventions can provide the substrate for additional sequelae, such as tissue surrounding surgical scars and/or operative patches as a nidus for arrhythmias and conduits contributing to worsening pressure overload.[9]

In their multivariable analysis, one center found age at the latest follow-up, history of infective endocarditis, end-organ dysfunction, history of atrial arrhythmia, New York Heart Association (NYHA) functional class (FC), heart rate, history of pacemaker implantation, ventricular dysfunction, and pulmonary hypertension severity were independently associated with the presence of HF in ACHD patients.[29] Some variables, including age, history of atrial arrhythmia, NYHA class, ventricular dysfunction, and history of pacemaker implantation, were related to HF across all anatomical/physiologic subgroups.[29]

ACHD patients with Eisenmenger syndrome may present even more of a challenge to providers given the sensitivity of hemodynamic homeostasis to any perturbations. The phenotype is associated with suprasystemic pulmonary artery pressures in ACHD patients with shunt lesions, leading to worsening pulmonary vascular disease and ultimately causing shunt reversal and central cyanosis.[30] Associated comorbidities, such as secondary erythrocytosis, iron deficiency, thrombotic diathesis, hemoptysis, and arrhythmias, can contribute to the progression of HF symptoms.[31]

Management

Pharmacologic Therapies

ACHD patients with failure of the systemic LV are often treated with medications established in the management of HF. Goal-directed medical therapy (GDMT) is focused on treatment of neurohormonal pathways established in those patients with acquired heart disease, such as appropriate use of beta-blockers, angiotensin receptor-neprilysin inhibitor (or angiotensin-converting enzyme inhibitor [ACEI] or angiotensin receptor blocker [ARB] as tolerated), mineralocorticoid receptor antagonists, sodium-glucose cotransporter 2 inhibitors, diuretics, and combined hydralazine and nitrates.[32] Some of these medications may be prescribed for treatment of comorbidities like diabetes, arrhythmias, and hypertension, allowing drug initiation despite the absence of significant evidence for use in ACHD patients given their historic exclusion from large HF medication trials.[33] Use of ivabradine in ACHD patients has notably not been studied.[33] As the ACHD population continues to age, therapies targeting the structural and functional abnormalities in HFpEF will require further investigation.[34] Additionally, for older patients with HFpEF risk factors and incidentally found shunts (both pre- and post-tricuspid), focused therapies for LV diastolic function will need to be balanced with the risks and benefits of shunt closure.

Those patients with systemic RVs may receive similar classes of medication, though caution with extrapolation of benefits seen in systemic LVs must be exercised. In a single-center experience with 60 patients, beta-blocker therapy with carvedilol and metoprolol XL has been used in transposition of the great arteries with systemic RV dysfunction with beta-blockers preventing RV remodeling and improving exercise tolerance, although therapy was not associated with a significant effect on RV EF, RV end-diastolic area, or degree of tricuspid regurgitation.[35] Use of those beta-blockers was an independent predictor of subsequent improvement in NYHA FC regardless of the use of other concurrent medication therapy with ACEI, ARB, spironolactone, digoxin, and/or diuretics; however, after adjustment of pacemaker therapy, this effect

was no longer associated with FC improvement.[35] Beta-blockers, such as carvedilol, metoprolol, and bisoprolol, have been associated with stabilized or improved systemic RV size and systolic function, NYHA FC, and exercise capacity in small case series and pilot studies.[36–38] A single-center randomized control trial with crossover in 7 patients with a history of atrial switch procedures showed a benefit of 2 months of losartan therapy with increased RV EF, longer exercise duration, and decreased regurgitant volume of the systemic atrioventricular (AV) valve.[39] In contrast, a multicenter, double-blind, randomized, placebo-controlled pilot trial of valsartan as therapy for 88 patients with systemic RVs showed no beneficial effect on EF, maximum exercise capacity, or quality of life over a 3-year period with a small but statistically significant difference in larger RV end-diastolic volume and mass in those treated with placebo rather than valsartan.[40] ACEIs have not demonstrated benefits in exercise capacity, hemodynamics, ventricular size, or EF.[41–43] Caution is required when using drugs that venodilate and reduce preload in patients with a prior history of atrial switch operation in D-loop transposition of the great arteries; additionally, ventricular filling may be compromised by baffle obstruction.[33] In the Eplerenone in systemic right ventrcle: Double blind randomized clinic trial, a double-blind, placebo-controlled trial of 12 months of eplerenone therapy in 26 patients with a history of atrial switch procedures found that RV mass and function were unchanged, though a decrease in neurohormones and collagen turnover biomarkers was noted.[44] Overall, clinical use of GDMT has yet to be proven significantly beneficial in those with systemic RVs and should be used as part of the shared decision-making plan of care.

Medication therapy for patients with failure of the subpulmonic RV has mainly been limited to those with repaired tetralogy of Fallot. The Ace inhibitors for Potential PRevention Of the deleterious effects of Pulmonary Regurgitation In Adults with repaired TEtralogy of Fallot study, a single-center, double-blinded, placebo-controlled study of ramipril vs. placebo in 64 stable patients with a repaired tetralogy of Fallot with moderate or greater pulmonary regurgitation, demonstrated no difference in the primary endpoint of improvement in RV EF after 6 months of therapy.[45] Ramipril therapy also did not result in a significant change in severity of pulmonary regurgitation, ventricular volumes, cardiopulmonary exercise performance, or neurohormonal activation but did show a decrease in LV end-systolic volume index and an increase in LV EF in a subgroup of patients with restrictive RV physiology.[45] Similarly, the Right Ventricular Dysfunction in Tetralogy of Fallot: Inhibition of the Renin-Angiotensin-Aldosterone System trial, which was a multicenter, prospective, randomized, double-blind, placebo-controlled study with the use of losartan in ACHD patients with repaired tetralogy of Fallot and RV EF <50% but without severe valvular dysfunction, found that losartan therapy failed to improve the primary endpoint of RV EF.[46] Analysis of secondary outcomes showed no improvement in LV EF, peak aerobic exercise capacity, and N-terminal pro-brain natriuretic peptide (NT-proBNP) though interestingly, in contrast with the APPROPRIATE study, losartan was associated with improved EF in a subgroup of patients with nonrestrictive RV physiology and incomplete remodeling.[46] Use of beta-blocker therapy in this group of patients has also been examined. A prospective, randomized, double-blind, placebo-controlled trial of bisoprolol in 33 patients with repaired tetralogy of Fallot who were asymptomatic or mildly symptomatic showed no effect on levels of brain natriuretic peptide, peak uptake of oxygen, and RV or LV EF.[47] NYHA FC also remained unchanged.[47] No medical treatment is indicated in patients without symptoms, and if RV failure is due to pulmonary arterial hypertension, then therapy should be focused on pulmonary vasodilators as appropriate.[33]

Therapy targeted toward the pulmonary vasculature in Fontan patients has also been performed. A single-center study of 27 patients with Fontan circulation showed a single dose of oral sildenafil increased rest and peak exercise pulmonary blood flow index and cardiac index without change in rest or peak exercise transcutaneous arterial blood oxygen saturations.[48] The Fontan Udenafil Exercise Longitudinal trial, which was a multicenter, randomized, phase III clinical trial of udenafil in 400 patients between ages 12 and 18 years with Fontan circulation, failed to demonstrate a benefit in change in oxygen consumption at peak exercise but did show an improvement in measures of exercise performance, including ventilatory equivalents of carbon dioxide, work rate, and myocardial performance index.[49] A randomized, prospective, multicenter open-label trial of bosentan in 32 patients with Fontan circulation showed no change in peak VO2, physical activity as measured by the Short Questionnaire to Assess Health-Enhancing Physical Activity score, NT-proBNP level, and mental quality of life as measured by the Short Form-36 questionnaire.[50] Subgroup analysis on age, type of Fontan circulation, baseline NT-proBNP, and ventricular morphology did not reveal an efficacious benefit of bosentan therapy.[50] Use of endothelin receptor antagonists (ERAs) can lower pulmonary vascular resistance (PVR) in patients with Fontan circulation and elevated PVR. In a study of 24 patients (8 children, 8 adolescents, and 8 adults) with PVR $\geq$2 Woods units*m^2 treated with ERAs (bosentan for minors and macitentan for adults) for 6 months, PVR decreased in all patients with 71% having a PVR <2 Woods units*m^2.[51] However, only adolescents gained a benefit in functional improvement assessed by cardiopulmonary exercise testing.[51] Additionally, in the Treatment With Endothelin Receptor Antagonist ini Fontan Patients trial, in which 69 adolescents and adults with Fontan circulation who completed the study were randomized to 14 weeks of treatment with bosentan or placebo, peak oxygen consumption and cardiopulmonary exercise time increased in the bosentan group, and 9 bosentan-treated patients improved by one NYHA FC.[52] Use of additional pulmonary vasodilator therapy has been investigated. In a single-center, double-blind, randomized, placebo-controlled, crossover trial, 15 patients with Fontan circulation (aged 12-49 years) were given a single nebulizer treatment of iloprost or placebo prior to cardiopulmonary exercise testing, and all patients demonstrated higher oxygen pulse (as a surrogate for stroke volume) and peak oxygen consumption.[53] Practice of care of ACHD patients with Fontan circulation across the United Kingdom demonstrated that of over 1500 patients followed in specialist centers, only 76 (4.9%) received pulmonary arterial hypertension therapies, with the vast majority (almost 91%) receiving a phosphodiesterase-5 inhibitor.[54] Four patients received sequential therapy with the addition of ERA with one patient substituting ERA therapy for inhaled prostanoid and no patients receiving triple therapy.[54] When matched with untreated patients with similar profiles, the treated group were more likely to improve in NYHA FC while on therapy for 12 months; however, the treated patients were more likely to have a lower FC at baseline, have ascites, have a history of protein-losing enteropathy (PLE), or receive loop diuretics.[54]

While all should undergo evaluation and correction of potential anatomic and arrhythmic etiologies, treatment of Fontan failure is targeted by the underlying phenotype. Those with reduced EF may benefit from traditional GDMT, such as beta-blockers, diuretics, ACEI or ARB therapy, and mineralocorticoid receptor antagonists, with particular attention paid to avoiding decreasing systemic vascular resistance in those with advanced hepatic dysfunction, who may be maximally vasodilated.[28,55] In combination with diuretics, digoxin, and ACEI, carvedilol has been shown to increase EF, decrease diuretic dose, and improve cardiothoracic ratio in a small cohort of patients with functionally univentricular hearts.[56,57] Patients with Fontan failure and preserved EF may also benefit from diuretics, sodium restriction, and control of pulmonary venous congestion with careful consideration of the use of pulmonary vasodilator therapies.[28,58] In patients with Fontan failure and normal hemodynamics, treatment should be tailored toward hemodynamic optimization as multiple abnormalities, such as renal dysfunction and advanced hepatic failure, may coexist and influence the hemodynamic profile.[28] For those with Fontan failure and abnormal lymphatics, the use of oral budesonide and pulmonary vasodilators may be appropriate for treatment of PLE.[59,60] High-dose spironolactone therapy may also be used for PLE though this effect was found in children.[61] Additionally, in this patient group, plastic bronchitis may be treated with thoracic duct

Table 1
Medical and device therapy for heart failure in adults with congenital heart disease

Systolic heart failure		
Systemic morphologic left ventricle (EF < 40%)	Symptomatic or asymptomatic	Beta-blockers ARNi/ARB/ACEi MRA Diuretics (loop and thiazide) SGLT2i Hydralazine/isosorbide dinitrate Antiarrhythmics (as indicated) EPS/ablation (as indicated) Pacemaker ± CRT (as indicated) ICD (as indicated) Advanced HF therapies (as indicated)
Systemic morphologic right ventricle (EF < 40%)	Asymptomatic	No medical treatment Antiarrhythmics (as indicated) EPS/ablation (as indicated) Pacemaker ± CRT (as indicated) ICD (as indicated)
	Symptomatic	Beta-blockers ARNi/ARB/ACEi MRA Diuretics (loop and thiazide) Antiarrhythmics (as indicated) EPS/ablation (as indicated) Pacemaker ± CRT (as indicated) ICD (as indicated) Advanced HF therapies (as indicated)
Subpulmonary ventricle (morphologic left or right) (EF < 40%)	Asymptomatic	No medical treatment Antiarrhythmics (as indicated) EPS/ablation (as indicated) Pacemaker ± CRT (as indicated) ICD (as indicated)
	Symptomatic	Diuretics Pulmonary vasodilators Antiarrhythmics (as indicated) EPS/ablation (as indicated) Pacemaker ± CRT (as indicated) ICD (as indicated) Advanced HF therapies (as indicated)
Single ventricle (EF < 40%)	Symptomatic or asymptomatic	Beta-blockers ARNi/ARB/ACEi MRA Diuretics (loop and thiazide) Digoxin Antiarrhythmics (as indicated) EPS/ablation (as indicated) Pacemaker (as indicated) ICD (as indicated) Advanced HF therapies (as indicated)
Eisenmenger physiology	Symptomatic or asymptomatic	Diuretics (loop and thiazide) Antiarrhythmics (as indicated) EPS/ablation (as indicated) Pacemaker (as indicated, consider epicardial for thromboembolism risk) ICD (as indicated, consider epicardial for thromboembolism risk) Advanced HF therapies (as indicated)
Heart failure with preserved ejection fraction	Asymptomatic	No medical treatment Antiarrhythmics (as indicated) EPS/ablation (as indicated) Pacemaker (as indicated)
	Symptomatic	Diuretics SGLT2i ARNi/ARB/ACEi MRA Antiarrhythmics (as indicated) EPS/ablation (as indicated) Pacemaker (as indicated)

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprolysin inhibitor; CRT, cardiac resynchronization therapy; EF, ejection fraction; EPS, electrophysiological study; HF, heart failure; ICD, implantable cardioverter-defibrillator; MRA, mineralocorticoid antagonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

ligation, percutaneous lymphatic interventions, inhaled tissue plasminogen activator, and vest therapy.[62–64] All patients with failing Fontan physiology should be considered for cardiac transplantation with the potential use of dual- or triple-organ transplants of the heart, liver, and/or lungs as appropriate.

Use of sacubitril/valsartan has been observed in two centers across a spectrum of primary ACHD diagnoses, including failure of the systemic RV, systemic LV, subpulmonic RV, and Fontan physiology. In one center, all 14 patients who tolerated the medication were NYHA FC II or III and already on medical therapy, including beta-blockers, diuretics,

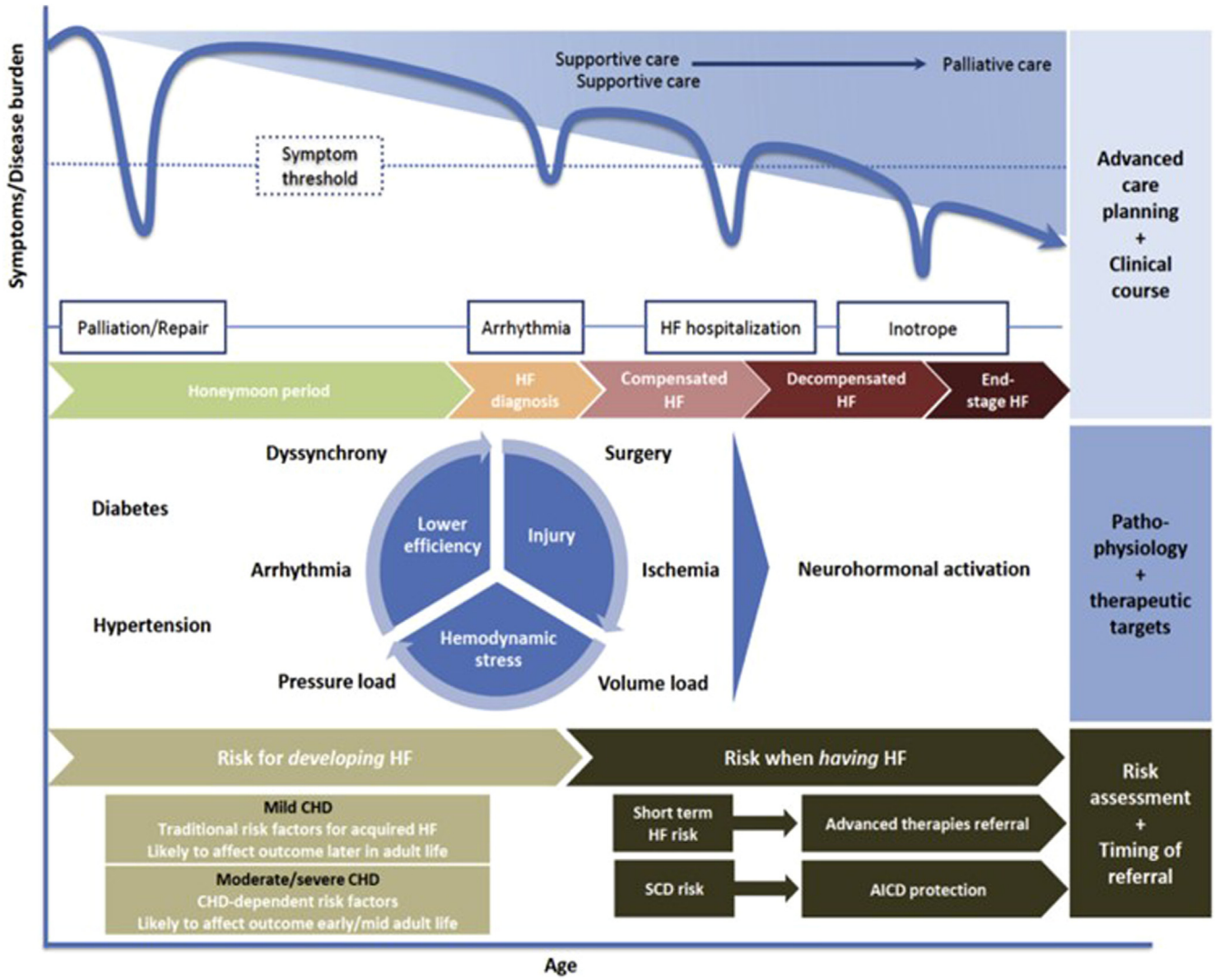

Figure 1. Lifetime health trajectory and shifts in health care focus in patients with CHD.
Abbreviations: AICD, automated implantable cardioverter-defibrillator; CHD, congenital heart disease; HF, heart failure; SCD, sudden cardiac death.
Reproduced with permission.[14]

antiarrhythmics, and/or pulmonary vasodilators, and symptoms were improved in 4 patients and stable in 10 patients.[65] In another center, 6 months of therapy with sacubitril/valsartan resulted in a mean improvement of one NYHA FC in five treated patients with good tolerance of the medication.[66]

Conservative measures are the mainstay of therapy for patients with Eisenmenger syndrome. Anticoagulation with vitamin K antagonist is recommended in the setting of thrombosis, embolism, and/or atrial arrhythmia.[31] Focus on adequate hydration, supplemental oxygen in the setting of concomitant lung disease, arrhythmia management, repletion of iron deficiency, antibiotic prophylaxis and prevention of endocarditis, and supportive treatment, such as antibiotics and cough suppression, for hemoptysis is done as appropriate.[31,67] In a German registry of 153 patients with Eisenmenger syndrome, use of digoxin was associated with increased mortality, while beta-blocker therapy trended toward survival.[68] ACEI/ARB therapy should be used with caution, as improved survival has not been seen.[69] Pulmonary vasodilator therapy is common in this patient group with the recommendation of starting ERA monotherapy and further escalation with phosphodiesterase-5 inhibitors and prostanoids as tolerated.[5,70] Drugs that reduce afterload and worsen right-to-left intracardiac shunting, increasing cyanosis, should be avoided.[71] Heart-lung transplantation and/or lung transplantation remain the mainstay surgical therapy for this population.[31]

Outpatient monitoring of drug therapy for ACHD patients is challenging given the complex and wide-ranging physiologies managed across the spectrum of congenital lesions. Efficacy may vary widely as the pharmacodynamics of each medication class could differ between patients with simple, moderate, and complex lesions. Use of traditional monitoring parameters may change in ACHD vs. acquired heart disease patients. For instance, cystatin C-based methods of glomerular filtration rate predicted clinical events more strongly than creatinine-based methods, possibly impacting efficacious dosages of renally-cleared drugs, such as ACEIs and ARBs, as well as their potential side effects, such as hyperkalemia.[72] Medications thought to improve exercise capacity and quality of life may be confounded by both increased frailty within ACHD patients and discordant self-estimation of FC.[73–75]

Furthermore, as more ACHD patients develop progressive HF symptoms, hospitalizations with management in the intensive care unit for advanced HF and cardiogenic shock have become more common. Short-term therapies, such as the use of vasoactive agents like vasopressin, norepinephrine, and milrinone, to improve hemodynamics and reverse end-organ dysfunction can be given as long as the patient's underlying anatomy, physiology, and surgical history are considered.[76] Therapies should be targeted toward treating precipitating factors, such as arrhythmia, infection, or ischemia, with evaluation for potential therapies like mechanical circulatory support and/or cardiac transplantation

reserved for specific populations. Early referral for advanced therapies should be performed given the disproportionate increase in mortality or de-listing in ACHD patients.[77]

Device Therapy

Sinus node dysfunction may be intrinsic due to underlying congenital anatomy or associated with postoperative complication, including both the immediate and delayed periods. Intrinsic pathology can be seen in patients with left-sided juxtaposition of the atrial appendages and/or left atrial isomerism.[78] Postoperative dysfunction can be seen in those undergoing atrial switch operation, hemi-Fontan or Fontan surgery with atriopulmonary or total cavopulmonary connections, Glenn shunt, sinus venosus atrial septal defect repair, arterial switch operation, tetralogy of Fallot repair, and Ebstein anomaly repair.[78] AV nodal dysfunction can also be seen in lesions associated with intrinsic block as well as a postoperative sequela after surgical repair.[78] Congenital AV block can be seen in congenitally corrected transposition of the great arteries, AV septal defects, L-looped single ventricles, and an anomalous left coronary artery arising from the pulmonary artery.[78] Those patients with a repaired ventricular septal defect or AV septal defect, mitral valve and/or multivalve surgery involving the tricuspid valve, and left ventricular outflow tract surgery can develop postoperative AV block.[78] Pacemaker placement is therefore recommended for those patients with symptoms related to bradycardia or loss of AV synchrony, exercise intolerance due to chronotropic incompetence, or bradyarrhythmia-related adverse hemodynamic effects noted on noninvasive and/or invasive testing.[78] Pacing-associated cardiomyopathy was seen in a small cohort of 25 patients in a single center with a ventricular pacing percentage of $\geq$70% with underlying transposition of the great arteries, tetralogy of Fallot, or complex biventricular repair.[79] Leadless pacemakers have also been used across a spectrum of nonrepaired and repaired ACHD, including those with systemic RVs and single ventricle physiology, with no major peri- and post-procedural complications encountered.[80]

Sudden cardiac death was noted to be the second-leading cause of death in a German registry of ACHD patients.[81] Indications for implantable cardioverter-defibrillators (ICDs) for primary prevention in ACHD patients include systemic LV dysfunction with EF $\leq$35%, biventricular physiology, and NYHA FC II or III despite optimal medical therapy; those with unexplained syncope of suspected arrhythmic etiology and either advanced ventricular dysfunction or inducible sustained ventricular arrhythmias; those with repaired tetralogy of Fallot and multiple risk factors for sudden cardiac death (including LV systolic or diastolic dysfunction, nonsustained ventricular tachycardia, QRS duration $\geq$180 milliseconds, RV scarring noted on MRI, and/or inducible sustained ventricular tachycardia); and those with advanced single or systemic RV dysfunction (RV EF $<$35%) in the presence of other risk factors, including complex ventricular arrhythmias, unexplained syncope, NYHA FC II or III, QRS duration $\geq$140 milliseconds, and/or severe systemic AV valve regurgitation.[5,78,82] Subcutaneous ICDs may be used in ACHD patients who pass electrocardiogram screening as well as those with Eisenmenger syndrome who are at high risk but have an acceptable FC and life expectancy greater than one year.[82–84] ICD implantation is recommended for survivors of an aborted cardiac arrest.[85] ICDs may also help with remote monitoring of new atrial arrhythmias, which could lead to initiation and/or change of antiarrhythmic drug therapy and anticoagulation.[86] Method of implantation via transvenous or epicardial lead placement is dictated by the underlying congenital anatomy and/or surgical repair.

Cardiac resynchronization therapy (CRT) has been examined in the ACHD population as a treatment for progressive HF, especially in those with prolonged QRS duration, decreased NYHA FC, ventricular dilation and/or dysfunction, and an anticipated $>$40% ventricular pacing requirement.[78] CRT has been associated with an improvement in early follow-up (1.8 ± 0.8 years) with NYHA FC, QRS duration, and cardiothoracic ratio with sustained improvement of NYHA class at late follow-up (4.7 ± 0.8 years), though only baseline QRS duration was predictive of a positive response.[87] Increase in EF has also been seen in patients with a systemic RV and a systemic LV.[88,89] The CRT effects also continued in older ACHD patients (median age 47 years) with a success rate comparable to the acquired heart disease population in spite of technical considerations due to more complex anatomy.[90] Lower mortality has been seen in ACHD patients who receive CRT in comparison to ischemic and nonischemic cardiomyopathy patients.[91] Patients with repaired tetralogy of Fallot, LV systolic dysfunction, and RV conduction delay have also demonstrated the benefits of CRT with improvements in LV EF and end-diastolic and end-systolic volumes.[92] Cardiac conduction system pacing, which is more physiologic pacing, has also been studied in ACHD patients with a systemic LV, showing that improvement in LV EF was noninferior and narrowing of QRS duration was more pronounced in similar patients receiving CRT.[93] Overall, CRT is an indicated therapy in appropriate populations with HF symptoms, conduction delay, and ventricular dysfunction.

Conclusions

HF is an increasing cause of morbidity and mortality in the ACHD population. While patients may have adapted to living with impairment of the cardiovascular system since childhood, rigorous follow-up with specialty care can potentially stabilize or improve FC and decrease hospitalizations and mortality. The heterogeneity of the ACHD population can present a unique challenge to the provider as patients can vary in their anatomic and physiologic status, but even those with simple anatomic lesions can remain at lifelong risk of developing HF. Appropriate evaluation of the potential sequelae related to the intrinsic anatomy as well as surgical repair is required, as these can involve valvular disease, residual shunts, ventricular function, arrhythmias, conduction abnormalities, and extracardiac systemic factors. In addition to an understanding of the anatomy and pathophysiology of congenital heart disease, providers should have an advanced knowledge of hemodynamics, appropriate use of pharmacology, and familiarity with complex interventional and surgical procedures in order to best serve this population. Caution should be used when extrapolating therapies used in other etiologies of HF for the ACHD population. Data on emerging therapies, including medications, implantable devices, and surgical techniques, may result in improved targeted management of specific populations, though there are knowledge gaps in the management of HF in ACHD, especially with regard to the use of surrogate end points. Further research should continue to evolve the treatment of and expand the diagnostic and therapeutic tools available to ACHD patients.

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Ethics Statement

The author attests he is in compliance with human studies committees and animal welfare regulations of the author's institution and Food and Drug Administration guidelines, including patient consent where appropriate.

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