AHA Scientific Statement

Chronic Heart Failure in Congenital Heart Disease

A Scientific Statement From the American Heart Association

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Part I: General Considerations

Introduction

The past 60 years have brought remarkable advancements in the diagnosis and treatment of congenital heart disease (CHD). Early diagnosis and improvements in cardiac surgery and interventional cardiology have resulted in unprecedented survival of patients with CHD, even those with the most complex lesions. Despite remarkable success in treatments, many interventions are palliative rather than curative, and patients often develop cardiac complications, including heart failure (HF). HF management in the setting of CHD is challenged by the wide range of ages at which HF occurs, the heterogeneity of the underlying anatomy and surgical repairs, the wide spectrum of HF causes, the lack of validated biomarkers for disease progression, the lack of reliable risk predictors or surrogate end points, and the paucity of evidence demonstrating treatment efficacy.

The purposes of this statement are to review the literature pertaining to chronic HF in CHD and to elucidate important gaps in our knowledge, emphasizing the need for specific studies of HF mechanisms and improving outcomes for those with HF. In this document, the definition of CHD severity is the definition common in CHD documents, including the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines[1] for the management of adults with CHD (Table 1[1–3]). The definition of HF corresponds to that found in the multiple guidelines on diagnosis and management of HF. Although nuances and specific details may be controversial,[4] the broad definition from the Heart Failure Society of America guidelines states the following: "In physiologic terms, HF is 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."[5] The definition of chronic HF in this document concurs with that of the European Society of Cardiology guidelines, which emphasize chronic HF (whether stable, progressively worsening, or decompensated) rather than acute HF. Although specific definitions of acute and chronic HF are not universally accepted, we focus here on chronic HF as a persistent syndrome that requires consideration of therapy to prevent progression, decompensation, or death.[4]

This document focuses on the mechanisms and treatment of myocardial dysfunction while recognizing that HF symptoms may be attributable to underlying hemodynamic abnormalities such as valve dysfunction, outflow obstruction, coronary abnormalities, or residual shunting. Therefore, all patients with CHD with HF symptoms should undergo a detailed hemodynamic assessment by CHD-experienced cardiologists for any reversible hemodynamic abnormalities and receive appropriately targeted interventions if possible. Treatment recommendations for HF caused by valve

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dysfunction or ischemic heart disease are addressed elsewhere in the respective ACC/AHA guidelines, including the 2008 guidelines on the care of the adult with CHD.[1] Although this document focuses on HF treatment, palliative care should be considered a valuable and needed component of care in all patients with CHD and end-stage HF.[6]

The content of this document covers the age spectrum of pediatric to adult patients with CHD and HF with input from both pediatric and adult cardiologists. However, the bulk of available literature focuses on adult patients, in whom there is a greater relative burden of HF, presumably reflecting the natural history of CHD. Thus, the majority of the discussion herein is more applicable to adults with CHD and HF, although, whenever possible, specific issues in pediatric patients are discussed.

Some features of HF in CHD are common across diagnoses and are discussed in the general overview. However, special emphasis is given to topics with unique anatomic and physiological considerations, in particular patients in whom the right ventricle (RV) is more vulnerable, whether in the normal subpulmonic position or as the systemic ventricle, and patients with single-ventricle (SV) physiology. In addition, there are variations in pressure or volume loading of the left ventricle (LV) that are unique to CHD, which are discussed separately.

Overview

Incidence of CHD

Structural heart disease is the most common congenital disorder diagnosed in newborns, with birth prevalence reported to be 10 per 1000 live births,[7,8] and registry studies have estimated an incidence between 3 and 20 per 1000 live births.[9] The incidence of CHD based on birth prevalence may be an underestimate, however, because CHD is not necessarily apparent at birth, and the diagnosis may be made in childhood or adulthood. In fact, more than one quarter of CHD diagnoses are made after infancy.[10]

Survival in Patients With CHD

Survival in children born with CHD has improved dramatically over the past several decades, in large part as a result of surgical advances for children with complex CHD. Survival of newborns with complex CHD now approaches 90%, and 96% of newborns with CHD who survive the first year of life remain alive at 16 years of age.[10] Infant survival in the present era is significantly better than in prior decades but varies with CHD complexity; only 56% of newborns with heart defects of great complexity survive to 18 years of age.[11] In an analysis, 76% of the deaths that occurred in patients with CHD who survived the first year of life occurred after 18 years of age.[12] Adults with CHD are also living longer, with the overall median age at death increasing from 37 years in 2002 to 57 years in 2007.[9] Even more striking is the change in mortality for patients with CHD of great complexity, in whom the median age at death has increased from 2 years before 1995 to almost 25 years currently[13] (Figure 1[14]).

Prevalence estimates of CHD and registry data indicate that there are >1 million adults with CHD in the United States and 1.2 million in Europe.[7,14,15] Although the majority of these

Table 1. Classification of CHD Diagnoses

Great complexity
Conduits, valved or nonvalved
Cyanotic congenital heart (all forms)
Double-outlet ventricle
Eisenmenger syndrome
Fontan procedure
Mitral atresia
SV (also called double inlet or outlet, common, or primitive)
Pulmonary atresia (all forms)
Pulmonary vascular obstructive disease
TGA
Tricuspid atresia
Truncus arteriosus/hemitruncus
Other abnormalities of atrioventricular or ventriculoarterial connection not included above (ie, crisscross heart, isomerism, heterotaxy syndromes, ventricular inversion)
Moderately complex
Aorto–left ventricular fistulas
Anomalous pulmonary venous drainage, partial or total
Atrioventricular septal defects (partial or complete)
Coarctation of the aorta
Ebstein anomaly
Infundibular RV outflow obstruction of significance
Ostium primum atrial septal defect
Patent ductus arteriosus (not closed)
Pulmonary valve regurgitation (moderate to severe)
Pulmonary valve stenosis (moderate to severe)
Sinus of Valsalva fistula/aneurysm
Sinus venosus atrial septal defect
Subvalvular or supravalvular aortic stenosis (except hypertrophic cardiomyopathy)
TOF
Ventricular septal defect with:
Absent valve or valves
Aortic regurgitation
Coarctation of the aorta
Mitral disease
RV outflow tract obstruction
Straddling tricuspid/mitral valve
Subaortic stenosis
Simple
Native disease
Isolated congenital aortic valve disease
Isolated congenital mitral valve disease (eg, except parachute valve, cleft leaflet)
Small atrial septal defect
Isolated small ventricular septal defect (no associated lesions)
Mild pulmonary stenosis
Small patent ductus arteriosus
Repaired conditions
Previously ligated or occluded ductus arteriosus
Repaired secundum or sinus venosus atrial septal defect without residua
Repaired ventricular septal defect without residua

CHD indicates congenital heart disease; RV, right ventricular; SV, single ventricle; TGA, transposition of the great arteries; and TOF, tetralogy of Fallot.

Data derived from Warnes et al[1] and Connelly et al.[2] Modified from Warnes et al[3] with permission from the publisher. Copyright © 2001, American College of Cardiology.

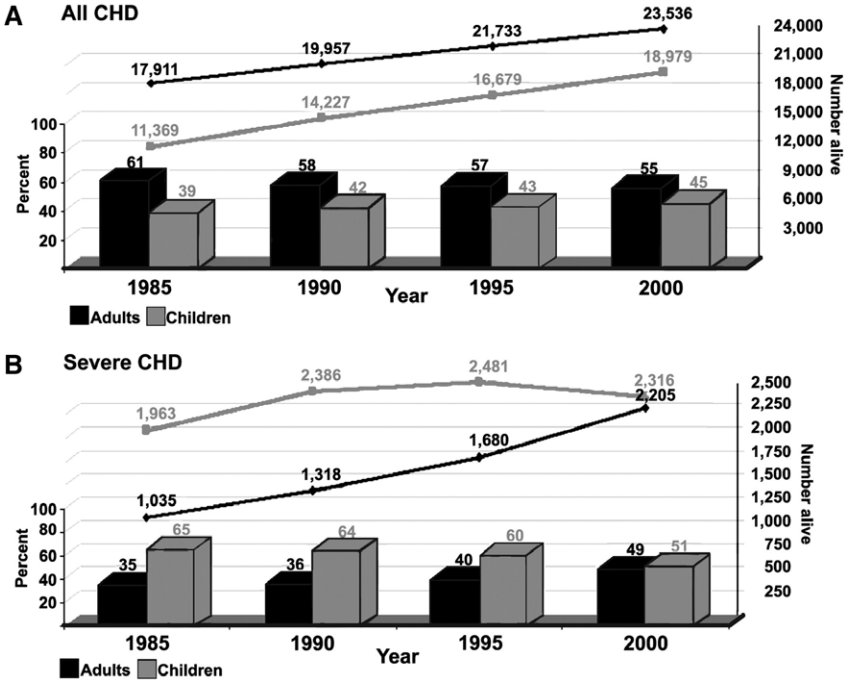

Figure 1. Prevalence/incidence of congenital heart disease (CHD). **A** and **B,** Prevalence of CHD in different age groups in 1985 and 2000 for all CHD (**A**) and severe CHD (**B**).[14] Black bars indicate adults; gray bars are children. The *y* axis on the **left** is percent alive; the *y* axis on the **right** is number alive.

survivors have simple forms of CHD such as atrial and ventricular septal defects, a significant number have more complex CHD, including 10% with defects of great complexity (such as SV) and 30% with moderately complex CHD (such as conotruncal defects and atrioventricular septal defects).[14]

Importance of HF in CHD

The impact of cumulative survival means that more patients are at risk for HF. Despite great success in the medical and surgical management of CHD, long-term survivors often have residual cardiac abnormalities, pulmonary abnormalities, or hepatic impairment caused by sequelae of cardiac dysfunction.[16,17] HF is an important problem for this expanding population of older children and adults, although the prevalence of HF in children and adults with CHD is unknown. However, HF has been reported to develop during childhood in ≈5% of all patients with CHD and up to 10% to 20% of patients after the Fontan procedure.[18–20] After the Fontan procedure, the prevalence of HF (variably defined) is nearly 50% by adulthood.[21,22]

HF Mortality and Morbidity in CHD

In a population-based study, HF was the major cause of late death (>30 days) in children after pediatric cardiac surgery, contributing to 27% of the deaths and occurring at a median age of 5.2 years.[23] HF also is the leading cause of death in adults with CHD, described in 26% of all deaths in a national registry of >8000 adults with CHD, with similar findings in other reports.[20,24,25] One study demonstrated that adults with CHD admitted with HF had a 5-fold increase in mortality compared with those who were not admitted. This study showed 1- and 3-year mortality rates of 24% and 35% after a first HF admission.[26]

In addition to decreased survival, adults with CHD face significant morbidity. The number of CHD hospitalizations increased 101% from 1998 to 2005, with rates 2 to 3 times higher than population norms. HF is a common reason for admission, although less common than arrhythmia.[18–20] Further highlighting the severity of the problem, CHD was the leading indication for heart transplantation in the pediatric age group.[27] In adulthood, because ischemic heart disease predominates, CHD was the indication for transplantation in only 3% of cases.[28] This represents a small subset of the adults with end-stage HF caused by CHD. One explanation may be that decisions about referral or transplantation listing are influenced by the higher early mortality after transplantation reported in the CHD population.[29]

HF Classification in CHD

The clinical presentation of the HF patient with CHD may vary significantly by defect or age. Patients with CHD can have classic symptoms of fatigue, dyspnea, and exercise intolerance but may manifest more subtle signs of malnutrition, growth failure, or cachexia.[1,30] Patients with CHD have often adapted to their long-standing limitations; therefore, they may not report symptoms despite significant objective exercise impairment.[31] Thus, application of general HF classifications such as the New York Heart Association (NYHA) categories or the modified Ross classification may underestimate the severity of disease, particularly in patients with complex or cyanotic CHD.[32] The Warnes-Somerville classification was developed to describe limitations in adults with CHD, although it is not commonly used. None of the available HF classification grading scales (Table 2[33–36]) have been validated in predicting outcomes.

The ACC/AHA buidelines for the diagnosis and management of HF, updated in 2013, specifically excluded children

Table 2. Classification Systems

Modified Ross HF Classification for Children	NYHA Functional Class	Canadian Cardiovascular Society Grading for Angina Pectoris	Warnes-Somerville Ability Index	Specific Activity Scale
Asymptomatic	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	Ordinary physical activity such as walking and climbing stairs does not cause angina. Angina with strenuous or rapid prolonged exertion at work or recreation.	Normal life; full-time work or school; can manage pregnancy.	Patients can perform to completion any activity requiring ≥7 metabolic equivalents (eg, can carry 24 lb up 8 steps, do outdoor work [shovel snow, spade soil], and do recreational activities [skiing, basketball, squash, handball, jog/walk 5 mph]).
Mild tachypnea or diaphoresis with feeding in infants Dyspnea on exertion in older children	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Slight limitation of ordinary activity. Walking or climbing stairs rapidly; walking uphill; walking or stair climbing after meals, in cold, in wind, or when under emotional stress; or only during the few hours after awakening. Walking >2 blocks on level ground and climbing >1 flight of ordinary stairs at a normal pace and in normal conditions.	Able to do part-time work; life modified by symptoms.	Patients can perform to completion any activity requiring ≤5 metabolic equivalents (eg, have sexual intercourse without stopping, garden, rake, weed, roller skate, dance fox trot, and walk at 4 mph on level ground), but cannot and do not perform to completion activities requiring ≥7 metabolic equivalents.
Marked tachypnea or diaphoresis with feeding in infants Prolonged feeding times with growth failure Marked dyspnea on exertion in older children	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.	Marked limitation of ordinary physical activity. Walking 1-2 blocks on level ground and climbing 1 flight in normal conditions.	Unable to work; noticeable limitation of activities.	Patients can perform to completion any activity requiring ≤2 metabolic equivalents (eg, shower without stopping, strip and make bed, clean windows, walk 2.5 mph, bowl, play golf, and dress without stopping), but cannot and do not perform to completion any activities requiring >5 metabolic equivalents.
Symptoms such as tachypnea, retractions, grunting, or diaphoresis at rest	Patient with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Inability to carry on any physical activity without discomfort; anginal syndrome may be present at rest.	Extreme limitation; dependent; almost housebound.	Patients cannot or do not perform to completion activities requiring >2 metabolic equivalents. Cannot carry out activities listed above (specific activity scale III).

HF indicates heart failure; and NYHA, New York Heart Association.
Data derived from the New York Heart Association,[33] Rosenthal et al,[34] Campeau,[35] and Goldman et al.[36]

and patients with CHD, valvular heart disease, and infiltrative cardiomyopathies.[37–39] The staging system described in the guidelines recognizes risk factors for the development of HF, including hypertension, diabetes mellitus, and coronary atherosclerosis. If the A through D staging in the HF guidelines were extrapolated to CHD, the vast majority of asymptomatic patients with CHD would be categorized as at least stage B (Figure 2). However, there are few data to show that the medical or device therapies recommended for stages B through D are effective in patients with CHD of any age, thus applying all the recommendations may not optimally suit the CHD population. There is inadequate evidence that categorizing patients with CHD by this system enables management decisions or improves outcome. However, portions of the guidelines should apply to patients with CHD. The guidelines are clear that HF is a clinical diagnosis and that the presence of ventricular dysfunction or the result of any other single diagnostic test is not sufficient to make the diagnosis. This definition of HF as a clinical diagnosis not based solely on a diagnostic test also applies to patients with CHD. Recommendations in the HF guidelines on the control of acquired heart disease risk factors, weight management, and the need for routine health maintenance screening are also broadly applicable to patients with CHD.

Potential Mechanisms of HF in CHD

General Considerations

Clinical HF in CHD is multifactorial. An ineffective cardiovascular system in CHD, even after repair, can be the cumulative

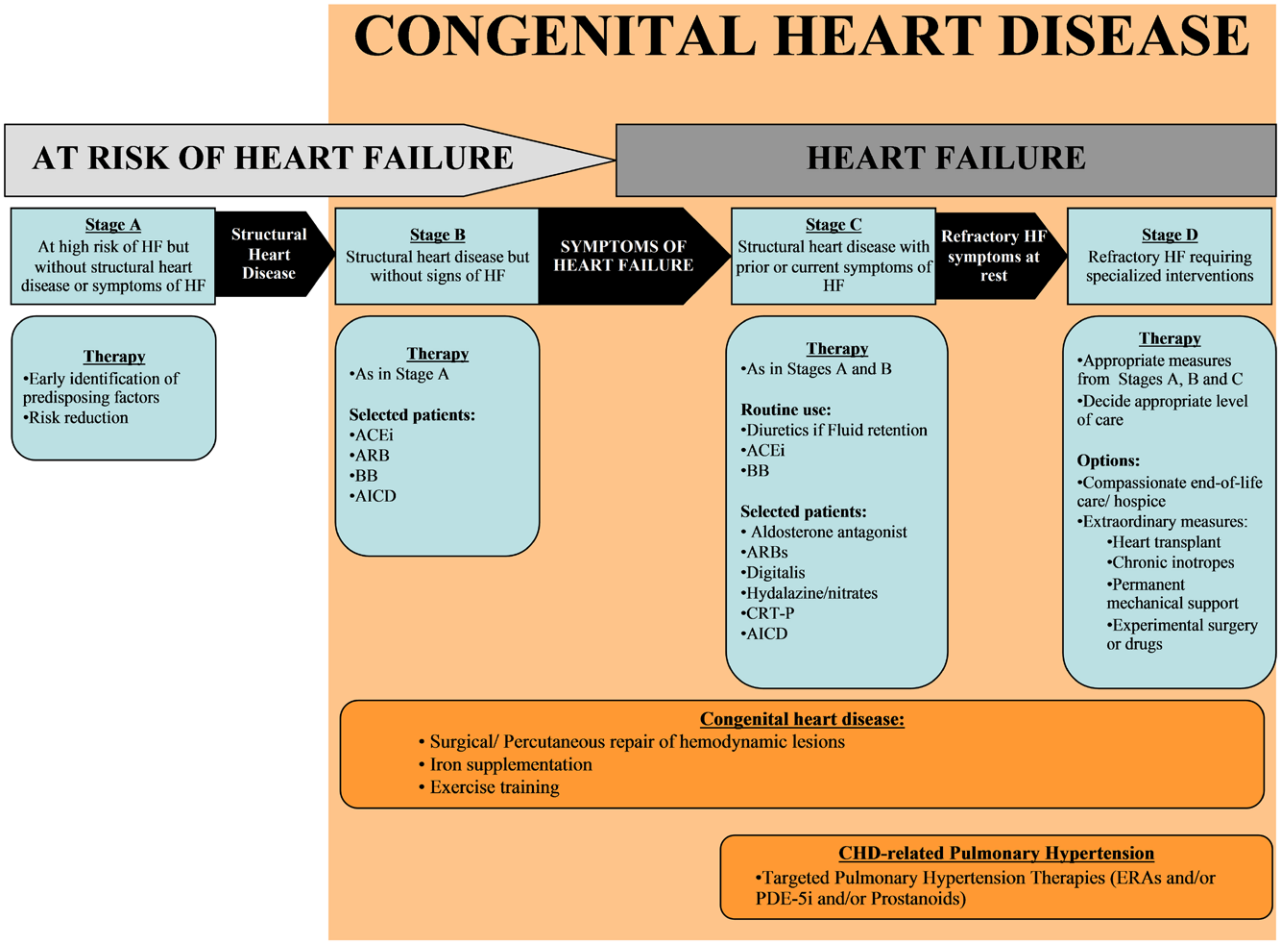

Figure 2. American Heart Association/American College of Cardiology congestive heart failure stages. Stages of the development of heart failure (HF) if applied to patients with adult congenital heart disease (CHD). Patients with adult CHD enter in stage B because structural heart disease is by definition present. Repair of hemodynamic lesions is the primary objective in patients with adult CHD, for both the treatment (stage C) but also the prevention (stage B) of HF. ACEi indicates angiotensin-converting enzyme inhibitor; AICD, automatic implantable cardioverter-defibrillator; ARB, angiotensin receptor blocker; BB, β-blocker; CRT-P, cardiac resynchronization therapy–pacemaker; ERA, endothelium-receptor antagonist; and PDE-5i, phosphodiesterase type 5 inhibitor.

result of valvular abnormalities, shunts, flow obstruction, arrhythmia, or persistent anatomic defects such as an SV, as well as dysfunction of the myocardium itself. Likewise, myocardial dysfunction in CHD can be the result of hemodynamic derangements such as abnormal pressure or volume loading, ventricular hypertrophy, myocardial ischemia, or effects of prior cardiopulmonary bypass or ventriculotomy. Any of these may incite systolic or diastolic impairment (Table 3) and clinical manifestations such as arrhythmia or exercise intolerance. In addition, constriction as a consequence of prior surgery may cause HF symptoms. This section acknowledges these many causes but focuses on potential origins of myocardial dysfunction, a final common pathway in CHD.[40] Much is unknown or speculative, based on extrapolation from other HF models, yet understanding specific mechanisms and pathways is vital to providing informed and effective treatment strategies.

Myocardial Architecture

The myocardial architecture in CHD can exhibit disarray of ventricular myocardial fibers.[41,42] This is especially the case for the RV. Development of the RV is controlled by a profile of transcriptional pathways different from that of the LV.[43] The normal RV myocardium has only a superficial circumferential layer and deep longitudinal layer but does not have the middle layer of circular fibers that normally makes up more than half the wall thickness of a morphological LV.[41] In an animal model of hypoplastic left heart syndrome (HLHS), abnormal RV and LV myocardial fiber orientation was noted prenatally, reflected in abnormal patterns of anisotropic RV and LV deformation.[44] Different myofiber and connective tissue architecture has also been observed in patients with tricuspid atresia. Although hypothetical, it is plausible that these alterations impart a disadvantage to the myocardium and make it vulnerable to dysfunction, although to what extent is unknown.

There is some evidence that LV noncompaction is more common in CHD. If pathological, this would pose an additional risk for the development of HF because of the abnormal myocardium characteristic of the disorder. Whether LV noncompaction is a concomitant genetic abnormality, a response to hemodynamic derangement, or a combination of these is not clear.[45]

Abnormal Perfusion

Many patients with CHD are cyanotic at birth, which can result in significant myocardial ischemia until repair or palliation.

Table 3. Causes of HF in Patients With CHD

Volume overload resulting from left-to-right shunt lesions and valvular regurgitation
Pressure overload resulting from valvular disease and other obstructive lesions
Ventricular failure related to intrinsic myocardial dysfunction
Pulmonary hypertension caused by CHD lesions, ventricular dysfunction, or comorbidities such as obstructive sleep apnea
Systemic arterial hypertension resulting from coarctation, acquired renal disease, essential hypertension, or arteriosclerosis
Coronary artery disease related to CHD, atherosclerosis, or comorbidities such as diabetes mellitus
Cyanosis
Intractable atrial arrhythmias

CHD indicates congenital heart disease; and HF, heart failure.

The early period of ischemia may not have a detectable impact on ventricular function in the short term but may jeopardize or preprogram the myocardium to more serious dysfunction later in life. In other cases, there may be a coronary flow–demand mismatch such as that which occurs in the systemic RV. Many studies demonstrated perfusion abnormalities in patients with a systemic RV in whom the typical coronary anatomy supplying the RV is insufficient for a hypertrophied, enlarged ventricle, although there are conflicting data on the frequency and clinical importance of these findings.[46–51] Some conditions such as transposition of the great arteries (TGA) are associated with coronary anomalies that may subject the myocardium to prolonged ischemia or infarction either before or as a result of surgical repair.[52,53] Myocardial perfusion assessed by positron emission tomography was often abnormal in those with Fontan repairs, congenitally corrected TGA (ccTGA), and dextro-looped TGA (dTGA) after an atrial switch procedure.[54–56] Even in the absence of coronary arterial abnormalities, tissue ischemia may be present. High wall stress from increased afterload in conjunction with decreased coronary flow reserve was associated with myocardial hypoperfusion and supply-demand mismatch,[57,58] the effects of which may only become manifest over decades.

Neurohormonal Activation

There is ample evidence from acquired heart disease that activation of cell signaling systems occurs in response to ischemia or abnormal cardiac distension from deranged pressure or volume loading.[40] Activation of natriuretic peptides and the sympathoadrenergic system, endothelin, and renin-angiotensin-aldosterone system (RAAS) can be driven by any of these adverse conditions,[59–63] which are ubiquitous in CHD. Although less is known about specific activation pathways in CHD, there is certainly growing evidence, mainly in the form of elevated biomarkers, to support similar activation in CHD. Brain natriuretic peptide (BNP) has been the most extensively documented biomarker, with elevated serum levels demonstrated in patients with poorer cardiovascular function or prognosis.[64–67] Data on RAAS and sympathoadrenergic axes in CHD are limited but also suggest activation[40,62] and argue in favor of HF pathways similar to those well studied in other models. However, studies in CHD are small with limited follow-up and, importantly, do not show uptitration of biomarkers in all individuals. Therefore, there is more to understand about the factors that govern neurohormonal activation than available biomarker evidence provides.

Myocardial Fibrosis

One downstream effect of neurohormonal and RAAS activation is alteration in collagen turnover by myofibroblasts, leading to detectable myocardial fibrosis. Some data suggest that an abnormal accumulation of fibrous tissue from an early stage may be an inherent part of some CHD defects in hearts exposed to ischemia and pressure and volume overload.[68,69] For example, biopsy studies demonstrated fibrosis in young patients with tetralogy of Fallot (TOF) undergoing surgery.[70] Ex vivo studies also demonstrated fibrosis in varying quantities. These postmortem studies were not performed in individuals who died of HF, and it may be that fibrosis burden in HF patients is greater.

There has been interest in the presence and impact of myocardial fibrosis in CHD as detected by delayed enhancement after gadolinium injection during cardiac magnetic resonance imaging (MRI), a phenomenon referred to as late gadolinium enhancement (LGE). Gadolinium increases signal intensity of extracellular material in myocardium late after injection, which correlates with fibrosis. This method has been used to demonstrate macroscopic areas of fibrosis in several different CHD subgroups, including TOF (53%),[71] systemic RV (61%),[72] Eisenmenger syndrome (73%),[73] and Fontan palliation (26%).[74] Collectively, these studies demonstrate that the presence of LGE is associated with poorer functional class, lower ventricular systolic function, reduced exercise capacity, and arrhythmia, although the quantity of enhancement is often small and sparse (apart from less common large subendocardial infarcts or surgical scars).

Microscopic fibrosis may be much more diffuse and abundant than the dense replacement fibrosis demonstrated by LGE. Patients studied with methods that quantify diffuse fibrosis using T1 mapping to measure the extracellular volume fraction, a marker of fibrosis, demonstrated significantly more fibrosis than healthy control subjects and more than the amount detected by LGE; the increased diffuse fibrosis correlated with ventricular enlargement and decreased ventricular systolic function.[75] Such methods may help explain the time course and specific inciting causes of fibrosis across the CHD spectrum.

There may be reasons other than pathological fibrosis for increased extracellular volume. Given the differences in extracellular architecture of the RV already discussed, the amount of extracellular matrix may be inherently different. Studies in TOF have shown increased volume density of endomysial collagen and remodeling of collagen matrix in the RV from birth.[76] However, the density of endomysial collagen may be adaptable to conditions. A significant reduction in extracellular collagenous matrix has been seen in patients with HLHS compared with normal control subjects.[77]

Remodeling

It is likely that adverse remodeling, the process by which an initial injury or stressor to the ventricle leads to progressive and predictable structural changes of the ventricle such as dilatation or hypertrophy, is another result of the adverse loading

and structural conditions driving subcellular signals and cellular changes discussed above, although our understanding of these processes is based almost entirely on other forms of heart disease. Regardless of initial insult, remodeling certainly occurs and in itself can lead to progressive ventricular failure and deterioration.

Fibrosis likely contributes to restriction and impairment of diastolic filling. The effect of RV restriction after TOF repair remains somewhat controversial, especially in patients with residual pulmonary regurgitation. In contrast to other patients with pulmonary valve regurgitation, patients with a stiff or restrictive RV manifest a smaller increase in end-diastolic volume and increased early filling. Under such circumstances, the RV acts as a conduit between right atrium and pulmonary artery (PA) in which forward flow into the PA during atrial contraction can be observed. In patients with pulmonary regurgitation, the effect of restrictive RV physiology remains unclear. Increased RV end-diastolic pressure can limit pulmonary regurgitant volume and result in less RV dilation and better exercise tolerance.[78]

However, RV restriction is also likely to result in longer-term complications, including sequelae of increased central venous pressure (CVP), congestive HF, and arrhythmias. Maintenance of sinus rhythm and effective right atrial contraction are particularly important in patients with a restrictive RV.

Geometric and Anatomic Disadvantage

There are hypothetical organ-level explanations for eventual myocardial dysfunction. Accepting that the geometry of a normal biventricular heart is the most efficient in terms of energetics and coupling of atria, ventricles, and great vessels, congenital defects that lack this ideal configuration are inherently disadvantaged. The contribution of adverse geometry to pump function is being studied with methodology such as echocardiographic myocardial strain. An inability to alter preload may limit the increase in stroke volume in response to exercise after an atrial switch or Fontan operation.[79–82] Ventricular-ventricular dependence, an interaction between the ventricles that results in RV dysfunction and eventually leads to LV dysfunction, can occur.[83,84] Another cause of HF in this population may be related to ventriculoarterial coupling in which myocardial function is affected by arterial hemodynamics (ie, pressure, resistance, and stiffness) and vice versa.

Exercise Intolerance in CHD

Overview

Exercise intolerance is common and an important component of the diagnosis of HF. Exercise intolerance is a major cause of morbidity and reduced quality of life in adults with CHD.[78] Almost half of patients with CHD followed up in tertiary centers, most commonly patients with complex cardiac anatomy, unrepaired or palliated lesions, or significant pulmonary hypertension, complain of some degree of exercise intolerance.[85] However, exercise intolerance also occurs in patients with anatomically repaired CHD, including simple lesions.[31]

Patients with CHD often have a reduced perception of ordinary activities and may underestimate their limitations. In fact, a discrepancy between NYHA class based on subjective description of symptoms and exercise capacity on cardiopulmonary exercise testing has been described.[31] Children may be unaware of any limitation. Therefore, objective assessment of exercise capacity is advocated for all patients with CHD, particularly those for whom management may be changed by results or who would benefit from understanding objective limitations to exercise. Patients with an objective reduction in exercise tolerance should be considered for earlier pharmacological or hemodynamic intervention that might improve myocardial performance and exercise capacity, regardless of symptoms. Cardiopulmonary exercise testing with the use of an incremental treadmill or a cycloergometer protocol adjusted to the level of exercise limitation appears ideally suited for assessing patients with CHD. Assessment of peak oxygen consumption ($\dot{V}o_2$), heart rate and blood pressure response, oxygen pulse, and the ventilatory response to exercise provides invaluable information about the severity and mechanisms of exercise intolerance. Baseline assessment can identify deterioration early and point to targets for intervention if repeated when symptoms develop or at intervals in the absence of symptoms.

Exercise testing can also be used to assess the effect of an intervention.

Mechanisms

In patients with CHD, exercise intolerance is related to cardiac dysfunction but also has other causes (Figure 3[1–3,13,18]). Hence, there are differences in exercise capacity between patients with differing CHD diagnoses. In CHD, cardiac dysfunction is a main driver and is related to ventricular dysfunction, valve disease, inflow or outflow obstruction, or chronotropic incompetence, either intrinsic or secondary to arrhythmia or permanent pacing. Noncardiac causes of exercise intolerance should also be considered in CHD and include parenchymal or vascular lung disease and altered chest wall mechanics. Patients with Eisenmenger syndrome, who are at the extreme end of the spectrum of CHD-related pulmonary hypertension, are by far the most limited.[31] They manifest severe lung hypoperfusion, significantly increased physiological dead space, and progressive oxygen desaturation during exercise, leading to pronounced chemoreflex activation. These mechanisms lead to early development of dyspnea, as revealed in an exaggerated ventilatory response to exercise.[86] Musculoskeletal abnormalities such as scoliosis are also common in this population and can affect lung mechanics and the cardiorespiratory response to exercise.[87] The peripheral circulation may also play a role, in particular chemoreflex and ergoreflex activation at the level of skeletal muscles, although less is known about their contribution. Finally, anemia resulting from iron deficiency is commonly seen; however, anemia for a cyanotic patient is relative, and normal hemoglobin for these patients is significantly higher than for noncyanotic patients.[88]

General Evaluation and Management

Because of the unique features of HF in CHD outlined above, we recommend that patients with CHD and HF should be evaluated and managed by or in consultation with cardiologists and cardiac surgeons with expertise in CHD, ideally at a center with expertise in both CHD and HF. Providers should

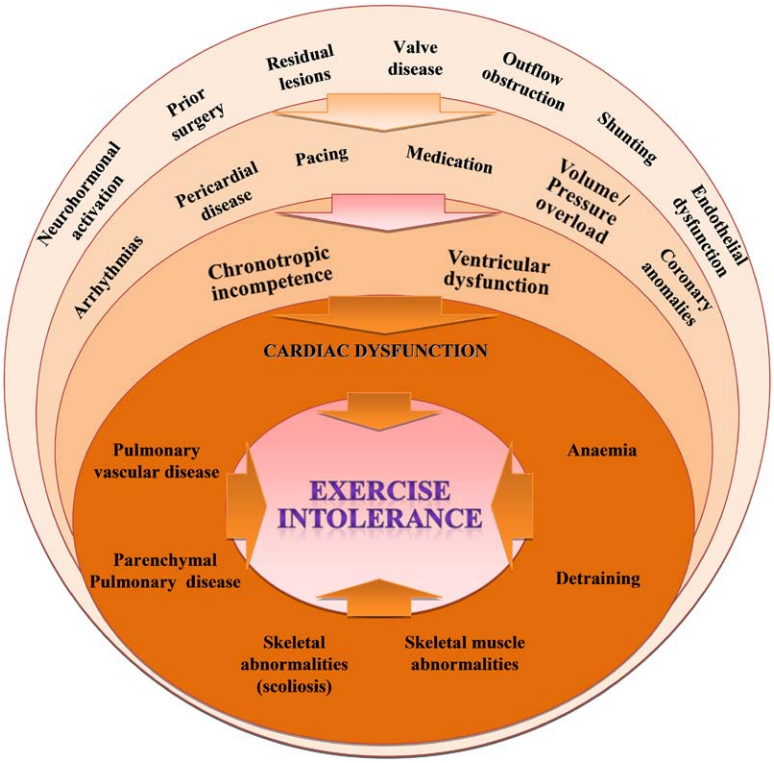

Figure 3. Mechanisms of exercise intolerance in patients with adult congenital heart disease (CHD). Exercise intolerance in adult CHD is the result of cardiac dysfunction, but also important are noncardiac factors relating to the congenital defect, previous surgery, and systemic effects of heart failure.[1–3,13,18]

have a thorough knowledge of an individual patient's anatomy and physiology, which requires a thorough review of all surgical and procedural records.

At the onset or worsening of symptoms, patients with CHD and HF should undergo right-sided and left-sided anatomic and hemodynamic evaluation (eg, echocardiography, cardiac MRI, cardiac computed tomography, and cardiac catheterization) for reversible or repairable structural abnormalities that may contribute to symptoms. Such abnormalities may include but are not limited to the following:

- Valvular dysfunction
- Inflow obstruction
- Outflow obstruction
- Conduit stenosis
- Residual shunting

Objective functional testing (ideally cardiopulmonary exercise testing or surrogate) can be considered to determine the extent of and reason for exercise limitation in the following circumstances:

- New-onset HF symptoms
- Worsening symptoms when a change in therapy may be guided by functional testing results
- New or worsening ventricular dysfunction, even if asymptomatic

Patients with CHD may develop pulmonary hypertension, which can present as or exacerbate HF. Thorough workup, including cardiac catheterization with reversibility challenge, should be considered to evaluate the cause of pulmonary hypertension, its severity, and eligibility for targeted advanced therapies for PA hypertension.

The diagnosis of pulmonary hypertension may not be straightforward in patients with CHD. Echocardiography can be misinterpreted, for example, in the presence of an RV outflow tract obstruction, when the tricuspid valve regurgitation (TR) velocity estimates the RV systolic pressure, but the obstruction to outflow must be taken into account in the estimation of PA pressures. Similarly, the Doppler flow of a restrictive perimembranous ventricular septal defects may be misinterpreted as a TR jet, leading to an erroneous diagnosis of pulmonary hypertension. Involvement of imagers with CHD expertise can be important in these situations and can preclude erroneous treatments or unnecessary invasive procedures.

Careful hemodynamic and anatomic evaluation for constrictive pericarditis or restrictive physiology should be considered in appropriate patients such as those with HF with preserved ejection fraction (EF).

Extrapolation of Standard HF Therapy to CHD Patients

Certain existing guidelines are reasonably presumed to be beneficial for all patients with CHD and HF, such as the application of existing HF guidelines for tobacco cessation, weight management, and routine screening for and treatment of cardiovascular risk factors. However, other guidelines should be extrapolated with the recognition that data are sparse and inconclusive, that benefit may not be proven, and that there may be risks to treatment that are unique to the CHD population.

Evidence supporting the efficacy of standard HF therapies in CHD is lacking, whether in pediatric or adult patients, as further detailed in subsequent sections on specific lesions. Morbidity and mortality resulting from HF in patients with

CHD may occur over many years, a longer time than seen in acquired HF. Despite the large number of patients with CHD, subgroups with specific diagnoses such as systemic RV or Fontan repair are relatively small. Existing data in CHD and HF are generally derived from small populations with poorly validated surrogate end points over relatively short periods of time during which a significant number of events would not be expected. With the recognition of these limitations in clinical studies, it may seem rational to extrapolate treatment strategies that are recommended in the ACC/AHA HF guidelines to patients with CHD because offering no therapy at all seems an unacceptable alternative.[89] However, we emphasize that extrapolation from HF data and guidelines in adult acquired heart disease requires that we assume that the mechanisms, surrogate end points, and responses to therapy are sufficiently similar in CHD, which may not be the case. These concerns apply to extrapolations of adult acquired heart disease data and guidelines to pediatric patients, whether they have acquired or inherited HF or CHD-associated HF. Clearly, more data specific to the patient with HF and CHD are needed. Until those data are available, any extrapolation of HF therapies with benefit demonstrated only in non-CHD populations, whether pediatric or adult, should be done with tempered expectations of efficacy and alertness to the possibility of adverse responses that may outweigh a theoretical benefit.

HF Pharmacotherapy Applied in CHD

Some studies suggest similarities in the pathophysiology of ventricular systolic dysfunction between CHD and various forms of acquired systolic dysfunction.[62,66,90–93] For example, as discussed above, studies have demonstrated neurohormonal changes in adults and children with CHD similar to those in acquired HF.[62,66,90,91] Therapies that reverse remodeling or slow the remodeling process were shown to improve survival in patients with LV systolic dysfunction caused by acquired heart disease.[94–102] Thus, the hope was that the use of the same therapies would, by extension, be of benefit in selected patients with 2-ventricle circulations and evidence of systemic systolic HF.

However, cautionary notes on the extrapolation of therapies effective in LV systolic dysfunction in acquired heart disease to other causes of HF can be found in the experience with HF with preserved EF. Therapies for HF with reduced EF have not shown a mortality benefit in patients with HF with preserved EF, despite a high event rate.[103–107] This suggests that therapies that provide a mortality benefit in patients with HF with reserved EF cannot necessarily be extrapolated to other types of HF. It should also be noted that therapies that improve exercise tolerance are not always beneficial and, in fact, may worsen mortality,[108] thus casting doubt on the use of exercise parameters as surrogate end points in any HF population.

Expectation of benefit is likely highest in those patients with 2-ventricle circulation with systemic LV systolic dysfunction. Medical treatment of patients with HF and CHD with an SV, Eisenmenger syndrome, systemic RV, or failing subpulmonic ventricle should be done in conjunction with a CHD cardiologist. In patients with biventricular circulation with a systemic RV with systolic dysfunction or those with SV physiology palliated with a Fontan repair, the benefit of standard HF therapies may be less than seen in patients with systemic LV dysfunction. The risk of adverse effects with these medications also may be greater, especially in those patients with either preserved systemic RV or SV systolic function.

Some physiological circumstances may pose a particularly high risk of adverse effect of systemic vasodilators, including angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blockade (ARB), or hydralazine. This may be particularly relevant to normotensive patients with Fontan physiology and vasodilation from cirrhosis or hepatorenal syndrome. Thus, these agents should be used cautiously, if at all, with an understanding of the patient unique physiology and serial evaluation for potential adverse effects.

Impact of Arrhythmia on HF and Its Medical Management

Arrhythmias are commonly encountered in CHD, in particular with increasing age. Arrhythmias are closely linked to ventricular function and HF. The full spectrum of arrhythmias can be anticipated, including bradyarrhythmias, atrial and ventricular tachycardias (VTs), and sudden cardiac death (SCD). Atrial arrhythmias, most often intra-atrial re-entrant tachycardia, are commonly encountered and are associated with an increased risk of stroke, HF, and death.[109] Antiarrhythmic drug therapy for the patient with CHD should be selected cautiously because underlying bradyarrhythmias and ventricular dysfunction predispose these patients to proarrhythmic and negative inotropic consequences of drug therapy. Anticoagulation may also be needed as prophylaxis against thromboembolism. Data on novel anticoagulants in CHD are scant, and not all patients with CHD will meet the indications for their use.[110]

The occurrence of sustained atrial or ventricular arrhythmias may be a cause or consequence of a change in hemodynamic status and should prompt the clinician to look for reversible causes of arrhythmia, especially structural lesions that can be treated.

Sinus node dysfunction or atrioventricular nodal conduction abnormalities can worsen functional capacity because bradycardia or atrioventricular dyssynchrony leads to impaired ventricular function. Junctional rhythm can lead to elevated atrial pressure in individuals palliated with a Fontan procedure for SV physiology or those with restrictive physiology, which can be reversed by permanent pacing to restore atrioventricular synchrony.[111–113]

Cardiac Rhythm Device Therapy in HF

In adults and children with CHD, the dominant modes of death are progressive HF and arrhythmia.[23,24,114] An implantable cardioverter-defibrillator (ICD) is an important strategy to consider in the treatment of high-risk patients such as those with HF, particularly in light of concerns about decades of antiarrhythmic therapy in patients who develop arrhythmia at a young age.

There are no prospective trials in individuals with CHD comparing ICD therapy with other strategies to prevent sudden death. Therefore, the role of ICD therapy must be inferred from natural history studies examining risk factors for sudden death and from reported ICD use in specific types of CHD,

as well as from data extrapolated from prospective studies in adults with acquired heart disease. Fewer than 1% of all ICDs are implanted in pediatric patients or patients with CHD.[115]

The survival benefit of ICD therapy in patients with CHD is unknown. Several multicenter studies assessed ICD use in CHD using appropriate shock rate as an outcome. Importantly, such studies showed the risk of lead failure to be 2%/y to 5%/y.[116] Appropriate shocks occur in 10% to 30% of patients with CHD, are highest in secondary prevention, but vary widely by diagnosis and time.[117,118] Inappropriate device therapy has been experienced by as many as 25% to 40% of patients regardless of whether the device was implanted for a primary or secondary indication.[118,119] Lead malfunction, oversensing, and sinus or other atrial tachycardias account for the majority of inappropriate therapies. Inappropriate therapies in acquired heart disease were associated with increased mortality, particularly death secondary to HF.[120,121] Careful attention to device programming and improved device algorithms for monitoring lead function hold promise for reducing the frequency of inappropriate therapies in patients with CHD.[122]

In large, prospective, clinical trials of adult patients with acquired HF and cardiac dyssynchrony,[123–125] cardiac resynchronization therapy (CRT) has been demonstrated to improve exercise capacity, quality of life, LV function, and survival. There are no equivalent data for CHD. Reports on CRT in CHD are largely retrospective evaluations of those in whom CRT was empirically applied.[126–129] In 2012, an ACC Foundation/AHA/Heart Rhythm Society (HRS) task force updated guidelines for device-based therapy of cardiac rhythm abnormalities.[130] Patients with CHD were not a specifically included subgroup, but it is likely that many aspects of the recommendations are relevant to the CHD population, despite the absence of data. Similar caution must be applied in regard to extrapolation, as discussed above in terms of HF therapies. A consensus statement on the recognition and management of arrhythmias in adult CHD addresses many of the arrhythmia issues germane to this population, augmenting the available HRS guidelines.[131,132] Consideration should also be given to the use of MRI-compatible devices when possible, given the benefit of MRI in many of these patients.

Unique Technical Challenges of Device Implantation in CHD

Application of device therapy in patients with CHD imparts unique challenges. Venous access can be difficult both for initial implantation and especially for follow-up lead replacement because patients had previous cardiac surgeries and because they need device therapy for extended periods of time. Before transvenous implantation, patients should be evaluated for venous stenosis and residual shunting, and identified shunts should be closed. Transvenous leads in patients with open intracardiac shunts were associated with a >2-fold increase in the risk of a systemic thromboembolic event.[133] For patients with limited or no venous access, an epicardial approach can be used but requires a limited thoracotomy or sternotomy. Novel arrangements for epicardial defibrillator lead placement have been described, mostly in the pediatric age group because in older patients adhesions from prior surgeries and high defibrillation energy requirements limit the feasibility of this approach.[134] Totally subcutaneous systems are another alternative for patients who can accommodate the increased mass of these devices. The report of successful outcomes with an entirely subcutaneous ICD is encouraging, given the relatively young age of patients with CHD and the potential need for very long-term device therapy.[135] With the use of a parasternal electrode and left lateral thoracic pulse generator, the capability of this device to appropriately detect and treat ventricular arrhythmias was shown after almost 1 year. However, the current device design does not provide bradycardia support, nor is the device capable of antitachycardia therapy, an important deficiency because patients may have frequent recurrences of VT.

Acute complications at implantation are not infrequent, reported in 12% to 13% of both children and adults,[119,136] and problems include lead dislodgement, inability to defibrillate, hematoma, infection, hemothorax, and pneumothorax. Lead-related problems, often necessitating lead extraction, remain a major late complication of device therapy in CHD.[136] When a defibrillator lead requires replacement, it is preferable to remove the lead, and laser lead extraction can be accomplished with success and complication rates comparable to those in the patient without CHD.[137]

Electrophysiology Care Considerations

In summary, patients with CHD, HF, and arrhythmia merit assessment of arrhythmia burden and therapeutic options performed by or in conjunction with a cardiologist with expertise in the management of arrhythmias in patients with CHD. Evaluation for arrhythmias should be performed at the onset or worsening of symptoms, including resting and ambulatory ECG monitoring, pacemaker interrogation, or other testing such as an electrophysiology study as deemed appropriate.[131] Because device implantation in those with CHD can be technically challenging, these procedures are best performed at a CHD center by an electrophysiologist or cardiac surgeon with expertise in CHD. The 2012 ACC Foundation/AHA/HRS task force[130] update on device-based therapy forms a basic primer for medical device use in adults and children with HF and states the following:

- The Class I and III recommendations are directly applicable to those with CHD.
- Consultation with a specialist in CHD is recommended to determine when device therapy is indicated for those situations in which there is no applicable Class I or III indication.

The 2014 consensus statement further addresses the broad range of electrophysiology issues encountered in this patient population and provides recommendations for diagnosis and management based on existing guidelines that were adapted for this specific patient population.[131]

Part II: Specific Lesions

Systemic RV

Definition and Prevalence

Patients with a systemic RV (also described as a subaortic RV) constitute a significant proportion of patients with CHD of

great complexity. Most commonly seen are those with ccTGA and dTGA (also described as complete TGA, classic TGA, or simple TGA) after an atrial switch procedure (Mustard or Senning baffles), as well as patients with a morphological RV functioning as a single systemic ventricle (especially HLHS and its variants).

In a study of adults with complex CHD and a systemic RV, the clinical syndrome of HF occurred in 22% of patients with dTGA with a Mustard procedure and 32% of patients with ccTGA.[22] The prevalence of RV dysfunction and HF increases over time. Reduced systemic RV systolic function was documented in up to 48% and clinical HF in 25% of atrial switch patients at 15 to 18 years of follow-up,[138,139] and after 25 years, more than half of patients with atrial switch had moderate to severe systemic RV dysfunction.[22,140]

Ventricular dysfunction is also more common in those with associated cardiac lesions (ventricular septal defects or pulmonary stenosis). In a large, multicenter, retrospective study of ccTGA, clinical HF was present by 45 years of age in 67% of patients with associated lesions and 25% of patients without associated lesions.[141] In another study, similar proportions of patients were found to have evidence of ventricular dysfunction by nongeometric metrics such as myocardial performance index and strain.[142]

Clinical HF is also associated with arrhythmia, pacemaker implantation, prior surgery of any type, and tricuspid valvuloplasty or replacement.[141] The importance of assessing concomitant tricuspid valve function in patients with a systemic RV has been emphasized, particularly in those with ccTGA. In 1 study, patients with preserved RV systolic function and HF symptoms had significant TR.[143]

Asymptomatic RV dysfunction and HF symptoms with preserved systolic function are also common in patients with systemic RVs.[143] Diastolic dysfunction may account for HF symptoms in patients with a systemic RV, although the prevalence is not known.[144] Patients with an atrial switch may have limited ability to augment venous return and thus stroke volume as a result of nondistensible baffles and conduits. Some data suggest that preload limitations are the primary driver of diminished augmentation of cardiac output in such patients. Limited augmentation of cardiac output and increased venous pressures can result in HF symptoms.[145–147]

In the atrial switch population, HF symptoms are associated with a 4.4-fold increase in the risk of sudden death,[148] although the cause is unclear and there are conflicting explanations in the literature.[148–150] Definitions of normal versus abnormal systemic RV function and methods to assess it are vague and inconsistent.[151,152] This makes comparison of single-center studies and interpretation of data challenging. Prognostic markers for the late development of HF or sudden death in the systemic RV population are also sparse.[153]

Assessment

In patients with a systemic RV, annual clinical evaluation is expected, with more frequent evaluations necessary in patients with HF. BNP has been found to be elevated in patients with a systemic RV, and the level of BNP correlated with a deterioration in clinical status, declining right ventricular ejection fraction (RVEF), decreasing exercise capacity, and worsening TR.[153–155] A specific cutoff value that signifies the presence of ventricular dysfunction or discriminates HF from other diagnoses in the patient with a systemic RV has not been defined.

Periodic imaging to assess RV function and TR is appropriate. For those with ventricular dysfunction, echocardiography should be done serially, at an interval determined by clinical stability and ventricular function. MRI is becoming a valuable imaging tool, and periodic MRI may allow more refined assessment of changes in RV size and function, as well as TR severity and myocardial fibrosis. Changes on imaging studies should prompt a detailed clinical evaluation and consideration for medical or surgical interventions as appropriate.

Cardiac MRI is useful to quantify RV function and volume, valvular regurgitation, and associated lesions. As noted, abnormal LGE denoting fibrosis has been associated with RV dysfunction, poor exercise tolerance, arrhythmia, and progressive clinical deterioration.[156] The presence of fibrosis may explain HF symptoms in the patient with normal RV systolic function. Patients with a systemic RV also have an abnormal response during stress cardiac MRI, manifesting as an inability to increase RVEF during pharmacological or exercise provocation, which, in a small series of patients at a single center, was shown to predict future cardiac events, including hospitalization for HF and cardiac death.[157]

Medical Therapy

Conclusive data on medical management of HF in patients with a systemic RV are lacking, despite the high incidence of late clinical HF and sudden death in this population.[117,148,158] Use of conventional HF medications may be problematic because of preexisting sinus node dysfunction, heart block, baffle stenosis, nondistensible atria, and restrictive RV physiology. β-Blockade may exacerbate bradyarrhythmias, whereas vasodilation could be counterproductive in patients with nondistensible atria or restrictive physiology. Vasodilation can increase venous capacitance, which may decrease ventricular filling rather than augment stroke volume. Thus, therapies shown to be effective in acquired LV dysfunction should be applied with caution to the patient with a systemic RV.

ACE Inhibition or ARB

Studies of ACE inhibition in patients with systemic RVs have mostly been small, single-center, uncontrolled trials using exercise parameters or changes in RV size or function as surrogate end points. A retrospective study of lisinopril in 14 patients,[159] a prospective study of lisinopril in 8 patients,[160] and a randomized, placebo-controlled trial of ramipril in 17 adult patients[161] showed no improvement in end points such as EF, $\dot{V}o_2$, and cardiac index, although there are limitations to the use of these end points. Although some patients with acquired HF may have an improved EF or LV volume with ACE inhibitors/ARB, this is not seen in all patients, and there is survival and symptomatic benefit that is independent of the change in ventricular size and function in that population. Thus, an argument can be made that neither RVEF nor RV end-diastolic volume necessarily would be expected to change with ACE inhibition and that ventricular size and function may not correlate directly with outcomes and thus may not be ideal end points.

A trial of enalapril in infants with a systemic RV in the setting of HLHS did not demonstrate a beneficial effect on

the end points of growth, ventricular function, or clinical HF.[162] However, 96% of infants in the study had normal or only mildly depressed ventricular function at baseline, and 80% were symptom free after superior cavopulmonary anastomosis surgery. Despite insufficient data, the use of an ACE inhibitor is common in SV patients with RV morphology and significant atrioventricular valve regurgitation, despite the fact that no direct correlation has been shown between ACE inhibitor use and an improvement in ventricular systolic or diastolic dysfunction.[163] No studies in children with ccTGA or after atrial switch for dTGA have been published.

A small, prospective, crossover study of losartan in patients with TGA demonstrated improved EF and exercise duration in an adolescent/young adult population.[164] However, in the only 2 published multicenter, randomized, placebo-controlled studies of ARB in adults with TGA and a systemic RV, no significant benefit was demonstrated.[141,142] The first of these found no benefit with respect to exercise duration, $\dot{V}o_2$, or N-terminal pro-BNP levels. Medical therapy was continued for only 4 months; 93% of patients were asymptomatic at baseline; and most had only mildly depressed RV systolic function and trivial or mild TR.[165] A larger placebo-controlled trial in 88 patients with 3 years of follow-up showed no conclusive benefit of valsartan on RVEF or exercise capacity, although there was a favorable preservation of RV end-diastolic volume.[166] These findings again raise questions about the routine applicability of ACE inhibition/ARB in this population, although they do not inherently preclude the possibility that benefit can exist if applied to the right population of patients or if used for a longer duration. Studies in children with a systemic RV have not been performed.

These studies were not powered to detect a small change. In addition, the end points chosen have not been shown to be useful in predicting mortality in patients with acquired HF, in whom beneficial remodeling is the only end point consistently associated with improved outcomes. Therefore, the limited studies available are not sufficient to determine whether RAAS inhibition is beneficial, neutral, or detrimental to pediatric and adult patients with systemic RV dysfunction and symptomatic HF. One argument would state that if these medications have few complications, then using them for possible benefit would be a reasonable strategy. However, the risk of adverse effects in these patients, particularly growing children, may not be understood well enough for such a strategy to be uniformly adopted. Thus, more data on both benefits and risks are needed in these populations.

β-Blockade

Several small, single-center studies have demonstrated a potential benefit of β-blockade in adult patients with systemic RVs, describing improvement in symptoms, less systemic TR, improved functional status, and positive effects on RV remodeling.[156,167,168] Small series in adults with TGA and a systemic RV have shown improvement in ventricular function and HF symptoms after short-term administration of β-blockers,[168] but the effects on hospital admission, sudden death, and HF-related death have not been studied. In a small, multicenter series of atrial switch patients with ICDs, treatment with β-blockers appeared protective against arrhythmic events.[117] The remaining reports in the literature are limited to case reports.[169]

Children with CHD were included in the only pediatric multicenter, prospective, randomized trial of β-blockade for the treatment of HF. In this trial, there was no significant difference overall in the primary outcome of HF symptoms, and there was a nonbeneficial trend in the group with a systemic RV.[170] Conversely, in another small study of older SV children primarily with a systemic RV, improvements in EF and symptoms of HF were seen.[171] There are no larger trials in children with systemic RVs.

Although theoretical rationales support both β-blockade and RAAS inhibition in asymptomatic patients with a systemic RV, the benefit of routine use of these medications is not evident. When the pathophysiology of the systemic RV has been better elucidated and adequately powered randomized studies have been carried out, there may be more evidence supporting their routine use. For patients with a systemic RV who have clinical HF, use of RAAS inhibition and β-blockade can be considered after interventional, surgical, and arrhythmia issues, including chronotropic incompetence, have been addressed. The efficacy of such medications will likely vary, depending on patient age and comorbidities, mechanism and severity of ventricular dysfunction, associated structural disease, SV versus systemic RV, and, in the case of the SV patient, stage of palliation (eg, precavopulmonary shunt, superior cavopulmonary shunt, Fontan operation). Therefore, each individual patient's clinical response to these medications must be assessed on initiation and uptitration of dose to ensure no adverse response, with therapy altered accordingly. Ascertaining benefit may be more difficult, particularly in the absence of data on whether medications prolong life independently of symptom improvement.

ICD and CRT Device Therapy

Implantable Cardioverter-Defibrillator

For patients with a systemic RV, progressive HF and sudden death run along the same timeline, and prevention of sudden death is an integral part of HF management. In ccTGA, the clinical presentation and natural history are strongly affected by the presence of associated anomalies, conduction system integrity, TR, and RV function. There are no studies on ICD use in ccTGA. ACC/AHA/HRS guidelines may reasonably be applied to patients with syncope or VT, but they do not address risk in patients with systemic RV dysfunction or significant TR. The guidelines for primary prevention ICD placement using EF and NYHA classification were developed for individuals with LV dysfunction and were based solely on prospective data in adults with coronary artery disease and nonischemic cardiomyopathy.

In patients with atrial switch, there are some data on ICD outcomes. A multicenter series of ICD recipients with dTGA after atrial switch operations found that the incidence of appropriate shocks was only 0.5%/y when the ICD was implanted for primary prevention compared with 6% when implanted for secondary prevention.[117] This low rate of appropriate ICD shocks calls into question current methods for identifying patients at risk for sudden death. The only risk factor identified in the

primary prevention group was nonuse of β-blockers. However, in that study, RVEF did not reach significance as a univariate predictor of appropriate shocks. Thus, ICD can be considered cautiously for primary prevention, although only after or in conjunction with the use of β-blockers to mitigate arrhythmias.

The technical challenges associated with ICD implantation in individuals with a systemic RV arise mainly from the difficulty of positioning the ICD coil to achieve successful defibrillation. In ccTGA, there is ventricular inversion, so the ICD lead crosses the mitral valve into an anterior LV, whereas in dTGA patients palliated with an atrial switch, the LV is posterior. Dextrocardia is present in 30% of individuals with ccTGA, necessitating right-sided placement of the ICD device. Residual intracardiac shunts, systemic venous anomalies, and systemic venous and baffle obstruction all may complicate placement of the ICD lead. These multiple issues must be accounted for in the consideration of ICDs for SCD prevention in HF patients with systemic RV.

Cardiac Resynchronization Therapy

Studies of CRT in CHD demonstrate that patients with TGA with a systemic RV make up 15% to 29% of patients with CHD receiving CRT.[1,4,5,127–129] There is a high obligate need for device therapy to manage bradyarrhythmia or tachyarrhythmia, and CRT is often an added modality considered when there is already an established indication for device implantation. The indication for CRT in these patients is predominantly electric dyssynchrony because there are no established ways to determine mechanical dyssynchrony in a systemic RV. Typical patients will have complete heart block, interventricular conduction delay, or right bundle-branch block. In ccTGA, cardiac malposition may obscure classification of bundle-branch block morphology. In reported patients who have received CRT, QRS duration has averaged ≈160 milliseconds. Small series have studied indexes of atrioventricular, interventricular, and intraventricular dyssynchrony.[8–10,172–174] The benefit of CRT in the treatment of HF in a systemic RV remains unknown, although limited data suggest trends toward modest improvement in RVEF and NYHA class. Reverse RV remodeling after CRT has not yet been shown. Data on the efficacy of CRT in a systemic RV consist only of retrospective cohort series; no prospective data are available.

The technical aspects of implementing CRT for an individual with a systemic RV are considerable. The implantation route for RV lead placement (ie, systemic ventricular pacing) can be either transvenous or epicardial, depending on the anatomy and need for concomitant cardiac surgery. Often, a hybrid system is used that involves both transvenous and epicardial approaches.[1,4,5,8–10,127–129,173–175]

In ccTGA, it may be possible to implant an RV lead via the coronary sinus in individuals with suitable coronary sinus anatomy. Multiple anatomic variations have been well described and need to be understood before any attempt to place a transvenous RV lead via the coronary sinus.[11,12,176,177] Drainage of the coronary sinus to the left atrium occurs in up 20% of ccTGA patients, thus precluding a transvenous approach in that subset of patients. It is prudent to obtain either cardiac computed tomography or MRI to fully delineate the coronary sinus anatomy before placement of a transvenous RV lead is attempted. If an epicardial RV lead is needed, then a left thoracotomy approach is necessary to access the posteriorly located RV.

In patients with dTGA palliated via an atrial switch, RV lead placement is usually done by an epicardial approach. Because the RV is anterior, an RV lead can often be placed with a subxiphoid incision or a mini-sternotomy. Placement of an RV lead transvenously via transbaffle puncture has been reported, although the long-term risk of systemic thromboembolism is concerning.[13,178] In addition, the standard risks associated with implantation of leads and devices apply to this population and may be magnified because of the nonstandard anatomy. LV and RV performance should be monitored closely after implantation because new subpulmonary LV dysfunction has been reported in 3 patients who had CRT for systemic RV failure.[14,179]

Surgical Therapy and Ventricular Assist Devices

Residual lesions such as outflow obstruction or valvular regurgitation should be addressed, preferably before the onset of significant ventricular dysfunction, as per other published guidelines.[1,180] Once the systemic RV has failed, further surgery carries an increased risk of mortality and a lower likelihood of ventricular recovery. Referral to a CHD transplantation center for advanced HF therapies (including mechanical support and heart transplantation) should be considered for patients with a systemic RV and a clinical syndrome of HF who fail medical therapy and do not have residual lesions amenable to repair.

A variety of ventricular assist devices have been used for the failing systemic RV in patients with ccTGA and dTGA after atrial switch operations. The systemic RV in both scenarios predisposes to inflow cannula occlusion as a result of the hypertrophied trabeculations in the RV, even if the RV is significantly dilated. Accordingly, extensive muscle resection has been carried out before inflow cannula placement in most reported cases.[181,182]

For patients who have undergone atrial switch procedures, the location and orientation of the systemic RV create additional complexity in the placement of the inflow cannula, in particular for implantable devices in which the angle of the inflow cannula is short and relatively fixed with regard to rotational degrees of freedom. However, for patients supported with paracorporeal devices, manipulation of the inflow and outflow cannulas can adjust for anomalies of cardiac situs or rotation.[183] Despite the technical difficulties in implantation, an RV inflow cannula would appear to be superior because of the difficulty of atrial inflow in the setting of Mustard or Senning baffles where the narrow caliber of the atrial baffle could cause obstruction of the inflow cannula. Future-generation devices, including catheter-based therapies[184] and smaller axial flow pumps,[185–187] may provide additional temporary and long-term alternatives that may be more forgiving of the size and orientation constraints described.

Palliated SV and Fontan

Definition and Prevalence

Many complex congenital lesions are characterized by inadequate development of 1 ventricle, leaving patients with a

single functional ventricle supplying both systemic and pulmonary blood flow. The vast majority of patients with an SV will have undergone some form of initial palliative procedure to control pulmonary blood flow, either restricting pulmonary blood flow with a PA banding procedure or increasing pulmonary blood flow with a systemic vein–to–PA shunt (such as a Blalock-Taussig-Thomas shunt) or systemic vein–to–PA anastomosis (such as a Glenn shunt or bidirectional superior cavopulmonary anastomosis). Initial palliation is usually followed by complete redirection of systemic venous return (superior and inferior vena cava) directly to the PAs, with shunt closure or debanding of the PA as appropriate. Cavopulmonary connections are characterized by passive pulmonary blood flow without the benefit of a subpulmonary pumping chamber, a surgically created arrangement generally called a Fontan after Francis Fontan, the surgeon who initially described the operation.[188] Since Fontan and Baudet's initial publication,[188] multiple surgical modifications have been developed, although all have a common physiology consisting of passive pulmonary blood flow at the expense of chronically elevated systemic venous pressure and relatively low and restricted cardiac output.

The Fontan repair improves systemic oxygen saturation, but because there is no subpulmonic pump, passive antegrade blood flow through the pulmonary vasculature requires an elevated CVP slightly higher than the mean PA pressure and higher than the pulmonary venous, atrial, and ventricular end-diastolic pressures. Respiratory mechanics are also important because negative intrathoracic pressure aids in moving blood through the pulmonary vasculature.[189] The surgical approach may also include the creation of a fenestration between the systemic venous circuit and the pulmonary venous atrium to allow decompression of the systemic venous circuit, allowing a lower CVP at the expense of some degree of systemic desaturation.[190]

HF in patients after a Fontan operation can be as unique as the Fontan physiology itself. HF may develop because of systolic or diastolic ventricular dysfunction, resulting in increased ventricular filling pressures. However, it can also occur because of abnormally high pulmonary vascular resistance, leading to a "preload-starved" ventricle, often despite preserved ventricular systolic and diastolic function. Furthermore, patients with Fontan physiology have a predilection to develop protein-losing enteropathy with symptoms that mimic HF, including fatigue, peripheral edema, effusions, and ascites. The prognosis for patients with protein-losing enteropathy is poor, with mortality as high as 46% to 62% despite either medical or surgical therapy.[191]

The distinction between Fontan failure with preserved or reduced systolic function is important because therapeutic options, expected responses, and long-term outcomes may vary, depending on systolic function. Some data confirm the importance of that dichotomy. In a study of Fontan patients undergoing transplantation, patients with preserved EF had significantly worse outcomes than those with reduced EF, suggesting that important mechanisms other than systolic dysfunction contributed to heart failure in the former group.[192] Understanding the specific mechanisms associated with HF in a patient with a Fontan repair is crucial.

Multiple long-term complications associated with Fontan physiology exacerbate HF symptoms. Over time, increased CVP and low cardiac output may lead to chronic congestive hepatopathy with hepatic dysfunction, cirrhosis, ascites, varices, hepatorenal syndrome, and risk of hepatocellular carcinoma.[16,193–209] Sluggish flow through an atriopulmonary connection increases the risk of thrombosis and embolism, which can further increase the pulmonary vascular resistance and thus CVP. Atrial arrhythmias and sinus node dysfunction are very common, both as a cause and as a consequence of abnormal Fontan hemodynamics, and are important contributors to HF symptoms. Cyanosis is common either because of right-to-left shunting through a surgically created fenestration or via other channels that develop between the systemic and pulmonary venous circulations, thus reducing systemic oxygen delivery. Although high CVP and low cardiac output are common among all Fontan patients with HF, the associated complications of cyanosis, hepatic dysfunction, and thrombi can contribute to HF symptoms in patients with preserved ventricular dysfunction. This emphasizes that HF in SV patients is due only to myocardial function.

The lack of a robust definition of Fontan failure has contributed to the limited understanding of the prevalence of HF in Fontan-palliated SVs. Estimates of HF prevalence range from 10% to 20% early after Fontan surgery, rising to 50% in adults who underwent the Fontan operation many years previously.[21,22] Fontan physiology imparts progressive risk for HF symptoms as patients age as a result of systemic ventricular dysfunction or an increased CVP. Additionally, the physiology of the SV before Fontan, whether shunt palliated or not, is one of significant volume overload. However, immediately after a Fontan procedure, preload will decrease, and the ventricle may be relatively underfilled, leading to a higher mass-to-volume ratio with implications for diastolic filling. Thus, as with other forms of CHD, irreversible changes may result from those early physiological derangements that manifest with advancing age and concomitant insult or injury. Progressive atrioventricular valve regurgitation is common in the Fontan patient and can exacerbate ventricular dysfunction and impair Fontan flow, worsening HF. In patients with HLHS, there is an additional risk of systolic dysfunction of the vulnerable systemic RV. Additionally, palliative procedures such as the Norwood repair for HLHS are prone to present increased afterload because of subaortic or aortic obstruction or aortic stiffness, further challenging the systemic RV.

Assessment

HF should be anticipated in the long-term care of Fontan patients. Because of the complexity, heterogeneity, and unusual nature and presentations of Fontan failure, management by CHD experts is required. It is particularly important to assess for potentially reversible causes of HF such as arrhythmias, obstruction of the Fontan pathway, residual shunts, and valve dysfunction. Further assessment may include ambulatory ECG monitoring, stress testing, and MRI or computed tomography imaging. Careful invasive anatomic and hemodynamic assessment by cardiac catheterization should be considered early, particularly if a reversible cause of the HF is not found in a noninvasive evaluation. Ideally, all diagnostic

procedures should be done and interpreted by technicians and providers with expertise in CHD. Evaluation should include, but may not be limited to, assessment for the following:

- Ventricular dysfunction
- Arrhythmias
- Thrombus in the Fontan pathways
- Protein-losing enteropathy
- Valvular dysfunction
- Residual right-to-left shunt
- Inflow or outflow obstruction, including a restrictive atrial or ventricular septal defect that can impede cardiac output
- Elevated systemic vascular resistance
- Elevated systemic venous pressures and pulmonary vascular resistance
- Plastic bronchitis

Medical Therapy

ACE inhibition is used for the treatment of HF in patients with SV physiology, but there have been few studies on which to base this use. Enalapril was tested in a relatively large, randomized trial in pediatric patients with SV physiology by the evaluation of ventricular function and somatic growth, both impaired in HF. There were no significant differences between the treatment and placebo groups in ventricular size (*z* score), Ross HF class, BNP levels, EF, or death/transplantation after 12 months.[162] In a smaller randomized, double-blind, placebo-controlled crossover trial, enalapril did not alter systemic vascular resistance, resting cardiac index, diastolic function, or exercise capacity.[210] There are no data evaluating ACE inhibitors in adults with SV and symptomatic HF.

Published clinical experience with the use of β-blockade in patients with SV with HF is also limited. There is only 1 report on β-blocker therapy in SV patients. In a retrospective study of 51 patients of varying ages (children, adolescents, and young adults) and nature of intervention (unoperated, after Glenn shunt, and after Fontan), carvedilol together with standard medical therapy (in this case, diuretics, digoxin, and ACE inhibitor at the providers' discretion) reduced the symptoms of HF and improved clinical parameters.[159,171] In a multicenter, double-blind, placebo-controlled study of carvedilol in children with systemic ventricular dysfunction, β-blockers appeared to have a negative or neutral effect in patients with SV or a systemic RV compared with patients with cardiomyopathies and no structural heart defects.[170] Diuretics and digoxin are widely used in clinical practice for patients with fluid retention and for those with gross abnormalities of SV function, the so-called congestive HF. There is no study proving the benefits of treating HF with diuretics and digoxin in SV patients, although anecdotal clinical experience suggests symptomatic improvement in some patients.

There is growing interest in the use of pulmonary vasodilator therapy to lower pulmonary vascular resistance and to improve ventricular preload. Although theoretically the results were beneficial, small series show mixed results. Most favorable changes were demonstrated with phosphodiesterase inhibitors. A single dose improved peak $\dot{V}o_2$ during exercise with a measurable increase in both pulmonary and systemic blood flow at peak exercise.[211,212] Others series showed a favorable impact on the Doppler-derived myocardial performance index[213] and systolic arterial and ventricular elastance.[214] With longer therapy, a double-blind, placebo-controlled crossover trial showed an improvement in the ventilatory efficiency slope during cardiopulmonary exercise testing, although other parameters were not improved.[215] Less success has been demonstrated with endothelin antagonists. Limited improvements in ventricular function were described in 1 study,[216] but other pilot studies found no benefit.[217,218] Regardless, a trial of endothelin antagonism in Fontan patients is ongoing.[219] This and other needed research will clarify the role of pulmonary vasodilators in these patients.

Optimal medical therapy of HF in SV patients palliated with the Fontan procedure remains under study. Multicenter, randomized, controlled, prospective trials are needed to elucidate the effect of treatments of HF in such patients to provide a basis for formulating future guidelines. It is not known whether pharmacological RAAS inhibition or adrenergic blockade produces similar effects in patients with a single LV versus a single RV.[162,165,220] Furthermore, there is some evidence that activation of the RAAS may not be the dominant pathophysiological contributor to HF in patients with SV physiology, in contrast to patients with LV dysfunction and 2 ventricles.[165] Research is also needed to discern possible differences in the effects of β-blocker therapy between children with SV physiology and adolescents and adults.[170]

Referral to a CHD transplantation center for advanced HF therapies (including mechanical support and heart transplantation) should be considered for patients with SV physiology and symptomatic HF refractory to medical therapy.

Device Therapy

Ventricular activation abnormalities contribute to HF in patients with SV. Loss of atrioventricular synchrony can worsen hemodynamics, and maintenance of atrioventricular synchrony can be of significant benefit.[111] Such patients may benefit from CRT, although in SV patients CRT is more properly called multisite pacing. Evidence supporting CRT in SV physiology is limited to case series in the acute postoperative setting and a single retrospective study.[127,221] These series demonstrated improved cardiac index, systolic blood pressure, and indexes of asynchrony after CRT, but in the heterogeneous patient population, technical limitations imposed by patient body size, need for epicardial access, and unique forms of ventricular dyssynchrony have made it difficult to draw strong conclusions or to rationalize widespread use. Furthermore, lead placement requires thoracotomy. The benefit of ICD implantation is untested and requires either a hybrid epicardial approach using epicardial pace/sense leads combined with subcutaneous and/or pericardial coils or a total subcutaneous system.

Left-Sided Pressure Overload Lesions

Overview

Left-sided pressure overload lesions encompass obstruction in the LV outflow tract (LVOT) below, at, or above the aortic valve and include subvalvular, valvular, and supravalvular aortic valve disease, as well as coarctation of the aorta. Although the physiological principles guiding the management of aortic

stenosis have similar application here, there are some nuances. Depending on the severity and duration of the LV pressure overload, any of the above pathologies may lead to ventricular hypertrophy and diastolic dysfunction. With severe obstruction, hypertrophy, subendocardial ischemia, and eventually impaired LV systolic function may result.

Whether subvalvular, valvular, or supravalvular, an LV obstructive lesion may impart significant risk for left-sided HF and is often an indication for corrective action, including catheter-based intervention or surgery. Current guidelines provide indications for intervention in LVOT obstructions in adults.[1,222] Unlike adults with calcific aortic valve disease, the CHD population of children, adolescents, and young adults may benefit from balloon valvotomy because of the differences in valvular anatomy and relative lack of calcification.[223–225] Thus, balloon valvotomy rather than aortic valve replacement may be a first-line therapy of aortic stenosis in selected young patients.

In some cases, HF may persist after intervention as a result of LV diastolic dysfunction or adverse LV remodeling, resulting in dysfunctional myocardium. This is a patient population in whom existing HF guidelines developed for acquired heart disease should be applied once the outflow obstruction has been relieved. Although some pressure-overload states such as severe congenital aortic valve stenosis may result in HF in early life, other lesions may not be cause for concern because of their mild severity throughout life. At other times, LV systolic dysfunction may become manifest after several surgical attempts to alleviate obstruction. Subaortic stenosis is particularly prone to need recurrent intervention, with incremental risk imparted by each successive surgery.

Medical Therapy

There is not a role for primary medical therapy for patients who meet accepted indications for intervention on LVOT obstructions unless the patient is inoperable and not a candidate for catheter-based therapies. Medical therapy for comorbid conditions such as hypertension may be a part of the overall management, but not in lieu of mechanical relief of LVOT obstruction. Recent AHA/ACC guidelines provide specific recommendations for the medical treatment of valvular disease and of LVOT obstruction and associated lesions in adult patients with CHD, although studies specific to CHD are limited.[1,223]

Coarctation of the aorta is a relatively common congenital cause of increased LV afterload. However, optimal medical management of hypertension or HF in patients with repaired coarctation has not been determined. One study of patients with repaired coarctation compared β-blockade with ARB for hypertension control.[226] Metoprolol improved systolic blood pressure compared with candesartan, implying that the RAAS did not play a significant role in the mechanism of hypertension and that β-blockers may be preferable agents in this patient population. However, the patients studied did not have HF.

Surgical Therapy

Surgical strategies for HF in the setting of LV pressure loading must first target repair of any obstructive lesion. There has been interest in "rehabilitation" of the LV itself in cases of borderline left-sided structures, in particular the targeted resection of endocardial fibroelastosis after either fetal balloon interventions or prior surgical repair. Resection of the endocardial fibroelastosis may ameliorate diastolic dysfunction, although experience is limited.[227]

When ventricular assist device therapy is considered to manage HF in patients with LV obstructive lesions, it is important to understand any residual lesions. Residual subaortic or valvar aortic stenosis is not a concern because the outflow cannula of the assist device sits distal to these areas of obstruction. However, concomitant aortic regurgitation may require oversewing of the aortic valve should the regurgitant fraction be significant. For patients with residual transverse aortic arch obstruction or coarctation who require emergency assist device implantation, a left thoracotomy off-pump approach, with implantation of the outflow cannula in the descending aorta, can be successful in larger patients. However, the risk of thrombus within the proximal aorta may be substantial when such a strategy is used as a result of areas of regional low flow, and there is concern about the adequacy of antegrade cerebral blood flow.

All left-sided outflow lesions should be addressed at the time of transplantation; intracardiac lesions are relieved by surgical repair, but residual arch or descending aortic obstruction should be relieved through reconstruction at the time of transplantation, preferably with donor aortic tissue in a fashion akin to that in primary transplantation for HLHS.

Device Therapy

In the setting of left-sided obstructive defects, ventricular arrhythmias, sudden death, left bundle-branch block, and atrial fibrillation are all potential arrhythmic manifestations. Conventional approaches for device implantation can be used per available consensus guideline statements for determining indications for pacemaker, ICD, and CRT, including the 2012 ACC Foundation/AHA/HRS update on device-based therapy.[130,132] The key challenge in the management of obstructive defects in CHD is determining the timing of intervention.

Subpulmonic RV Volume-Loading Lesions

Overview

Volume-loading lesions affecting the subpulmonic RV in patients with CHD are most often encountered in the form of valve dysfunction, either congenital regurgitation (eg, Ebstein anomaly) or as long-term sequelae of previous surgery (such as after congenital pulmonary stenosis or repair of TOF). The deleterious effects of long-standing pulmonary regurgitation are now clear, and the benefits of pulmonary valve replacement are well established, although there is less consensus on optimal timing.[228–234]

Right-sided volume overload often results from Ebstein anomaly of the tricuspid valve with severe TR. Apical displacement of the tricuspid valve results in a small "functional" RV, often limited to the outflow tract, and the inlet of the RV becomes "atrialized." RV enlargement and dysfunction are common and related to the geometric change in the RV: The inlet portion behaves as part of the right atrium, whereas the RV outflow tract dilates to accommodate a larger volume in an attempt to maintain cardiac output. In each of these RV volume-loading states, delayed intervention can result in myocardial dysfunction and clinical HF.

Long-term changes in RV volume load are better tolerated than short-term changes, and RV adaptation depends not only on intrinsic (myocardial) factors but also on factors outside the RV itself such as the LV and the pericardium. Notwithstanding the benefit of adaptation, chronic volume loading of the RV eventually leads to progressive RV dilation and dysfunction, associated with decreasing exercise intolerance and fatigue. An increase in RV diastolic and systolic volume and RV mass leads to progressively reduced EF despite preserved cardiac output and wall stress.[235] In fact, an inverse relation between RV mass and RVEF has been described.[236,237] RV fibrosis, altered RV geometry, abnormal electromechanical coupling, and abnormal perfusion likely also contribute to RV dysfunction.[238] Excessive volume loading of the RV may contribute to low cardiac output because of septal deviation to the left, adversely affecting ventricular function. Myocardial fibrosis and scarring from long-standing RV volume overload and previous surgery, as well as the effects of neurohormonal activation and hypertrophy, which can affect both ventricles, can also result in malignant VT and sudden death.[78]

Diastolic RV dysfunction is not uncommon in patients with TOF and appears to affect pathophysiology and outcome. The effect of RV restriction late after primary repair remains somewhat controversial, especially in patients with residual pulmonary regurgitation. RV stiffness limits end-diastolic volume, causing the RV to act more as a conduit between the right atrium and PA. Consequently, the diagnosis of restrictive RV filling may be based on finding forward flow within the PA during atrial contraction. However, this phenomenon requires the resistance to RV filling to exceed that of the pulmonary vascular bed, so transtricuspid flow during atrial contraction will produce antegrade PA blood flow. Conditions that elevate PA pressure such as elevated left-sided pressures from LV restriction may impede antegrade flow into the PA during atrial systole and mask RV restriction.[239–242] It is unclear how the presence of restriction alters management, although ACE inhibition improved LV structure and function.[243]

Ventricular Interdependence and LV Dysfunction

Ventricular-ventricular interaction plays an important role in the development of LV dysfunction through mechanical, electric, and neurohormonal coupling. The RV and LV share myofibers. Therefore, significant changes in intrinsic myocardial shortening of the RV are likely to affect the LV and vice versa (cross-talk gain). In the normal heart, elegant experimental data showed that the LV contributes significantly to the development of RV pressure, whereas the RV contributes little to the LV. However, abnormalities in RV size and geometry in patients with significant right-sided volume overload can lead to pericardial constraint that affects both systolic and diastolic LV function. A diastolic shift of the ventricular septum, limiting LV diastolic expansion, is common in patients with RV volume overload, especially those with patch repair of large ventricular septal defects and those with Ebstein anomaly with a large atrialized portion of the RV inlet. Poor RV output also contributes to low LV preload.

LV dysfunction late after repair of TOF is not uncommon. LVEF is significantly lower in TOF patients compared with control subjects.[235] Reduced LVEF can be found in 21% of patients with repaired TOF, and in one third of those patients, LV dysfunction was moderate to severe.[84] LV dysfunction was found more often in men and in those with late repair, LV enlargement, history of arrhythmia, longer QRS duration, an ICD, or moderate to severe RV dysfunction. Patients with a late repair are often those who underwent surgery in an earlier surgical era when perioperative complications, accidental resection of a left anterior descending artery passing across the RV outflow tract, suboptimal myocardial perfusion, and longer periods of volume loading and hypoxia resulting from palliative arterial shunts before repair were more common. LV dysfunction is also common in patients with Ebstein anomaly, is a strong predictor of adverse outcome, and contributes to the decrease in exercise capacity. LV dysfunction in Ebstein anomaly is multifactorial, most likely driven by diastolic compression of the LV by the enlarged RV in the context of a relatively fixed pericardial volume and significant septal deviation, coupled with reduced output from the RV. In fact, decompression of the RV by surgical repair has been shown to improve LV function.[244]

As further evidence for interventricular interaction, myocardial fibrosis has been described in both ventricles in patients with repaired TOF or Ebstein anomaly.[71,84,210,245,246] Neurohormonal activation, a stimulus for hypertrophy and fibrosis, is likely to be shared between the ventricles, promoting subtle but important structural changes in the myocardium of both the RV and LV.

Medical Therapy

Two studies described increased sympathetic nervous system activity in patients late after surgical repair of TOF.[90,247] As a consequence, neurohormonal therapies are increasingly used in RV volume-loading conditions. However, existing trials have not demonstrated the postulated benefits.

In a trial of bisoprolol compared with placebo in asymptomatic or mildly symptomatic patients with repaired TOF and depressed RV function, elevated BNP, and impaired peak $\dot{V}o_2$, there was no improvement in NYHA functional class, exercise capacity, or RV or LV size or function. In addition, patients randomized to bisoprolol actually demonstrated an increase in BNP that was not seen in the placebo group.[248]

Ramipril in 64 TOF patients with pulmonary regurgitation and RV dilation, in whom the mean baseline RVEF was only mildly reduced (53%), produced no improvement in RV or LV function, exercise capacity, or degree of pulmonary regurgitation. However, RV and LV long-axis shortening significantly improved in the ramipril group, and as mentioned above, ramipril also improved LV volume and EF in patients with restrictive physiology.[243]

Device Therapy

Although the long-term outcome for patients with TOF is generally excellent, SCD is a devastating, and not rare, late complication after surgical correction.[114,249,250] The reported prevalence of SCD, VT, or appropriate ICD shocks in TOF varies from 6.0% to 14%.[13,118,251] It is appropriate to apply standard guidelines for the secondary prevention of SCD in this population. However, the patients who may benefit from ICD when implanted for primary prevention are unclear. In

a cohort of patients with TOF receiving ICDs for primary and secondary prevention, there was no difference in survival between the primary and secondary prevention groups. With a median of 3.7 years of follow-up, the average actuarial mortality rate was 2.2%/y, accounted for equally by HF and SCD.[118]

Although a wide variety of noninvasive and invasive clinical tools were studied in an attempt to optimize risk prediction for SCD after repair of TOF, there is no consensus on optimal risk stratification, and none of the proposed models of risk assessment were studied prospectively. It is widely accepted that older age at repair, transannular patch repair, QRS ≥180 milliseconds, accelerated rate of QRS prolongation, presence of frequent or complex ventricular ectopy, and ventricular dysfunction are independent predictors of clinical VT and SCD.[78,251,252] Although RV dilatation and dysfunction have long been recognized as predictive of SCD and VT in this patient population, LV dysfunction (EF <45%) is also associated with a risk of sudden death.[253] In a study of patients with TOF who received an ICD, an LV end-diastolic pressure ≥12 mm Hg was the strongest predictor of appropriate ICD discharges.[118] The extent of LGE at MRI[71] has been found to add predictive value for the development of clinical arrhythmia in patients with TOF. Inducibility of monomorphic or polymorphic VT at electrophysiological study is predictive of subsequent clinical events and thus can be useful in risk stratification of patients, particularly those with symptoms such as syncope.[254]

The rate of appropriate device therapy in patients with TOF was high, reported to be 18% to 30% in medium-term follow-up.[118,119] Not surprisingly, patients receiving ICDs for secondary indications are more likely to receive appropriate therapy than those receiving devices for primary prevention (30% and 23.5%, respectively).[118] Independent predictors of appropriate ICD therapy include elevated LV end-diastolic pressure (which inversely correlates with LVEF and positively correlates with age), nonsustained VT, VT inducibility, and elevated RV systolic pressure. As a result of these findings, a risk score has been proposed, although not yet validated, to assist in identifying high-risk patients who might benefit from device therapy for primary prevention.[118]

Cardiac Resynchronization Therapy

Success of CRT is dependent on patient selection, yet the optimal technique and measurements for selecting patients with RV dysfunction and dyssynchrony who will benefit are unclear. Various echocardiographic measurements for evaluating atrioventricular or interventricular and intraventricular dyssynchrony were proposed in patients with RV loading.[255] In TOF, both RV and LV systolic dysfunction must be taken into account when resynchronization is being considered. As stated earlier, there is a known ventricular-ventricular interaction such that dysfunction of each ventricle is independently associated with clinical status.[245]

When LV systolic dysfunction is present, guidelines for CRT derived from large-scale clinical trials in acquired heart disease can be applied. However, it is unknown whether TOF patients with RV dysfunction and right bundle-branch block will derive long-term hemodynamic improvement from RV or biventricular pacing or whether CRT for RV dysfunction will protect against progressive LV dysfunction. In the absence of data, patients with RV dysfunction should first be evaluated for a reversible hemodynamic cause for the symptoms or ventricular dysfunction.[1] Then, if no further correctable cause is found, they should be managed on a case-by-case basis with respect to CRT.

Hemodynamic improvement after CRT was demonstrated acutely at the time of cardiac catheterization in 2 studies in TOF patients with right bundle-branch block.[256,257] The first study explored RV pacing in patients without left HF and demonstrated an increase in RV dP/dtmax and cardiac index. In the second study, biventricular pacing with leads positioned in the right atrium, RV apex, and lateral vein via the coronary sinus was examined acutely in 8 TOF patients with QRS >120 milliseconds, NYHA class II to III symptoms, and RV dysfunction. RV and LV dP/dtmax increased significantly compared with sinus rhythm with intact conduction and was associated with significant shortening of the QRS duration.

Medium- to long-term outcomes from CRT in patients with TOF have not been reported. Most studies report pooled data on outcomes in CHD as a single cohort, and pediatric studies include patients with cardiomyopathies. The largest series reporting outcomes of CRT in pediatric and/or adult patients included 11 and 6 patients with TOF, respectively.[127–129] The results were favorable overall for CRT in these reports, but outcomes for patients with TOF were not specified. Marked improvement in LV systolic function was reported after epicardial RV and LV pacing in a child with TOF and severe biventricular dysfunction.[258]

For the TOF patient with symptomatic HF caused by LV dysfunction, it is reasonable to extrapolate from existing guidelines developed for patients with dilated or ischemic cardiomyopathy. However, it has yet to be determined whether patients with predominant RV dysfunction benefit from CRT, whether this should involve resynchronization of the right ventricule or both ventricles, or whether resynchronization will prevent ventricular arrhythmias. The optimal method for determining ventricular dysfunction is unresolved, and the long-term impact and viability of CRT leads in this relatively young population are unknown. Prospective clinical studies of anatomically discrete lesions are required to address these questions.

Surgical Treatment

The timing of valve surgery for TOF or Ebstein anomaly is not clear. The ideal timing would not subject patients to excess surgeries over their lifetime while avoiding risk of ventricular dysfunction from prolonged volume loading. Pulmonary regurgitation after prior repair is a common indication for surgical referral in TOF. Indications for pulmonary valve replacement are addressed in the 2008 adult CHD guidelines.[1] In general, pulmonary valve replacement should be offered to all symptomatic patients with severe PR, severe RV dilatation, evidence of RV systolic dysfunction, or reduced exercise tolerance attributable to PR, ideally before clinical HF is manifest. Percutaneous valve replacements are available for many with RV-PA conduits, and use in other anatomic substrates (ie,

pulmonary valve replacement without conduit, native outflow tract) is evolving.

In Ebstein anomaly, progressive cardiomegaly can be an indication for surgical repair or replacement, although this is often driven primarily by dilatation of the right atrium and atrialized portion of the RV.[1] Residual RV dysfunction is common even after optimal surgical treatment, especially affecting the previously atrialized RV inlet. Moreover, plication of the RV and tricuspid valve replacement, rather than repair, may contribute to impaired RV function.

Part III: Transplantation

Heart transplantation remains a surgical procedure of choice for eligible patients with severe advanced HF that persists after maximal medical, surgical, and arrhythmia treatment. The body of information related to transplantation for CHD is derived almost entirely from registry and single-center–based outcome data; no randomized, clinical trial or meta-analysis data are available.

Adult patients with CHD represent an increasing proportion of heart transplant recipients. However, adults with CHD were less likely to receive ICD therapy or a ventricular assist device as a bridge to transplantation, were more likely to be listed at lower-urgency status, and were less likely to achieve transplantation at any given time after listing than patients without CHD.[259] In addition, patients with CHD wait longer on the list than their non-CHD counterparts despite a higher percentage of time spent as status 1/1A/1B.[260] In the United States, there is no special listing status for adult patients with CHD, who, by virtue of being less amenable to application of ventricular assist device or inotropes, may be disadvantaged from the perspective of organ allocation.[261] Other countries have tried to address the high mortality of adult patients with CHD on the wait list by prioritizing patients with cyanosis, patients with high panel reactive antibody, and those awaiting heart-lung transplantation.[262,263]

Adults with end-stage CHD have unique pathophysiology and comorbidities requiring specialized care. Pediatric patients with CHD also have unique challenges. Similar to adult transplantations, the number of pediatric transplantations remained fairly constant in the United States at 300 to 350 per year for the past 6 years. The ratio of new candidates to recipients also remained constant at 1.4:1.[264] The makeup of those who received a transplant remained the same except for the <1-year age group, in whom CHD decreased from 79% between 1988 and 1995 to 62% from 1996 to 2010.[264]

Indications for Transplantation

Because evidence-guided medical therapy for HF in CHD in children or adults is largely lacking, the decision to transplant is often an empirical one, after attempts at medical or surgical treatment have failed. Hence, difficult situations arise concerning the timing of transplantation such as whether to pursue transplantation before primary or additional repair and whether certain lesions or conditions make transplantation outcomes more favorable. There are CHD-specific challenges for cardiac transplantation that must be addressed. The 2013 ACC/AHA guidelines on the management of HF in adults[38] and the 2004 International Society for Heart and Lung Transplantation guidelines for children[34] do not specifically address transplantation in patients with CHD.

Determining the optimal timing for transplantation in the CHD population requires consideration of many unique circumstances, including a lack of data on outcomes of medical therapy, risks of alternative surgical therapy, development of potentially irreversible abnormalities of other organ systems, and anticipated long-term outcomes of surgical treatment, especially for children in whom growth may detrimentally affect the adequacy of palliative repairs.

The natural history of end-stage HF in CHD is that it likely will be progressive. Thus, transplantation may be considered in otherwise stable patients for whom the short-term or intermediate outcomes are expected to result in progressive HF or other organ damage, especially if heart transplantation would be precluded as a consequence. Whether to recommend high-risk surgery to improve the circulation rather than or before consideration of heart transplantation is a common clinical dilemma. A procedure that is definitive and results in a high quality of life (eg, valve replacement in symptomatic aortic stenosis) cannot be equated to a palliative procedure in a patient with an SV whose likely decline over time is anticipated even if surgical repair is successful. Furthermore, the clinician has to account for the growth of the patient because it affects the durability of repair. For example, patients with failed Norwood palliation for HLHS have to combat HF and the prospect of worsening hypoxemia as they outgrow the systemic-pulmonary shunt.

Circumstances that may prompt consideration of transplantation in stable patients include chronic excessive pulmonary blood flow, elevated PA pressure, cyanosis, and other end-organ or system-wide dysfunction secondary to HF. In addition to the morbidity and mortality associated with these additional issues, each may lead to organ dysfunction such that heart transplantation alone may not be an option and higher-risk heart-lung or other multiple organ transplantations will need to be considered.

The prognosis in adult patients with CHD remains difficult to predict; hence, the timing of consideration of and listing for transplantation is difficult. Many markers predictive of prognosis in acquired heart disease, including functional class, hospitalizations, poor ventricular function, LGE on MRI, serum sodium, anemia, renal dysfunction, BNP, underlying disease pathogenesis, and cardiopulmonary testing, have also been shown to have predictive ability in adults with CHD. However, although those markets may identify individuals at risk for adverse events, the time course is less clear. Additionally, the use of HF survival scores to predict outcomes or timing of transplantation has not been evaluated in CHD. Thus, although there are some risk markers in patients with CHD, their use in predicting the need for transplantation is less clear than in those patients with acquired LV dysfunction.

Cardiopulmonary testing has been shown to correlate with prognosis in adult CHD across CHD diagnoses.[31,265–268] Serial testing may be helpful to identify changes in cardiopulmonary

performance. Heart transplantation may be considered if the peak maximum $\dot{V}o_2$ during metabolic exercise testing is <50% predicted for age and sex.

All patients listed for transplantation need close and frequent reassessment of clinical status to detect the development of comorbidities that would preclude transplantation. Reported risk factors for wait-list mortality include albumin <3.5 mg/dL, assisted ventilation, male sex, and hospital admission.[269]

General Contraindications

Patients with adult CHD should be evaluated at centers with surgical and medical expertise in HF, transplantation, and adult CHD. Contraindications to transplantation for patients with CHD include traditional risk factors[270] and CHD-specific risk factors. It is often not any individual risk factor that precludes transplantation but the additive risk of multiple relative contraindications. CHD-specific issues are listed in Table 4.[37,263,264,270–282]

Heart transplantation alone in patients with CHD is not efficacious when contraindications are present, including but not limited to the following:

- Heart disease associated with severe, irreversible disease in other organ systems or when it is part of a severe, irreversible, multisystemic disease process. Multiorgan transplantation could be considered in appropriate circumstances.
- Heart disease associated with severe, irreversible, fixed elevation of pulmonary vascular resistance. Heart-lung transplantation may be considered.
- Heart disease associated with severe hypoplasia of the central branch PAs or pulmonary veins. Heart-lung transplant may be considered.

Pediatric-Specific Issues

Formal guidelines providing indications for pediatric heart transplantation were previously published.[34,284] There are no lesion-specific recommendations supported by a high level of evidence on the indications and timing of transplantation and comparison with medical and surgical therapy. For the pediatric SV population, there are considerations that may be of use in deciding the timing of transplantation. The stage at which transplantation is undertaken may be important. For example, there may be a survival advantage in patients with SV transplanted at the bidirectional Glenn stage of palliation.[285] Patients with HLHS transplanted after a failed Norwood procedure may have a higher mortality than recipients who were not palliated.[286–288] However, overall survival from listing to post-transplantation was similar to the overall Norwood outcome

Table 4. CHD-Specific Issues That May Affect Candidacy for and Risk of Transplantation

Issue	Reason	Outcome
Sensitization[271,272]	Use of homografts	Requirement for a prospective crossmatch or presence of PRA >25% associated with wait-list time and increased mortality[271,273]
		Strategies to address sensitization, including need for negative crossmatch, delaying time to transplantation; desensitization strategies may increase risk[263]
	Previous blood transfusions	Presence of donor-specific antibodies increases risk of antibody-mediated rejection and allograft vascular disease[274–278]
Pulmonary hypertension[37,270]	High left atrial filling pressures, cyanosis, volume overload, high shear force, and abnormal development of the vasculature and lungs	Increased risk of right heart failure after transplantation associated with increased perioperative mortality[279]
Surgical challenges	Adhesions, AP collaterals	Increased risk of bleeding, prolonged operative times
	PA reconstruction	Increased mortality[280]
	Previous sternotomy	Increased ischemic times
Liver issues	Passive congestion	Increased morbidity and mortality with increasing MELD scores
	Cirrhosis	
	Portal hypertension	Increased frequency in CHD[281]
	Hepatitis B and C	
Fontan physiology	PLE, liver dysfunction secondary to passive congestion	Increased risk vs other CHD diagnosis, increased risk of bleeding and infection
Eisenmenger syndrome	Severe pulmonary hypertension	Need for heart-lung transplantation associated with poorer outcomes (ISHLT registry 2012 data)[264]
		Consider lung transplantation with primary cardiac repair[282]

AP indicates aortopulmonary; CHD, congenital heart disease; ISHLT, International Society for Heart and Lung Transplantation; MELD, Model for End-Stage Liver Disease; PA, pulmonary artery; PLE, protein-losing enteropathy; and PRA, panel-reactive antibody.

Table 5. Policy and Funding Considerations to Improve Care of Patients With CHD

Funding agencies prioritize funding research on HF in CHD
Patients with HF and CHD have the opportunity and be encouraged to participate in funded registries.
Healthcare delivery systems and payers ensure that all patients with HF and CHD can access the subspecialty care needed to optimize outcomes.
Training programs and healthcare systems ensure funded training of pediatric cardiology and adult CHD cardiologists to care for a rapidly growing population.
Funding agencies, healthcare systems, educational programs, and patient advocacy groups are stakeholders in defining clinically meaningful quality metrics and ensuring that the highest-quality care is available to all patients with CHD.
A culture of participation is created in clinical trials and registries in which patients and physicians are aware of and seek opportunities to participate.

CHD indicates congenital heart disease; and HF, heart failure.

of 54% at 5 years reported in a cohort from a similar era.[289] With improved Norwood outcomes, a standard-risk patient with HLHS should undergo SV surgical palliation rather than primary listing for transplantation. No study has compared high-risk Fontan completion with transplantation. No study has compared overall survival by contrasting immediate listing for candidates who were rejected for Fontan completion with those whose listing was delayed until more advanced HF. However, the failed Fontan group of patients have a higher mortality on the wait list if failure and listing occur soon after attempted Fontan completion.[290] Fontan patients also have a slightly inferior outcome after transplantation, with increased mortality typically seen in the early postoperative period.[290–292] Transplantation corrects protein-losing enteropathy[290] and plastic bronchitis.[293] Patients with pulmonary atresia and intact ventricular septum with RV-dependent coronary circulation may have a higher risk of death resulting from palliation, especially after an aortic-to-pulmonary shunt.[294–299] Transplantation can be considered in these patients. Patients with SV and heterotaxy syndrome do not seem to have a long-term outcome that is as good as for other SV patients.[300–302] Therefore, consideration should include transplantation if the success of their palliation is questionable, although anatomic factors may complicate anastomoses.

Certain situations in which transplantation is a reasonable consideration in pediatric patients include the following:

- HF associated with systemic ventricular dysfunction with previously repaired or palliated CHD when it is associated with significant growth failure attributable to the heart disease
- HF in patients with CHD and severe limitation of exercise and activity
- CHD with normal ventricular function if the following anatomic and physiological 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 valve(s)
  - — Symptomatic arterial oxygen desaturation (cyanosis) that is not considered amenable to surgical correction
  - — Persistent protein-losing enteropathy despite optimal medical-surgical therapy

Heart Transplantation Outcomes

Early survival after transplantation is poorer in CHD than in other conditions. There are many possible explanations, including risk factors that are independent of CHD such as anatomy, the need for extracorporeal membrane oxygenation support, antibody sensitization, and acuity of HF. Equally relevant to patients with CHD is the common requirement of repeat sternotomy and the need for reconstruction at the time of transplantation, which may demand more donor tissue and result in longer ischemic time. Adding to the challenge is the long wait time, particularly in the infant population.

Long term, the median life expectancy (13 years) was better for adult patients with CHD than for any other pretransplantation diagnosis, and median survival conditional on survival to year 1 (18 years) was also superior to that for any other diagnoses. In children, conditional survival beyond 1 year after transplantation was better for young infants with CHD such that over time their survival catches up with that of other groups who have higher perioperative survival.[262,263] Independent risk factors for death after transplantation in adult patients with CHD by Cox regression analysis included black race, longer ischemic time, and pulmonary valve replacement exceeding 4 Wood units.[279]

Summary

With the expectation of rising numbers of patients with CHD with HF referred for transplantation, the questions explored here are concerning. Although patients with CHD are at higher risk early after transplantation, long-term outcomes for patients with CHD are superior to those for patients transplanted for other reasons. Predicting prognosis in patients with CHD with HF is difficult, and further studies are needed to guide optimal timing of transplantation consideration. The role of biomarkers and survival scores for patients with CHD with HF has not been addressed. More longitudinal data on risk and predictive models of risk may aid prognostication. Patients with CHD are less likely to have ventricular assist devices at listing and hence have a lower listing status.[261] Patients with CHD on mechanical circulatory support (a considerable minority) have a higher listing status and thus higher priority for available organs, but they still face a longer time on the wait list and higher wait-list mortality.

Despite the uncertainties, it is clear that patients with CHD are complex and require multidisciplinary evaluation and care by informed providers. Because evidence-based data directly comparing medical therapy, surgical palliation, and transplantation are lacking, healthcare teams caring for patients with CHD must use foresight to determine the optimal time for referral and listing for transplantation. It is important that patients with CHD and HF be considered earlier for advanced therapies. However, issues specific to adults with CHD such as anatomy, pulmonary hypertension, renal

Table 6. Important Clinical Issues With Insufficient Data on Benefit or Harm

The routine use of standard HF medical therapies in:
SV patients palliated with a Fontan repair with normal ventricular systolic function
Asymptomatic systolic dysfunction of the systemic or subpulmonic RV
Prevention of HF in asymptomatic patients with normal ventricular function, especially a systemic RV
Appropriate surrogate end points for clinically meaningful outcomes.
Predictors of prognosis in CHD, including but not limited to:
The role of measurement of BNP and other markers of neurohormonal activation in patients with CHD
HF scores
CPET parameters
Imaging parameters such as EF, ventricular size, and valvular function
Issues of liver dysfunction, cirrhosis, and hepatocellular carcinoma in patients with cardiac physiology that predisposes to congestive hepatopathy (ie, Fontan physiology, failing subpulmonic ventricle), specifically:
Morbidity and mortality associated with the development of liver dysfunction
Screening strategy
Effective medical or invasive therapies to prevent or treat liver dysfunction
Timing of heart transplantation and/or heart-liver transplantation for optimal patient outcomes and organ use
Timing and options for mechanical circulatory support or heart transplantation
Sudden death risk stratification in patients with CHD
The role of CRT

BNP indicates brain natriuretic peptide; CHD, congenital heart disease; CPET, cardiopulmonary exercise test; CRT, cardiac resynchronization therapy; EF, ejection fraction; HF, heart failure; RV, right ventricle; and SV, single ventricle.

and liver disease, and high prevalence of anti–human leukocyte antigen antibodies require appropriate pretransplantation assessment and may identify patients at greater risk for perioperative events.

Part IV: Conclusions

Although the incidence of CHD remains relatively constant, the prevalence of pediatric and adult CHD continues to increase as a result of the success of surgical and interventional treatment facilitated by advanced diagnostic techniques. Although many patients do well, HF remains a common, difficult, and often final complication of CHD. Therefore, preservation of myocardial function should be a major overarching goal throughout the life of patients with CHD. Because there is a relative lack of data supporting pharmacological therapy, optimizing myocardial remodeling and function necessitates the identification and reversal of pressure- or volume-loading lesions, residual shunts, and conduit malfunction. Data are lacking to guide the diagnosis and treatment of HF in the patient with CHD.

Extrapolation from existing HF data and guidelines may not be appropriate in many CHD circumstances. More data are needed (Table 5). Randomized, controlled trials are ideal, but the dispersed, heterogeneous CHD population limits the feasibility of large trials. Other research needs include meaningful surrogate end points, large detailed registries, and support for the growing collaborative infrastructure for multicenter research. New knowledge will advance our understanding of risk, prevention, and the value of medical and invasive therapies (Table 6).

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Wendy M. Book	Emory University	Actelion*	None	None	None	None	None	None
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Yuk Law	Seattle Children's Hospital	None	None	None	None	None	None	None
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*Modest.

†Significant.

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References

1. Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA, del Nido P, Fasules JW, Graham TP Jr, Hijazi ZM, Hunt SA, King ME, Landzberg MJ, Miner PD, Radford MJ, Walsh EP, Webb GD. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines on the Management of Adults With Congenital Heart Disease). *Circulation*. 2008;118:e714–e833. doi: 10.1161/CIRCULATIONAHA.108.190690.
2. Connelly MS, Webb GD, Somerville J, Warnes CA, Perloff JK, Liberthson RR, Puga FJ, Collins-Nakai RL, Williams WG, Mercier LA, Huckell VF, Finley JP, McKay R. Canadian Consensus Conference on Adult Congenital Heart Disease 1996. *Can J Cardiol*. 1998;14:395–452.
3. Warnes CA, Liberthson R, Danielson GK, Dore A, Harris L, Hoffman JI, Somerville J, Williams RG, Webb GD. Task Force 1: the changing profile of congenital heart disease in adult life. *J Am Coll Cardiol*. 2001;37:1170–1175.
4. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, McDonagh T, Sechtem U, Bonet LA, Avraamides P, Ben Lamin HA, Brignole M, Coca A, Cowburn P, Dargie H, Elliott P, Flachskampf FA, Guida GF, Hardman S, Iung B, Merkely B, Mueller C, Nanas JN, Nielsen OW, Orn S, Parissis JT, Ponikowski P; ESC Committee for Practice Guidelines. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology [published correction appears in *Eur J Heart Fail*. 2013;15:361–362]. *Eur J Heart Fail*. 2012;14:803–869. doi: 10.1093/eurjhf/hfs105.
5. Heart Failure Society of America. Executive summary: HFSA 2006 comprehensive heart failure practice guideline. *J Card Fail*. 2006;12:10–38.
6. Tobler D, Greutmann M, Colman JM, Greutmann-Yantiri M, Librach LS, Kovacs AH. End-of-life care in hospitalized adults with complex congenital heart disease: care delayed, care denied. *Palliat Med*. 2012;26:72–79. doi: 10.1177/0269216311407694.
7. Hoffman JI, Kaplan S, Liberthson RR. Prevalence of congenital heart disease. *Am Heart J*. 2004;147:425–439. doi: 10.1016/j.ahj.2003.05.003.
8. Tennant PW, Pearce MS, Bythell M, Rankin J. 20-Year survival of children born with congenital anomalies: a population-based study. *Lancet*. 2010;375:649–656. doi: 10.1016/S0140-6736(09)61922-X.
9. van der Bom T, Zomer AC, Zwinderman AH, Meijboom FJ, Bouma BJ, Mulder BJ. The changing epidemiology of congenital heart disease. *Nat Rev Cardiol*. 2011;8:50–60. doi: 10.1038/nrcardio.2010.166.
10. Wren C, O'Sullivan JJ. Survival with congenital heart disease and need for follow up in adult life. *Heart*. 2001;85:438–443.
11. Moons P, Bovijn L, Budts W, Belmans A, Gewillig M. Temporal trends in survival to adulthood among patients born with congenital heart disease from 1970 to 1992 in Belgium. *Circulation*. 2010;122:2264–2272. doi: 10.1161/CIRCULATIONAHA.110.946343.
12. Gilboa SM, Salemi JL, Nembhard WN, Fixler DE, Correa A. Mortality resulting from congenital heart disease among children and adults in the United States, 1999 to 2006. *Circulation*. 2010;122:2254–2263. doi: 10.1161/CIRCULATIONAHA.110.947002.
13. Khairy P, Ionescu-Ittu R, Mackie AS, Abrahamowicz M, Pilote L, Marelli AJ. Changing mortality in congenital heart disease. *J Am Coll Cardiol*. 2010;56:1149–1157. doi: 10.1016/j.jacc.2010.03.085.
14. Marelli AJ, Mackie AS, Ionescu-Ittu R, Rahme E, Pilote L. Congenital heart disease in the general population: changing prevalence and age distribution. *Circulation*. 2007;115:163–172. doi: 10.1161/CIRCULATIONAHA.106.627224.
15. Moons P, Engelfriet P, Kaemmerer H, Meijboom FJ, Oechslin E, Mulder BJ; Expert Committee of Euro Heart Survey on Adult Congenital Heart Disease. Delivery of care for adult patients with congenital heart disease in Europe: results from the Euro Heart Survey. *Eur Heart J*. 2006;27:1324–1330. doi: 10.1093/eurheartj/ehi858.
16. Wu FM, Ukomadu C, Odze RD, Valente AM, Mayer JE Jr, Earing MG. Liver disease in the patient with Fontan circulation. *Congenit Heart Dis*. 2011;6:190–201. doi: 10.1111/j.1747-0803.2011.00504.x.
17. van der Bom T, Luijendijk P, Bouma BJ, Koolbergen DR, de Groot JR, Mulder BJ, Mulder BB. Treatment of congenital heart disease: risk-reducing measures in young adults [published correction appears in *Future Cardiol*. 2011;7:441]. *Future Cardiol*. 2011;7:227–240. doi: 10.2217/fca.11.5.
18. Mackie AS, Pilote L, Ionescu-Ittu R, Rahme E, Marelli AJ. Health care resource utilization in adults with congenital heart disease. *Am J Cardiol*. 2007;99:839–843. doi: 10.1016/j.amjcard.2006.10.054.
19. Opotowsky AR, Siddiqi OK, Webb GD. Trends in hospitalizations for adults with congenital heart disease in the U.S. *J Am Coll Cardiol*. 2009;54:460–467. doi: 10.1016/j.jacc.2009.04.037.
20. Verheugt CL, Uiterwaal CS, van der Velde ET, Meijboom FJ, Pieper PG, van Dijk AP, Vliegen HW, Grobbee DE, Mulder BJ. Mortality in adult congenital heart disease. *Eur Heart J*. 2010;31:1220–1229. doi: 10.1093/eurheartj/ehq032.
21. Norozi K, Wessel A, Alpers V, Arnhold JO, Geyer S, Zoege M, Buchhorn R. Incidence and risk distribution of heart failure in adolescents and adults with congenital heart disease after cardiac surgery. *Am J Cardiol*. 2006;97:1238–1243. doi: 10.1016/j.amjcard.2005.10.065.
22. Piran S, Veldtman G, Siu S, Webb GD, Liu PP. Heart failure and ventricular dysfunction in patients with single or systemic right ventricles. *Circulation*. 2002;105:1189–1194.
23. Nieminen HP, Jokinen EV, Sairanen HI. Causes of late deaths after pediatric cardiac surgery: a population-based study. *J Am Coll Cardiol*. 2007;50:1263–1271. doi: 10.1016/j.jacc.2007.05.040.
24. Oechslin EN, Harrison DA, Connelly MS, Webb GD, Siu SC. Mode of death in adults with congenital heart disease. *Am J Cardiol*. 2000;86:1111–1116.
25. Zomer AC, Vaartjes I, Uiterwaal CS, van der Velde ET, van den Merkhof LF, Baur LH, Ansink TJ, Cozijnsen L, Pieper PG, Meijboom FJ, Grobbee DE, Mulder BJ. Circumstances of death in adult congenital heart disease. *Int J Cardiol*. 2012;154:168–172. doi: 10.1016/j.ijcard.2010.09.015.
26. Zomer AC, Vaartjes I, van der Velde ET, de Jong HM, Konings TC, Wagenaar LJ, Heesen WF, Eerens F, Baur LH, Grobbee DE, Mulder BJ. Heart failure admissions in adults with congenital heart disease; risk factors and prognosis. *Int J Cardiol*. 2013;168:2487–2493. doi: 10.1016/j.ijcard.2013.03.003.
27. Kirk R, Edwards LB, Kucheryavaya AY, Aurora P, Christie JD, Dobbels F, Rahmel AO, Stehlik J, Hertz MI. The Registry of the International Society for Heart and Lung Transplantation: thirteenth official pediatric heart transplantation report–2010. *J Heart Lung Transplant*. 2010;29:1119–1128. doi: 10.1016/j.healun.2010.08.009.
28. Stehlik J, Edwards LB, Kucheryavaya AY, Aurora P, Christie JD, Kirk R, Dobbels F, Rahmel AO, Hertz MI. The Registry of the International Society for Heart and Lung Transplantation: twenty-seventh official adult heart transplant report–2010. *J Heart Lung Transplant*. 2010;29:1089–1103. doi: 10.1016/j.healun.2010.08.007.
29. Lamour JM, Kanter KR, Naftel DC, Chrisant MR, Morrow WR, Clemson BS, Kirklin JK; Cardiac Transplant Registry Database; Pediatric Heart Transplant Study. The effect of age, diagnosis, and previous surgery in children and adults undergoing heart transplantation for congenital heart disease. *J Am Coll Cardiol*. 2009;54:160–165. doi: 10.1016/j.jacc.2009.04.020.
30. Jayakumar KA, Addonizio LJ, Kichuk-Chrisant MR, Galantowicz ME, Lamour JM, Quaegebeur JM, Hsu DT. Cardiac transplantation after the Fontan or Glenn procedure. *J Am Coll Cardiol*. 2004;44:2065–2072. doi: 10.1016/j.jacc.2004.08.031.
31. Diller GP, Dimopoulos K, Okonko D, Li W, Babu-Narayan SV, Broberg CS, Johansson B, Bouzas B, Mullen MJ, Poole-Wilson PA, Francis DP, Gatzoulis MA. Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. *Circulation*. 2005;112:828–835. doi: 10.1161/CIRCULATIONAHA.104.529800.
32. Hsu DT, Pearson GD. Heart failure in children, part I: history, etiology, and pathophysiology. *Circ Heart Fail*. 2009;2:63–70. doi: 10.1161/CIRCHEARTFAILURE.108.820217.
33. Criteria Committee of the New York Heart Association. *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels*. Boston, MA: Little, Brown, & Co; 1994.
34. Rosenthal D, Chrisant MR, Edens E, Mahony L, Canter C, Colan S, Dubin A, Lamour J, Ross R, Shaddy R, Addonizio L, Beerman L, Berger S, Bernstein D, Blume E, Boucek M, Checchia P, Dipchand A, Drummond-Webb J, Fricker J, Friedman R, Hallowell S, Jaquiss R, Mital S, Pahl E, Pearce B, Rhodes L, Rotondo K, Rusconi P, Scheel J, Pal Singh T, Towbin J. International Society for Heart and Lung Transplantation: practice guidelines for management of heart failure in children [published

correction appears in *J Heart Lung Transplant*. 2009;28:987]. *J Heart Lung Transplant*. 2004;23:1313–1333. doi: 10.1016/j.healun.2004.03.018.
35. Campeau L. Letter: grading of angina pectoris. *Circulation*. 1976;54:522–523.
36. Goldman L, Hashimoto B, Cook EF, Loscalzo A. Comparative reproducibility and validity of systems for assessing cardiovascular functional class: advantages of a new specific activity scale. *Circulation*. 1981;64:1227–1234.
37. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 Focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines [published correction appears in *Circulation*. 2010;121:e258]. *Circulation*. 2009;119:e391–e479. doi: 10.1161/CIRCULATIONAHA.109.192065.
38. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;128:1810–1852. doi: 10.1161/CIR.0b013e31829e8807.
39. Acker MA, Pagani FD, Stough WG, Mann DL, Jessup M, Kormos R, Slaughter MS, Baldwin T, Stevenson L, Aaronson KD, Miller L, Naftel D, Yancy C, Rogers J, Teuteberg J, Starling RC, Griffith B, Boyce S, Westaby S, Blume E, Wearden P, Higgins R, Mack M. Statement regarding the pre and post market assessment of durable, implantable ventricular assist devices in the United States. *Circ Heart Fail*. 2013;6:e1–e11. doi: 10.1161/HHF.0b013e318279f6b5.
40. Bolger AP, Coats AJ, Gatzoulis MA. Congenital heart disease: the original heart failure syndrome. *Eur Heart J*. 2003;24:970–976.
41. Sanchez-Quintana D, Climent V, Ho SY, Anderson RH. Myoarchitecture and connective tissue in hearts with tricuspid atresia. *Heart*. 1999;81:182–191.
42. Sedmera D. Form follows function: developmental and physiological view on ventricular myocardial architecture. *Eur J Cardiothorac Surg*. 2005;28:526–528. doi: 10.1016/j.ejcts.2005.07.001.
43. Black BL. Transcriptional pathways in second heart field development. *Semin Cell Dev Biol*. 2007;18:67–76. doi: 10.1016/j.semcdb.2007.01.001.
44. Tobita K, Keller BB. Right and left ventricular wall deformation patterns in normal and left heart hypoplasia chick embryos. *Am J Physiol Heart Circ Physiol*. 2000;279:H959–H969.
45. Stähli BE, Gebhard C, Biaggi P, Klaassen S, Valsangiacomo Buechel E, Attenhofer Jost CH, Jenni R, Tanner FC, Greutmann M. Left ventricular non-compaction: prevalence in congenital heart disease. *Int J Cardiol*. 2013;167:2477–2481. doi: 10.1016/j.ijcard.2012.05.095.
46. Rutz T, de Marchi SF, Schwerzmann M, Vogel R, Seiler C. Right ventricular absolute myocardial blood flow in complex congenital heart disease. *Heart*. 2010;96:1056–1062. doi: 10.1136/hrt.2009.191718.
47. Lubiszewska B, Gosiewska E, Hoffman P, Teresińska A, Rózański J, Piotrowski W, Rydlewska-Sadowska W, Kubicka K, Ruzyłło W. Myocardial perfusion and function of the systemic right ventricle in patients after atrial switch procedure for complete transposition: long-term follow-up. *J Am Coll Cardiol*. 2000;36:1365–1370.
48. Millane T, Bernard EJ, Jaeggi E, Howman-Giles RB, Uren RF, Cartmill TB, Hawker RE, Celermajer DS. Role of ischemia and infarction in late right ventricular dysfunction after atrial repair of transposition of the great arteries. *J Am Coll Cardiol*. 2000;35:1661–1668.
49. Fratz S, Hauser M, Bengel FM, Hager A, Kaemmerer H, Schwaiger M, Hess J, Stern HC. Myocardial scars determined by delayed-enhancement magnetic resonance imaging and positron emission tomography are not common in right ventricles with systemic function in long-term follow up. *Heart*. 2006;92:1673–1677. doi: 10.1136/hrt.2005.086579.
50. Singh TP, Humes RA, Muzik O, Kottamasu S, Karpawich PP, Di Carli MF. Myocardial flow reserve in patients with a systemic right ventricle after atrial switch repair. *J Am Coll Cardiol*. 2001;37:2120–2125.
51. Grewal J, Crean A, Garceau P, Wald R, Woo A, Rakowski H, Silversides CK. Subaortic right ventricular characteristics and relationship to exercise capacity in congenitally corrected transposition of the great arteries. *J Am Soc Echocardiogr*. 2012;25:1215–1221. doi: 10.1016/j.echo.2012.08.014.
52. Khairy P, Clair M, Fernandes SM, Blume ED, Powell AJ, Newburger JW, Landzberg MJ, Mayer JE Jr. Cardiovascular outcomes after the arterial switch operation for D-transposition of the great arteries. *Circulation*. 2013;127:331–339. doi: 10.1161/CIRCULATIONAHA.112.135046.
53. Ou P, Khraiche D, Celermajer DS, Agnoletti G, Le Quan Sang KH, Thalabard JC, Quintin M, Raisky O, Vouhe P, Sidi D, Bonnet D. Mechanisms of coronary complications after the arterial switch for transposition of the great arteries. *J Thorac Cardiovasc Surg*. 2013;145:1263–1269. doi: 10.1016/j.jtcvs.2012.06.009.
54. Hauser M, Bengel FM, Kühn A, Sauer U, Nekolla SG, Eicken A, Schwaiger M, Hess J. Myocardial perfusion and coronary flow reserve assessed by positron emission tomography in patients after Fontan-like operations. *Pediatr Cardiol*. 2003;24:386–392. doi: 10.1007/s00246-002-0355-5.
55. Hauser M, Bengel FM, Hager A, Kuehn A, Nekolla SG, Kaemmerer H, Schwaiger M, Hess J. Impaired myocardial blood flow and coronary flow reserve of the anatomical right systemic ventricle in patients with congenitally corrected transposition of the great arteries. *Heart*. 2003;89:1231–1235.
56. Hauser M, Kuehn A, Hess J. Myocardial perfusion in patients with transposition of the great arteries after arterial switch operation. *Circulation*. 2003;107:e126; author reply e126. doi: 10.1161/01.CIR.0000071211.20538.25.
57. Sluysmans T, Sanders SP, van der Velde M, Matitiau A, Parness IA, Spevak PJ, Mayer JE Jr, Colan SD. Natural history and patterns of recovery of contractile function in single left ventricle after Fontan operation. *Circulation*. 1992;86:1753–1761.
58. Sugishita Y, Iida K, Ohtsuka S, Yamaguchi I. Ventricular wall stress revisited: a keystone of cardiology. *Jpn Heart J*. 1994;35:577–587.
59. Lang RE, Thölken H, Ganten D, Luft FC, Ruskoaho H, Unger T. Atrial natriuretic factor: a circulating hormone stimulated by volume loading. *Nature*. 1985;314:264–266.
60. Scammell AM, Diver MJ. Plasma renin activity in infants with congenital heart disease. *Arch Dis Child*. 1987;62:1136–1138.
61. Yoshibayashi M, Nishioka K, Nakao K, Saito Y, Matsumura M, Ueda T, Temma S, Shirakami G, Imura H, Mikawa H. Plasma endothelin concentrations in patients with pulmonary hypertension associated with congenital heart defects. Evidence for increased production of endothelin in pulmonary circulation. *Circulation*. 1991;84:2280–2285.
62. Bolger AP, Sharma R, Li W, Leenarts M, Kalra PR, Kemp M, Coats AJ, Anker SD, Gatzoulis MA. Neurohormonal activation and the chronic heart failure syndrome in adults with congenital heart disease. *Circulation*. 2002;106:92–99.
63. Ohuchi H, Takasugi H, Ohashi H, Okada Y, Yamada O, Ono Y, Yagihara T, Echigo S. Stratification of pediatric heart failure on the basis of neurohormonal and cardiac autonomic nervous activities in patients with congenital heart disease. *Circulation*. 2003;108:2368–2376. doi: 10.1161/01.CIR.0000101681.27911.FA.
64. Lang RE, Unger T, Ganten D, Weil J, Bidlingmaier F, Dohlemann D. Alpha atrial natriuretic peptide concentrations in plasma of children with congenital heart and pulmonary diseases. *Br Med J (Clin Res Ed)*. 1985;291:1241.
65. Hopkins WE, Hall C. Paradoxical relationship between N-terminal proatrial natriuretic peptide and filling pressure in adults with cyanotic congenital heart disease. *Circulation*. 1997;96:2215–2220.
66. Tulevski II, Groenink M, van Der Wall EE, van Veldhuisen DJ, Boomsma F, Stoker J, Hirsch A, Lemkes JS, Mulder BJ. Increased brain and atrial natriuretic peptides in patients with chronic right ventricular pressure overload: correlation between plasma neurohormones and right ventricular dysfunction. *Heart*. 2001;86:27–30.
67. Reardon LC, Williams RJ, Houser LS, Miner PD, Child JS, Aboulhosn JA. Usefulness of serum brain natriuretic peptide to predict adverse events in patients with the Eisenmenger syndrome. *Am J Cardiol*. 2012;110:1523–1526. doi: 10.1016/j.amjcard.2012.06.061.
68. Fuster V, Danielson MA, Robb RA, Broadbent JC, Brown AL Jr, Elveback LR. Quantitation of left ventricular myocardial fiber hypertrophy and interstitial tissue in human hearts with chronically increased volume and pressure overload. *Circulation*. 1977;55:504–508.
69. Hein S, Arnon E, Kostin S, Schönburg M, Elsässer A, Polyakova V, Bauer EP, Klövekorn WP, Schaper J. Progression from compensated hypertrophy to failure in the pressure-overloaded human heart: structural deterioration and compensatory mechanisms. *Circulation*. 2003;107:984–991.
70. Chowdhury UK, Sathia S, Ray R, Singh R, Pradeep KK, Venugopal P. Histopathology of the right ventricular outflow tract and its relationship to clinical outcomes and arrhythmias in patients with tetralogy of Fallot. *J Thorac Cardiovasc Surg*. 2006;132:270–277. doi: 10.1016/j.jtcvs.2006.04.001.
71. Babu-Narayan SV, Kilner PJ, Li W, Moon JC, Goktekin O, Davlouros PA, Khan M, Ho SY, Pennell DJ, Gatzoulis MA. Ventricular fibrosis suggested by cardiovascular magnetic resonance in adults with repaired tetralogy of Fallot and its relationship to adverse

markers of clinical outcome. *Circulation*. 2006;113:405–413. doi: 10.1161/CIRCULATIONAHA.105.548727.
72. Babu-Narayan SV, Goktekin O, Moon JC, Broberg CS, Pantely GA, Pennell DJ, Gatzoulis MA, Kilner PJ. Late gadolinium enhancement cardiovascular magnetic resonance of the systemic right ventricle in adults with previous atrial redirection surgery for transposition of the great arteries. *Circulation*. 2005;111:2091–2098. doi: 10.1161/01.CIR.0000162463.61626.3B.
73. Broberg CS, Prasad SK, Carr C, Babu-Narayan SV, Dimopoulos K, Gatzoulis MA. Myocardial fibrosis in Eisenmenger syndrome: a descriptive cohort study exploring associations of late gadolinium enhancement with clinical status and survival. *J Cardiovasc Magn Reson*. 2014;16:32. doi: 10.1186/1532-429X-16-32.
74. Rathod RH, Prakash A, Powell AJ, Geva T. Myocardial fibrosis identified by cardiac magnetic resonance late gadolinium enhancement is associated with adverse ventricular mechanics and ventricular tachycardia late after Fontan operation. *J Am Coll Cardiol*. 2010;55:1721–1728. doi: 10.1016/j.jacc.2009.12.036.
75. Broberg CS, Chugh SS, Conklin C, Sahn DJ, Jerosch-Herold M. Quantification of diffuse myocardial fibrosis and its association with myocardial dysfunction in congenital heart disease. *Circ Cardiovasc Imaging*. 2010;3:727–734. doi: 10.1161/CIRCIMAGING.108.842096.
76. Krymsky LD. Pathologic anatomy of congenital heart disease. *Circulation*. 1965;32:814–827.
77. Salih C, McCarthy KP, Ho SY. The fibrous matrix of ventricular myocardium in hypoplastic left heart syndrome: a quantitative and qualitative analysis. *Ann Thorac Surg*. 2004;77:36–40.
78. Gatzoulis MA, Till JA, Somerville J, Redington AN. Mechanoelectrical interaction in tetralogy of Fallot: QRS prolongation relates to right ventricular size and predicts malignant ventricular arrhythmias and sudden death. *Circulation*. 1995;92:231–237.
79. Lenfant C. Report of the Task Force on Research in Pediatric Cardiovascular Disease. *Circulation*. 2002;106:1037–1042.
80. Senzaki H, Masutani S, Kobayashi J, Kobayashi T, Sasaki N, Asano H, Kyo S, Yokote Y, Ishizawa A. Ventricular afterload and ventricular work in Fontan circulation: comparison with normal two-ventricle circulation and single-ventricle circulation with Blalock-Taussig shunts [retracted in *Circulation*. 2012;125:e1020]. *Circulation*. 2002;105:2885–2892.
81. Szabó G, Buhmann V, Graf A, Melnitschuk S, Bährle S, Vahl CF, Hagl S. Ventricular energetics after the Fontan operation: contractility-afterload mismatch. *J Thorac Cardiovasc Surg*. 2003;125:1061–1069. doi: 10.1067/mtc.2003.405.
82. de Leval MR. The Fontan circulation: a challenge to William Harvey? *Nat Clin Pract Cardiovasc Med*. 2005;2:202–208. doi: 10.1038/ncpcardio0157.
83. Walker RE, Moran AM, Gauvreau K, Colan SD. Evidence of adverse ventricular interdependence in patients with atrial septal defects. *Am J Cardiol*. 2004;93:1374–1377, A6. doi: 10.1016/j.amjcard.2004.02.033.
84. Broberg CS, Aboulhosn J, Mongeon FP, Kay J, Valente AM, Khairy P, Earing MG, Opotowsky AR, Lui G, Gersony DR, Cook S, Ting JG, Webb G, Gurvitz MZ; Alliance for Adult Research in Congenital Cardiology (AARCC). Prevalence of left ventricular systolic dysfunction in adults with repaired tetralogy of Fallot. *Am J Cardiol*. 2011;107:1215–1220. doi: 10.1016/j.amjcard.2010.12.026.
85. Engelfriet P, Boersma E, Oechslin E, Tijssen J, Gatzoulis MA, Thilén U, Kaemmerer H, Moons P, Meijboom F, Popelová J, Laforest V, Hirsch R, Daliento L, Thaulow E, Mulder B. The spectrum of adult congenital heart disease in Europe: morbidity and mortality in a 5 year follow-up period: the Euro Heart Survey on adult congenital heart disease. *Eur Heart J*. 2005;26:2325–2333. doi: 10.1093/eurheartj/ehi396.
86. Dimopoulos K, Diller GP, Piepoli MF, Gatzoulis MA. Exercise intolerance in adults with congenital heart disease. *Cardiol Clin*. 2006;24:641–660, vii. doi: 10.1016/j.ccl.2006.08.002.
87. Alonso-Gonzalez R, Borgia F, Diller GP, Inuzuka R, Kempny A, Martinez-Naharro A, Tutarel O, Marino P, Wustmann K, Charalambides M, Silva M, Swan L, Dimopoulos K, Gatzoulis MA. Abnormal lung function in adults with congenital heart disease: prevalence, relation to cardiac anatomy, and association with survival. *Circulation*. 2013;127:882–890. doi: 10.1161/CIRCULATIONAHA.112.126755.
88. Broberg CS, Bax BE, Okonko DO, Rampling MW, Bayne S, Harries C, Davidson SJ, Uebing A, Khan AA, Thein S, Gibbs JS, Burman J, Gatzoulis MA. Blood viscosity and its relationship to iron deficiency, symptoms, and exercise capacity in adults with cyanotic congenital heart disease. *J Am Coll Cardiol*. 2006;48:356–365. doi: 10.1016/j.jacc.2006.03.040.
89. Roche SL, Redington AN. Right ventricle: wrong targets? Another blow for pharmacotherapy in congenital heart diseases. *Circulation*. 2013;127:314–316. doi: 10.1161/CIRCULATIONAHA.112.155887.
90. Daliento L, Folino AF, Menti L, Zanco P, Baratella MC, Dalla Volta S. Adrenergic nervous activity in patients after surgical correction of tetralogy of Fallot. *J Am Coll Cardiol*. 2001;38:2043–2047.
91. Ohuchi H, Hasegawa S, Yasuda K, Yamada O, Ono Y, Echigo S. Severely impaired cardiac autonomic nervous activity after the Fontan operation [published correction appears in *Circulation*. 2004;109:3257]. *Circulation*. 2001;104:1513–1518.
92. Leuchte HH, Holzapfel M, Baumgartner RA, Ding I, Neurohr C, Vogeser M, Kolbe T, Schwaiblmair M, Behr J. Clinical significance of brain natriuretic peptide in primary pulmonary hypertension. *J Am Coll Cardiol*. 2004;43:764–770. doi: 10.1016/j.jacc.2003.09.051.
93. Book WM. Heart failure in the adult patient with congenital heart disease. *J Card Fail*. 2005;11:306–312.
94. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med*. 1991;325:293–302.
95. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure: Randomized Aldactone Evaluation Study Investigators. *N Engl J Med*. 1999;341:709–717. doi: 10.1056/NEJM199909023411001.
96. Bristow MR. Beta-adrenergic receptor blockade in chronic heart failure. *Circulation*. 2000;101:558–569.
97. Packer M, Poole-Wilson PA, Armstrong PW, Cleland JG, Horowitz JD, Massie BM, Rydén L, Thygesen K, Uretsky BF. Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbidity and mortality in chronic heart failure: ATLAS Study Group. *Circulation*. 1999;100:2312–2318.
98. Fowler MB. Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) trial: carvedilol in severe heart failure. *Am J Cardiol*. 2004;93:35B–39B. doi: 10.1016/j.amjcard.2004.01.004.
99. Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjekshus J, Wikstrand J, El Allaf D, Vítovec J, Aldershvile J, Halinen M, Dietz R, Neuhaus KL, Jánosi A, Thorgeirsson G, Dunselman PH, Gullestad L, Kuch J, Herlitz J, Rickenbacher P, Ball S, Gottlieb S, Deedwania P. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF): MERIT-HF Study Group. *JAMA*. 2000;283:1295–1302.
100. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet*. 1999;353:9–13.
101. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, Shusterman NH. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure: U.S. Carvedilol Heart Failure Study Group. *N Engl J Med*. 1996;334:1349–1355. doi: 10.1056/NEJM199605233342101.
102. Bristow MR, Gilbert EM, Abraham WT, Adams KF, Fowler MB, Hershberger RE, Kubo SH, Narahara KA, Ingersoll H, Krueger S, Young S, Shusterman N. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure: MOCHA Investigators. *Circulation*. 1996;94:2807–2816.
103. Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC; ADHERE Scientific Advisory Committee and Investigators. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database [published correction appears in *J Am Coll Cardiol*. 2006;47:1502]. *J Am Coll Cardiol*. 2006;47:76–84. doi: 10.1016/j.jacc.2005.09.022.
104. Lam CS, Lyass A, Kraigher-Krainer E, Massaro JM, Lee DS, Ho JE, Levy D, Redfield MM, Pieske BM, Benjamin EJ, Vasan RS. Cardiac dysfunction and noncardiac dysfunction as precursors of heart failure with reduced and preserved ejection fraction in the community [published correction appears in *Circulation*. 2011;124:e458]. *Circulation*. 2011;124:24–30. doi: 10.1161/CIRCULATIONAHA.110.979203.
105. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, Michelson EL, Olofsson B, Ostergren J; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. *Lancet*. 2003;362:777–781. doi: 10.1016/S0140-6736(03)14285-7.
106. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, Anderson S, Donovan M, Iverson E, Staiger C, Ptaszynska A; I-PRESERVE Investigators. Irbesartan in patients with heart failure and

preserved ejection fraction. *N Engl J Med*. 2008;359:2456–2467. doi: 10.1056/NEJMoa0805450.
107. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J; PEP-CHF Investigators. The Perindopril in Elderly People With Chronic Heart Failure (PEP-CHF) study. *Eur Heart J*. 2006;27:2338–2345. doi: 10.1093/eurheartj/ehl250.
108. Packer M, Carver JR, Rodeheffer RJ, Ivanhoe RJ, DiBianco R, Zeldis SM, Hendrix GH, Bommer WJ, Elkayam U, Kukin ML, Mallis GI, Sollano JA, Shannon J, Tandon PK, DeMets DL; PROMISE Study Research Group. Effect of oral milrinone on mortality in severe chronic heart failure: the PROMISE Study Research Group. *N Engl J Med*. 1991;325:1468–1475. doi: 10.1056/NEJM199111213252103.
109. Bouchardy J, Therrien J, Pilote L, Ionescu-Ittu R, Martucci G, Bottega N, Marelli AJ. Atrial arrhythmias in adults with congenital heart disease. *Circulation*. 2009;120:1679–1686. doi: 10.1161/CIRCULATIONAHA.109.866319.
110. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society [published correction appears in *Circulation*. 2014;130:e270–e271]. *Circulation*. 2014;130:2071–2104. doi: 10.1161/CIR.0000000000000040.
111. Hasselman T, Schneider D, Madan N, Jacobs M. Reversal of fenestration flow during ventricular systole in Fontan patients in junctional or ventricular paced rhythm. *Pediatr Cardiol*. 2005;26:638–641. doi: 10.1007/s00246-005-0879-6.
112. Dodge-Khatami A, Rahn M, Prêtre R, Bauersfeld U. Dual chamber epicardial pacing for the failing atriopulmonary Fontan patient. *Ann Thorac Surg*. 2005;80:1440–1444. doi: 10.1016/j.athoracsur.2005.03.128.
113. Barber BJ, Burch GH, Tripple D, Balaji S. Resolution of plastic bronchitis with atrial pacing in a patient with Fontan physiology. *Pediatr Cardiol*. 2004;25:73–76. doi: 10.1007/s00246-003-0529-9.
114. Silka MJ, Hardy BG, Menashe VD, Morris CD. A population-based prospective evaluation of risk of sudden cardiac death after operation for common congenital heart defects. *J Am Coll Cardiol*. 1998;32:245–251.
115. Kozak LJ, Owings MF, Hall MJ. National hospital discharge survey: 2002 annual summary with detailed diagnosis and procedure data. *Vital Health Stat 13*. 2005:1–199.
116. Atallah J, Erickson CC, Cecchin F, Dubin AM, Law IH, Cohen MI, Lapage MJ, Cannon BC, Chun TU, Freedenberg V, Gierdalski M, Berul CI; Pediatric and Congenital Electrophysiology Society (PACES). Multi-institutional study of implantable defibrillator lead performance in children and young adults: results of the Pediatric Lead Extractability and Survival Evaluation (PLEASE) study. *Circulation*. 2013;127:2393–2402. doi: 10.1161/CIRCULATIONAHA.112.001120.
117. Khairy P, Harris L, Landzberg MJ, Fernandes SM, Barlow A, Mercier LA, Viswanathan S, Chetaille P, Gordon E, Dore A, Cecchin F. Sudden death and defibrillators in transposition of the great arteries with intra-atrial baffles: a multicenter study. *Circ Arrhythm Electrophysiol*. 2008;1:250–257. doi: 10.1161/CIRCEP.108.776120.
118. Khairy P, Harris L, Landzberg MJ, Viswanathan S, Barlow A, Gatzoulis MA, Fernandes SM, Beauchesne L, Therrien J, Chetaille P, Gordon E, Vonder Muhll I, Cecchin F. Implantable cardioverter-defibrillators in tetralogy of Fallot. *Circulation*. 2008;117:363–370. doi: 10.1161/CIRCULATIONAHA.107.726372.
119. Yap SC, Roos-Hesselink JW, Hoendermis ES, Budts W, Vliegen HW, Mulder BJ, van Dijk AP, Schalij MJ, Drenthen W. Outcome of implantable cardioverter defibrillators in adults with congenital heart disease: a multi-centre study. *Eur Heart J*. 2007;28:1854–1861. doi: 10.1093/eurheartj/ehl306.
120. Poole JE, Johnson GW, Hellkamp AS, Anderson J, Callans DJ, Raitt MH, Reddy RK, Marchlinski FE, Yee R, Guarnieri T, Talajic M, Wilber DJ, Fishbein DP, Packer DL, Mark DB, Lee KL, Bardy GH. Prognostic importance of defibrillator shocks in patients with heart failure. *N Engl J Med*. 2008;359:1009–1017. doi: 10.1056/NEJMoa071098.
121. Daubert JP, Zareba W, Cannom DS, McNitt S, Rosero SZ, Wang P, Schuger C, Steinberg JS, Higgins SL, Wilber DJ, Klein H, Andrews ML, Hall WJ, Moss AJ; MADIT II Investigators. Inappropriate implantable cardioverter-defibrillator shocks in MADIT II: frequency, mechanisms, predictors, and survival impact. *J Am Coll Cardiol*. 2008;51:1357–1365. doi: 10.1016/j.jacc.2007.09.073.
122. Khairy P, Mansour F. Implantable cardioverter-defibrillators in congenital heart disease: 10 programming tips. *Heart Rhythm*. 2011;8:480–483. doi: 10.1016/j.hrthm.2010.10.046.
123. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L; Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med*. 2005;352:1539–1549. doi: 10.1056/NEJMoa050496.
124. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NA 3rd, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W; MADIT-CRT Trial Investigators. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med*. 2009;361:1329–1338. doi: 10.1056/NEJMoa0906431.
125. Tang AS, Wells GA, Talajic M, Arnold MO, Sheldon R, Connolly S, Hohnloser SH, Nichol G, Birnie DH, Sapp JL, Yee R, Healey JS, Rouleau JL; Resynchronization-Defibrillation for Ambulatory Heart Failure Trial Investigators. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med*. 2010;363:2385–2395. doi: 10.1056/NEJMoa1009540.
126. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA 3rd, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Buller CE, Creager MA, Ettinger SM, Faxon DP, Halperin JL, Hiratzka LF, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura RA, Ornato JP, Page RL, Riegel B, Tarkington LG, Yancy CW. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) [published correction appears in *Circulation*. 2009;120:e34–e35]. *Circulation*. 2008;117:e350–e408. doi: 10.1161/CIRCUALTIONAHA.108.189742.
127. Cecchin F, Frangini PA, Brown DW, Fynn-Thompson F, Alexander ME, Triedman JK, Gauvreau K, Walsh EP, Berul CI. Cardiac resynchronization therapy (and multisite pacing) in pediatrics and congenital heart disease: five years experience in a single institution. *J Cardiovasc Electrophysiol*. 2009;20:58–65. doi: 10.1111/j.1540-8167.2008.01274.x.
128. Dubin AM, Janousek J, Rhee E, Strieper MJ, Cecchin F, Law IH, Shannon KM, Temple J, Rosenthal E, Zimmerman FJ, Davis A, Karpawich PP, Al Ahmad A, Vetter VL, Kertesz NJ, Shah M, Snyder C, Stephenson E, Emmel M, Sanatani S, Kanter R, Batra A, Collins KK. Resynchronization therapy in pediatric and congenital heart disease patients: an international multicenter study. *J Am Coll Cardiol*. 2005;46:2277–2283. doi: 10.1016/j.jacc.2005.05.096.
129. Janousek J, Gebauer RA, Abdul-Khaliq H, Turner M, Kornyei L, Grollmuss O, Rosenthal E, Villain E, Früh A, Paul T, Blom NA, Happonen JM, Bauersfeld U, Jacobsen JR, van den Heuvel F, Delhaas T, Papagiannis J, Trigo C; Working Group for Cardiac Dysrhythmias and Electrophysiology of the Association for European Paediatric Cardiology. Cardiac resynchronisation therapy in paediatric and congenital heart disease: differential effects in various anatomical and functional substrates. *Heart*. 2009;95:1165–1171. doi: 10.1136/hrt.2008.160465.
130. Tracy CM, Epstein AE, Darbar D, DiMarco JP, Dunbar SB, Estes NA 3rd, Ferguson TB Jr, Hammill SC, Karasik PE, Link MS, Marine JE, Schoenfeld MH, Shanker AJ, Silka MJ, Stevenson LW, Stevenson WG, Varosy PD, Ellenbogen KA, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hayes DL, Page RL, Stevenson LW, Sweeney MO. 2012 ACCF/AHA/HRS focused update of the 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society [published correction appears in *Circulation*. 2013;127:e357–e359]. *Circulation*. 2012;126:1784–1800. doi: 10.1161/CIR.0b013e3182618569.
131. Khairy P, Van Hare GF, Balaji S, Berul CI, Cecchin F, Cohen MI, Daniels CJ, Deal BJ, Dearani JA, Groot Nd, Dubin AM, Harris L, Janousek J, Kanter RJ, Karpawich PP, Perry JC, Seslar SP, Shah MJ, Silka MJ, Triedman JK, Walsh EP, Warnes CA. PACES/HRS expert consensus statement on the recognition and management of arrhythmias in adult congenital heart disease: developed in partnership between the Pediatric and Congenital Electrophysiology Society (PACES) and the Heart Rhythm Society (HRS). *Heart Rhythm*. 2014;11:e102–e165. doi: 10.1016/j.hrthm.2014.05.009.
132. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA 3rd, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy

of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2013;127:e283–e352. doi: 10.1161/CIR.0b013e318276ce9b.

133. Khairy P, Landzberg MJ, Gatzoulis MA, Mercier LA, Fernandes SM, Côté JM, Lavoie JP, Fournier A, Guerra PG, Frogoudaki A, Walsh EP, Dore A; Epicardial Versus ENdocardial pacing and Thromboembolic events Investigators. Transvenous pacing leads and systemic thromboemboli in patients with intracardiac shunts: a multicenter study. *Circulation*. 2006;113:2391–2397. doi: 10.1161/CIRCULATIONAHA.106.622076.
134. Tomaske M, Prêtre R, Rahn M, Bauersfeld U. Epicardial and pleural lead ICD systems in children and adolescents maintain functionality over 5 years. *Europace*. 2008;10:1152–1156. doi: 10.1093/europace/eun214.
135. Bardy GH, Smith WM, Hood MA, Crozier IG, Melton IC, Jordaens L, Theuns D, Park RE, Wright DJ, Connelly DT, Fynn SP, Murgatroyd FD, Sperzel J, Neuzner J, Spitzer SG, Ardashev AV, Oduro A, Boersma L, Maass AH, Van Gelder IC, Wilde AA, van Dessel PF, Knops RE, Barr CS, Lupo P, Cappato R, Grace AA. An entirely subcutaneous implantable cardioverter-defibrillator. *N Engl J Med*. 2010;363:36–44. doi: 10.1056/NEJMoa0909545.
136. Berul CI, Van Hare GF, Kertesz NJ, Dubin AM, Cecchin F, Collins KK, Cannon BC, Alexander ME, Triedman JK, Walsh EP, Friedman RA. Results of a multicenter retrospective implantable cardioverter-defibrillator registry of pediatric and congenital heart disease patients. *J Am Coll Cardiol*. 2008;51:1685–1691. doi: 10.1016/j.jacc.2008.01.033.
137. Khairy P, Roux JF, Dubuc M, Thibault B, Guerra PG, Macle L, Mercier LA, Dore A, Roy D, Talajic M, Pagé P. Laser lead extraction in adult congenital heart disease. *J Cardiovasc Electrophysiol*. 2007;18:507–511. doi: 10.1111/j.1540-8167.2007.00782.x.
138. Kirjavainen M, Happonen JM, Louhimo I. Late results of Senning operation. *J Thorac Cardiovasc Surg*. 1999;117:488–495.
139. Puley G, Siu S, Connelly M, Harrison D, Webb G, Williams WG, Harris L. Arrhythmia and survival in patients >18 years of age after the Mustard procedure for complete transposition of the great arteries. *Am J Cardiol*. 1999;83:1080–1084.
140. Roos-Hesselink JW, Meijboom FJ, Spitaels SE, van Domburg R, van Rijen EH, Utens EM, McGhie J, Bos E, Bogers AJ, Simoons ML. Decline in ventricular function and clinical condition after Mustard repair for transposition of the great arteries (a prospective study of 22-29 years). *Eur Heart J*. 2004;25:1264–1270. doi: 10.1016/j.ehj.2004.03.009.
141. Graham TP Jr, Bernard YD, Mellen BG, Celermajer D, Baumgartner H, Cetta F, Connolly HM, Davidson WR, Dellborg M, Foster E, Gersony WM, Gessner IH, Hurwitz RA, Kaemmerer H, Kugler JD, Murphy DJ, Noonan JA, Morris C, Perloff JK, Sanders SP, Sutherland JL. Long-term outcome in congenitally corrected transposition of the great arteries: a multi-institutional study. *J Am Coll Cardiol*. 2000;36:255–261.
142. Bos JM, Hagler DJ, Silvilairat S, Cabalka A, O'Leary P, Daniels O, Miller FA, Abraham TP. Right ventricular function in asymptomatic individuals with a systemic right ventricle. *J Am Soc Echocardiogr*. 2006;19:1033–1037. doi: 10.1016/j.echo.2006.03.007.
143. Szymański P, Klisiewicz A, Lubiszewska B, Lipczyńska M, Michałek P, Janas J, Hoffman P. Application of classic heart failure definitions of asymptomatic and symptomatic ventricular dysfunction and heart failure symptoms with preserved ejection fraction to patients with systemic right ventricles. *Am J Cardiol*. 2009;104:414–418. doi: 10.1016/j.amjcard.2009.03.057.
144. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure, part I: diagnosis, prognosis, and measurements of diastolic function. *Circulation*. 2002;105:1387–1393.
145. Derrick GP, Narang I, White PA, Kelleher A, Bush A, Penny DJ, Redington AN. Failure of stroke volume augmentation during exercise and dobutamine stress is unrelated to load-independent indexes of right ventricular performance after the Mustard operation. *Circulation*. 2000;102(suppl III):III154–III159.
146. Page E, Perrault H, Flore P, Rossignol AM, Pironneau S, Rocca C, Aguilaniu B. Cardiac output response to dynamic exercise after atrial switch repair for transposition of the great arteries. *Am J Cardiol*. 1996;77:892–895. doi: 10.1016/S0002-9149(97)89193-X.
147. Fratz S, Hager A, Busch R, Kaemmerer H, Schwaiger M, Lange R, Hess J, Stern HC. Patients after atrial switch operation for transposition of the great arteries can not increase stroke volume under dobutamine stress as opposed to patients with congenitally corrected transposition. *Circ J*. 2008;72:1130–1135.
148. Kammeraad JA, van Deurzen CH, Sreeram N, Bink-Boelkens MT, Ottenkamp J, Helbing WA, Lam J, Sobotka-Plojhar MA, Daniels O, Balaji S. Predictors of sudden cardiac death after Mustard or Senning repair for transposition of the great arteries. *J Am Coll Cardiol*. 2004;44:1095–1102. doi: 10.1016/j.jacc.2004.05.073.
149. Janousek J, Paul T, Luhmer I, Wilken M, Hruda J, Kallfelz HC. Atrial baffle procedures for complete transposition of the great arteries: natural course of sinus node dysfunction and risk factors for dysrhythmias and sudden death. *Z Kardiol*. 1994;83:933–938.
150. Gatzoulis MA, Walters J, McLaughlin PR, Merchant N, Webb GD, Liu P. Late arrhythmia in adults with the Mustard procedure for transposition of great arteries: a surrogate marker for right ventricular dysfunction? *Heart*. 2000;84:409–415.
151. Salehian O, Schwerzmann M, Merchant N, Webb GD, Siu SC, Therrien J. Assessment of systemic right ventricular function in patients with transposition of the great arteries using the myocardial performance index: comparison with cardiac magnetic resonance imaging. *Circulation*. 2004;110:3229–3233. doi: 10.1161/01.CIR.0000147284.54140.73.
152. Moroseos T, Mitsumori L, Kerwin WS, Sahn DJ, Helbing WA, Kilner PJ, Shurman A, Litt H, Sheehan FH. Comparison of Simpson's method and three-dimensional reconstruction for measurement of right ventricular volume in patients with complete or corrected transposition of the great arteries. *Am J Cardiol*. 2010;105:1603–1609. doi: 10.1016/j.amjcard.2010.01.025.
153. Book WM, Hott BJ, McConnell M. B-type natriuretic peptide levels in adults with congenital heart disease and right ventricular failure. *Am J Cardiol*. 2005;95:545–546. doi: 10.1016/j.amjcard.2004.10.031.
154. Koch AM, Zink S, Singer H. B-type natriuretic peptide in patients with systemic right ventricle. *Cardiology*. 2008;110:1–7. doi: 10.1159/000109399.
155. Chow PC, Cheung EW, Chong CY, Lun KS, Yung TC, Wong KT, Chau AK, Cheung YF. Brain natriuretic peptide as a biomarker of systemic right ventricular function in patients with transposition of great arteries after atrial switch operation. *Int J Cardiol*. 2008;127:192–197. doi: 10.1016/j.ijcard.2007.06.004.
156. Giardini A, Lovato L, Donti A, Formigari R, Gargiulo G, Picchio FM, Fattori R. A pilot study on the effects of carvedilol on right ventricular remodelling and exercise tolerance in patients with systemic right ventricle. *Int J Cardiol*. 2007;114:241–246. doi: 10.1016/j.ijcard.2006.01.048.
157. Winter MM, Scherptong RW, Kumar S, Bouma BJ, Tulevski II, Tops LF, Roest AA, Vliegen HW, de Roos A, Groenink M, Mulder BJ. Ventricular response to stress predicts outcome in adult patients with a systemic right ventricle. *Am Heart J*. 2010;160:870–876. doi: 10.1016/j.ahj.2010.07.015.
158. Moons P, Gewillig M, Sluysmans T, Verhaaren H, Viart P, Massin M, Suys B, Budts W, Pasquet A, De Wolf D, Vliers A. Long term outcome up to 30 years after the Mustard or Senning operation: a nationwide multicentre study in Belgium. *Heart*. 2004;90:307–313.
159. Hechter SJ, Fredriksen PM, Liu P, Veldtman G, Merchant N, Freeman M, Therrien J, Benson L, Siu S, Webb G. Angiotensin-converting enzyme inhibitors in adults after the Mustard procedure. *Am J Cardiol*. 2001;87:660–663, A11.
160. Robinson B, Heise CT, Moore JW, Anella J, Sokoloski M, Eshaghpour E. Afterload reduction therapy in patients following intraatrial baffle operation for transposition of the great arteries. *Pediatr Cardiol*. 2002;23:618–623. doi: 10.1007/s00246-002-0046-2.
161. Therrien J, Provost Y, Harrison J, Connelly M, Kaemmerer H, Webb GD. Effect of angiotensin receptor blockade on systemic right ventricular function and size: a small, randomized, placebo-controlled study. *Int J Cardiol*. 2008;129:187–192. doi: 10.1016/j.ijcard.2008.04.056.
162. Hsu DT, Zak V, Mahony L, Sleeper LA, Atz AM, Levine JC, Barker PC, Ravishankar C, McCrindle BW, Williams RV, Altmann K, Ghanayem NS, Margossian R, Chung WK, Border WL, Pearson GD, Stylianou MP, Mital S; Pediatric Heart Network Investigators. Enalapril in infants with single ventricle: results of a multicenter randomized trial. *Circulation*. 2010;122:333–340. doi: 10.1161/CIRCULATIONAHA.109.927988.
163. Anderson PA, Breitbart RE, McCrindle BW, Sleeper LA, Atz AM, Hsu DT, Lu M, Margossian R, Williams RV. The Fontan patient: inconsistencies in medication therapy across seven pediatric heart network centers. *Pediatr Cardiol*. 2010;31:1219–1228. doi: 10.1007/s00246-010-9807-5.
164. Lester SJ, McElhinney DB, Viloria E, Reddy GP, Ryan E, Tworetzky W, Schiller NB, Foster E. Effects of losartan in patients with a systemically functioning morphologic right ventricle after atrial repair of transposition of the great arteries. *Am J Cardiol*. 2001;88:1314–1316.
165. Dore A, Houde C, Chan KL, Ducharme A, Khairy P, Juneau M, Marcotte F, Mercier LA. Angiotensin receptor blockade and exercise capacity in adults with systemic right ventricles: a multicenter, randomized,

placebo-controlled clinical trial. *Circulation*. 2005;112:2411–2416. doi: 10.1161/CIRCULATIONAHA.105.543470.
166. van der Bom T, Winter MM, Bouma BJ, Groenink M, Vliegen HW, Pieper PG, van Dijk AP, Sieswerda GT, Roos-Hesselink JW, Zwinderman AH, Mulder BJ. Effect of valsartan on systemic right ventricular function: a double-blind, randomized, placebo-controlled pilot trial. *Circulation*. 2013;127:322–330. doi: 10.1161/CIRCULATIONAHA.112.135392.
167. Josephson CB, Howlett JG, Jackson SD, Finley J, Kells CM. A case series of systemic right ventricular dysfunction post atrial switch for simple D-transposition of the great arteries: the impact of beta-blockade. *Can J Cardiol*. 2006;22:769–772.
168. Doughan AR, McConnell ME, Book WM. Effect of beta blockers (carvedilol or metoprolol XL) in patients with transposition of great arteries and dysfunction of the systemic right ventricle. *Am J Cardiol*. 2007;99:704–706. doi: 10.1016/j.amjcard.2006.10.025.
169. Lindenfeld J, Keller K, Campbell DN, Wolfe RR, Quaife RA. Improved systemic ventricular function after carvedilol administration in a patient with congenitally corrected transposition of the great arteries. *J Heart Lung Transplant*. 2003;22:198–201.
170. Shaddy RE, Boucek MM, Hsu DT, Boucek RJ, Canter CE, Mahony L, Ross RD, Pahl E, Blume ED, Dodd DA, Rosenthal DN, Burr J, LaSalle B, Holubkov R, Lukas MA, Tani LY; Pediatric Carvedilol Study Group. Carvedilol for children and adolescents with heart failure: a randomized controlled trial. *JAMA*. 2007;298:1171–1179. doi: 10.1001/jama.298.10.1171.
171. Ishibashi N, Park IS, Waragai T, Yoshikawa T, Murakami Y, Mori K, Mimori S, Ando M, Takahashi Y, Doi S, Mizutani S, Nakanishi T. Effect of carvedilol on heart failure in patients with a functionally univentricular heart. *Circ J*. 2011;75:1394–1399.
172. Janousek J. Electrical resychronization of failing right ventricle. *Circulation*. 2004;109:e5; author reply e5. doi: 10.1161/01.CIR.0000111125.72039.83.
173. Van de Veire NR, Blom NA, Holman ER, Schalij MJ, Bax JJ. Triplane tissue Doppler imaging to evaluate mechanical dyssynchrony before and after cardiac resynchronization in a patient with congenitally corrected transposition of the great arteries. *J Cardiovasc Electrophysiol*. 2007;18:222–225.
174. Jauvert G, Rousseau-Paziaud J, Villain E, Iserin L, Hidden-Lucet F, Ladouceur M, Sidi D. Effects of cardiac resynchronization therapy on echocardiographic indices, functional capacity, and clinical outcomes of patients with a systemic right ventricle. *Europace*. 2009;11:184–190. doi: 10.1093/europace/eun319.
175. Janousek J, Tomek V, Chaloupecký VA, Reich O, Gebauer RA, Kautzner J, Hucín B. Cardiac resynchronization therapy: a novel adjunct to the treatment and prevention of systemic right ventricular failure. *J Am Coll Cardiol*. 2004;44:1927–1931. doi: 10.1016/j.jacc.2004.08.044.
176. Bottega NA, Kapa S, Edwards WD, Connolly HM, Munger TM, Warnes CA, Asirvatham SJ. The cardiac veins in congenitally corrected transposition of the great arteries: delivery options for cardiac devices. *Heart Rhythm*. 2009;6:1450–1456. doi: 10.1016/j.hrthm.2009.07.037.
177. Uemura H, Ho SY, Anderson RH, Gerlis LM, Devine WA, Neches WH, Yagihara T, Kawashima Y. Surgical anatomy of the coronary circulation in hearts with discordant atrioventricular connections. *Eur J Cardiothorac Surg*. 1996;10:194–200.
178. Chakrabarti S, Szantho G, Turner MS, Stuart G, Martin RP. Use of radiofrequency perforation for lead placement in biventricular or conventional endocardial pacing after mustard or senning operations for D-transposition of the great arteries. *Pacing Clin Electrophysiol*. 2009;32:1123–1129. doi: 10.1111/j.1540-8159.2009.02453.x.
179. Kiesewetter C, Michael K, Morgan J, Veldtman GR. Left ventricular dysfunction after cardiac resynchronization therapy in congenital heart disease patients with a failing systemic right ventricle. *Pacing Clin Electrophysiol*. 2008;31:159–162. doi: 10.1111/j.1540-8159.2007.00963.x.
180. Bonow RO, Carabello BA, Kanu C, de Leon AC Jr, Faxon DP, Freed MD, Gaasch WH, Lytle BW, Nishimura RA, O'Gara PT, O'Rourke RA, Otto CM, Shah PM, Shanewise JS, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Lytle BW, Nishimura R, Page RL, Riegel B. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease) [published corrections appear in *Circulation*. 2007;115:e409 and *Circulation*. 2010;121:e443]. *Circulation*. 2006;114:e84–e231.
181. Joyce DL, Crow SS, John R, St. Louis JD, Braunlin EA, Pyles LA, Kofflin P, Joyce LD. Mechanical circulatory support in patients with heart failure secondary to transposition of the great arteries. *J Heart Lung Transplant*. 2010;29:1302–1305. doi: 10.1016/j.healun.2010.05.030.
182. Jouan J, Grinda JM, Bricourt MO, Iserin L, Fabiani JN. Non-pulsatile axial flow ventricular assist device for right systemic ventricle failure late after Senning procedure. *Int J Artif Organs*. 2009;32:243–245.
183. Sugiura T, Kurosawa H, Shin'oka T, Kawai A. Successful explantation of ventricular assist device for systemic ventricular assistance in a patient with congenitally corrected transposition of the great arteries. *Interact Cardiovasc Thorac Surg*. 2006;5:792–793. doi: 10.1510/icvts.2006.139337.
184. Fishberger SB, Asnes JD, Rollinson NL, Cleman MW. Percutaneous right ventricular support during catheter ablation of intra-atrial reentrant tachycardia in an adult with a mustard baffle: a novel use of the Impella device. *J Interv Card Electrophysiol*. 2010;29:69–72. doi: 10.1007/s10840-010-9478-4.
185. Strueber M, O'Driscoll G, Jansz P, Khaghani A, Levy WC, Wieselthaler GM; HeartWare Investigators. Multicenter evaluation of an intrapericardial left ventricular assist system. *J Am Coll Cardiol*. 2011;57:1375–1382. doi: 10.1016/j.jacc.2010.10.040.
186. Huebler M, Stepanenko A, Krabatsch T, Potapov EV, Hetzer R. Mechanical circulatory support of systemic ventricle in adults with transposition of great arteries. *ASAIO J*. 2012;58:12–14. doi: 10.1097/MAT.0b013e31823a82df.
187. Jacobs S, Rega F, Burkhoff D, Meyns B. The use of a CircuLite micropump for congenitally corrected transposition of the great arteries. *Eur J Cardiothorac Surg*. 2012;42:741–743. doi: 10.1093/ejcts/ezs308.
188. Fontan F, Baudet E. Surgical repair of tricuspid atresia. *Thorax*. 1971;26:240–248.
189. Williams DB, Kiernan PD, Metke MP, Marsh HM, Danielson GK. Hemodynamic response to positive end-expiratory pressure following right atrium-pulmonary artery bypass (Fontan procedure). *J Thorac Cardiovasc Surg*. 1984;87:856–861.
190. Bridges ND, Lock JE, Castaneda AR. Baffle fenestration with subsequent transcatheter closure: modification of the Fontan operation for patients at increased risk. *Circulation*. 1990;82:1681–1689.
191. Mertens L, Hagler DJ, Sauer U, Somerville J, Gewillig M. Protein-losing enteropathy after the Fontan operation: an international multicenter study: PLE Study Group. *J Thorac Cardiovasc Surg*. 1998;115:1063–1073.
192. Griffiths ER, Kaza AK, Wyler von Ballmoos MC, Loyola H, Valente AM, Blume ED, del Nido P. Evaluating failing Fontans for heart transplantation: predictors of death. *Ann Thorac Surg*. 2009;88:558–563. doi: 10.1016/j.athoracsur.2009.03.085.
193. Kendall TJ, Stedman B, Hacking N, Haw M, Vettukattill JJ, Salmon AP, Cope R, Sheron N, Millward-Sadler H, Veldtman GR, Iredale JP. Hepatic fibrosis and cirrhosis in the Fontan circulation: a detailed morphological study. *J Clin Pathol*. 2008;61:504–508. doi: 10.1136/jcp.2007.052365.
194. Friedrich-Rust M, Koch C, Rentzsch A, Sarrazin C, Schwarz P, Herrmann E, Lindinger A, Sarrazin U, Poynard T, Schäfers HJ, Zeuzem S, Abdul-Khaliq H. Noninvasive assessment of liver fibrosis in patients with Fontan circulation using transient elastography and biochemical fibrosis markers. *J Thorac Cardiovasc Surg*. 2008;135:560–567. doi: 10.1016/j.jtcvs.2007.09.039.
195. Camposilvan S, Milanesi O, Stellin G, Pettenazzo A, Zancan L, D'Antiga L. Liver and cardiac function in the long term after Fontan operation. *Ann Thorac Surg*. 2008;86:177–182. doi: 10.1016/j.athoracsur.2008.03.077.
196. Baek JS, Bae EJ, Ko JS, Kim GB, Kwon BS, Lee SY, Noh CI, Park EA, Lee W. Late hepatic complications after Fontan operation; non-invasive markers of hepatic fibrosis and risk factors. *Heart*. 2010;96:1750–1755. doi: 10.1136/hrt.2010.201772.
197. Guha IN, Bokhandi S, Ahmad Z, Sheron N, Cope R, Marshall C, Veldtman G. Structural and functional uncoupling of liver performance in the Fontan circulation. *Int J Cardiol*. 2013;164:77–81. doi: 10.1016/j.ijcard.2011.06.062.
198. Schwartz MC, Sullivan L, Cohen MS, Russo P, John AS, Guo R, Guttenberg M, Rand EB. Hepatic pathology may develop before the Fontan operation in children with functional single ventricle: an autopsy study. *J Thorac Cardiovasc Surg*. 2012;143:904–909. doi: 10.1016/j.jtcvs.2011.08.038.
199. Furukawa T, Akimoto K, Ohtsuki M, Sato K, Suzuki M, Takahashi K, Kishiro M, Shimizu T, Kawasaki S. Non-invasive assessment of liver fibrosis in patients after the Fontan operation. *Pediatr Int*. 2011;53:980–984. doi: 10.1111/j.1442-200X.2011.03497.x.
200. Ginde S, Hohenwalter MD, Foley WD, Sowinski J, Bartz PJ, Venkatapuram S, Weinberg C, Tweddell JS, Earing MG. Noninvasive assessment of liver fibrosis in adult patients following the Fontan procedure. *Congenit Heart Dis*. 2012;7:235–242. doi: 10.1111/j.1747-0803.2012.00632.x.

201. Rychik J, Veldtman G, Rand E, Russo P, Rome JJ, Krok K, Goldberg DJ, Cahill AM, Wells RG. The precarious state of the liver after a Fontan operation: summary of a multidisciplinary symposium. *Pediatr Cardiol*. 2012;33:1001–1012. doi: 10.1007/s00246-012-0315-7.
202. Krieger EV, Moko LE, Wu F, Landzberg MJ, Valente AM, Assenza GE, Ukomadu C, Opotowsky AR. Single ventricle anatomy is associated with increased frequency of nonalcoholic cirrhosis. *Int J Cardiol*. 2013;167:1918–1923. doi: 10.1016/j.ijcard.2012.05.002.
203. McCabe N, Farris AB, Hon H, Ford R, Book WM. Hepatocellular carcinoma in an adult with repaired tetralogy of Fallot. *Congenit Heart Dis*. 2013;8:E139–E144. doi: 10.1111/j.1747-0803.2012.00700.x.
204. Wallihan DB, Podberesky DJ. Hepatic pathology after Fontan palliation: spectrum of imaging findings. *Pediatr Radiol*. 2013;43:330–338. doi: 10.1007/s00247-012-2531-y.
205. Johnson JA, Cetta F, Graham RP, Smyrk TC, Driscoll DJ, Phillips SD, John AS. Identifying predictors of hepatic disease in patients after the Fontan operation: a postmortem analysis. *J Thorac Cardiovasc Surg*. 2013;146:140–145. doi: 10.1016/j.jtcvs.2012.09.005.
206. Assenza GE, Graham DA, Landzberg MJ, Valente AM, Singh MN, Bashir A, Fernandes S, Mortele KJ, Ukomadu C, Volpe M, Wu F. MELD-XI score and cardiac mortality or transplantation in patients after Fontan surgery. *Heart*. 2013;99:491–496. doi: 10.1136/heartjnl-2012-303347.
207. Asrani SK, Warnes CA, Kamath PS. Hepatocellular carcinoma after the Fontan procedure. *N Engl J Med*. 2013;368:1756–1757. doi: 10.1056/NEJMc1214222.
208. Elder RW, McCabe NM, Hebson C, Veledar E, Romero R, Ford RM, Mahle WT, Kogon BE, Sahu A, Jokhadar M, McConnell ME, Book WM. Features of portal hypertension are associated with major adverse events in Fontan patients: the VAST study. *Int J Cardiol*. 2013;168:3764–3769. doi: 10.1016/j.ijcard.2013.06.008.
209. Kutty SS, Peng Q, Danford DA, Fletcher SE, Perry D, Talmon GA, Scott C, Kugler JD, Duncan KF, Quiros-Tejeira RE, Kutty S; Liver Adult-Pediatric-Congenital-Heart-Disease Dysfunction Study (LADS) Group. Increased hepatic stiffness as consequence of high hepatic afterload in the Fontan circulation: a vascular Doppler and elastography study. *Hepatology*. 2014;59:251–260. doi: 10.1002/hep.26631.
210. Vonder Muhll I, Liu P, Webb G. Applying standard therapies to new targets: the use of ACE inhibitors and B-blockers for heart failure in adults with congenital heart disease. *Int J Cardiol*. 2004;97(suppl 1):25–33. doi: 10.1016/j.ijcard.2004.08.006.
211. Giardini A, Balducci A, Specchia S, Gargiulo G, Bonvicini M, Picchio FM. Effect of sildenafil on haemodynamic response to exercise and exercise capacity in Fontan patients. *Eur Heart J*. 2008;29:1681–1687. doi: 10.1093/eurheartj/ehn215.
212. Van De Bruaene A, La Gerche A, Claessen G, De Meester P, Devroe S, Gillijns H, Bogaert J, Claus P, Heidbuchel H, Gewillig M, Budts W. Sildenafil improves exercise hemodynamics in Fontan patients. *Circ Cardiovasc Imaging*. 2014;7:265–273.
213. Goldberg DJ, French B, Szwast AL, McBride MG, Marino BS, Mirarchi N, Hanna BD, Wernovsky G, Paridon SM, Rychik J. Impact of sildenafil on echocardiographic indices of myocardial performance after the Fontan operation. *Pediatr Cardiol*. 2012;33:689–696. doi: 10.1007/s00246-012-0196-9.
214. Shabanian R, Shahbaznejad L, Razaghian A, Kiani A, Rahimzadeh M, Seifirad S, Kocharian A, Gilani JS, Navabi MA. Sildenafil and ventriculo-arterial coupling in Fontan-palliated patients: a noninvasive echocardiographic assessment. *Pediatr Cardiol*. 2013;34:129–134. doi: 10.1007/s00246-012-0400-y.
215. Goldberg DJ, French B, McBride MG, Marino BS, Mirarchi N, Hanna BD, Wernovsky G, Paridon SM, Rychik J. Impact of oral sildenafil on exercise performance in children and young adults after the Fontan operation: a randomized, double-blind, placebo-controlled, crossover trial. *Circulation*. 2011;123:1185–1193. doi: 10.1161/CIRCULATIONAHA.110.981746.
216. Bowater SE, Weaver RA, Thorne SA, Clift PF. The safety and effects of bosentan in patients with a Fontan circulation. *Congenit Heart Dis*. 2012;7:243–249. doi: 10.1111/j.1747-0803.2012.00635.x.
217. Ovaert C, Thijs D, Dewolf D, Ottenkamp J, Dessy H, Moons P, Gewillig M, Mertens L. The effect of bosentan in patients with a failing Fontan circulation. *Cardiol Young*. 2009;19:331–339. doi: 10.1017/S1047951109990023.
218. Schuuring MJ, Vis JC, van Dijk AP, van Melle JP, Vliegen HW, Pieper PG, Sieswerda GT, de Bruin-Bon RH, Mulder BJ, Bouma BJ. Impact of bosentan on exercise capacity in adults after the Fontan procedure: a randomized controlled trial. *Eur J Heart Fail*. 2013;15:690–698. doi: 10.1093/eurjhf/hft017.
219. Hebert A, Jensen AS, Idorn L, Sørensen KE, Søndergaard L. The effect of bosentan on exercise capacity in Fontan patients; rationale and design for the TEMPO study. *BMC Cardiovasc Disord*. 2013;13:36. doi: 10.1186/1471-2261-13-36.
220. Koide M, Carabello BA, Conrad CC, Buckley JM, DeFreyte G, Barnes M, Tomanek RJ, Wei CC, Dell'Italia LJ, Cooper G 4th, Zile MR. Hypertrophic response to hemodynamic overload: role of load vs. renin-angiotensin system activation. *Am J Physiol*. 1999;276(pt 2):H350–H358.
221. Bacha EA, Zimmerman FJ, Mor-Avi V, Weinert L, Starr JP, Sugeng L, Lang RM. Ventricular resynchronization by multisite pacing improves myocardial performance in the postoperative single-ventricle patient. *Ann Thorac Surg*. 2004;78:1678–1683. doi: 10.1016/j.athoracsur.2004.04.065.
222. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM 3rd, Thomas JD. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [published correction appears in *Circulation*. 2014;129:e650]. *Circulation*. 2014;129:2440–2492. doi: 10.1161/CIR.0000000000000029.
223. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM 3rd, Thomas JD. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [published corrections appear in *Circulation*. 2014;130:e120 and *Circulation*. 2014;129:e651]. *Circulation*. 2014;129:e521–e643. doi: 10.1161/CIR.0000000000000031.
224. McCrindle BW. Independent predictors of immediate results of percutaneous balloon aortic valvotomy in children: Valvuloplasty and Angioplasty of Congenital Anomalies (VACA) Registry Investigators. *Am J Cardiol*. 1996;77:286–293.
225. Moore P, Egito E, Mowrey H, Perry SB, Lock JE, Keane JF. Midterm results of balloon dilation of congenital aortic stenosis: predictors of success. *J Am Coll Cardiol*. 1996;27:1257–1263. doi: 10.1016/0735-1097(95)00608-7.
226. Moltzer E, Mattace Raso FU, Karamermer Y, Boersma E, Webb GD, Simoons ML, Danser AH, van den Meiracker AH, Roos-Hesselink JW. Comparison of Candesartan versus Metoprolol for treatment of systemic hypertension after repaired aortic coarctation. *Am J Cardiol*. 2010;105:217–222. doi: 10.1016/j.amjcard.2009.08.674.
227. Emani SM, Bacha EA, McElhinney DB, Marx GR, Tworetzky W, Pigula FA, del Nido PJ. Primary left ventricular rehabilitation is effective in maintaining two-ventricle physiology in the borderline left heart. *J Thorac Cardiovasc Surg*. 2009;138:1276–1282. doi: 10.1016/j.jtcvs.2009.08.009.
228. Carvalho JS, Shinebourne EA, Busst C, Rigby ML, Redington AN. Exercise capacity after complete repair of tetralogy of Fallot: deleterious effects of residual pulmonary regurgitation. *Br Heart J*. 1992;67:470–473.
229. Dave HH, Buechel ER, Dodge-Khatami A, Kadner A, Rousson V, Bauersfeld U, Prêtre R. Early insertion of a pulmonary valve for chronic regurgitation helps restoration of ventricular dimensions. *Ann Thorac Surg*. 2005;80:1615–1620. doi: 10.1016/j.athoracsur.2005.04.058.
230. Gengsakul A, Harris L, Bradley TJ, Webb GD, Williams WG, Siu SC, Merchant N, McCrindle BW. The impact of pulmonary valve replacement after tetralogy of Fallot repair: a matched comparison. *Eur J Cardiothorac Surg*. 2007;32:462–468. doi: 10.1016/j.ejcts.2007.06.009.
231. Harrild DM, Berul CI, Cecchin F, Geva T, Gauvreau K, Pigula F, Walsh EP. Pulmonary valve replacement in tetralogy of Fallot: impact on survival and ventricular tachycardia. *Circulation*. 2009;119:445–451. doi: 10.1161/CIRCULATIONAHA.108.775221.
232. Karamlou T, McCrindle BW, Williams WG. Surgery insight: late complications following repair of tetralogy of Fallot and related surgical strategies for management. *Nat Clin Pract Cardiovasc Med*. 2006;3:611–622. doi: 10.1038/ncpcardio0682.
233. Rowe SA, Zahka KG, Manolio TA, Horneffer PJ, Kidd L. Lung function and pulmonary regurgitation limit exercise capacity in postoperative tetralogy of Fallot. *J Am Coll Cardiol*. 1991;17:461–466.
234. Scherptong RW, Hazekamp MG, Mulder BJ, Wijers O, Swenne CA, van der Wall EE, Schalij MJ, Vliegen HW. Follow-up after pulmonary valve replacement in adults with tetralogy of Fallot: association between QRS duration and outcome. *J Am Coll Cardiol*. 2010;56:1486–1492. doi: 10.1016/j.jacc.2010.04.058.

235. Davlouros PA, Kilner PJ, Hornung TS, Li W, Francis JM, Moon JC, Smith GC, Tat T, Pennell DJ, Gatzoulis MA. Right ventricular function in adults with repaired tetralogy of Fallot assessed with cardiovascular magnetic resonance imaging: detrimental role of right ventricular outflow aneurysms or akinesia and adverse right-to-left ventricular interaction. *J Am Coll Cardiol*. 2002;40:2044–2052.
236. Coats L, Khambadkone S, Derrick G, Sridharan S, Schievano S, Mist B, Jones R, Deanfield JE, Pellerin D, Bonhoeffer P, Taylor AM. Physiological and clinical consequences of relief of right ventricular outflow tract obstruction late after repair of congenital heart defects. *Circulation*. 2006;113:2037–2044. doi: 10.1161/CIRCULATIONAHA.105.591438.
237. Romeih S, Kroft LJ, Bokenkamp R, Schalij MJ, Grotenhuis H, Hazekamp MG, Groenink M, de Roos A, Blom NA. Delayed improvement of right ventricular diastolic function and regression of right ventricular mass after percutaneous pulmonary valve implantation in patients with congenital heart disease. *Am Heart J*. 2009;158:40–46. doi: 10.1016/j.ahj.2009.04.023.
238. Uebing A, Gibson DG, Babu-Narayan SV, Diller GP, Dimopoulos K, Goktekin O, Spence MS, Andersen K, Henein MY, Gatzoulis MA, Li W. Right ventricular mechanics and QRS duration in patients with repaired tetralogy of Fallot: implications of infundibular disease. *Circulation*. 2007;116:1532–1539. doi: 10.1161/CIRCULATIONAHA.107.688770.
239. Gatzoulis MA, Sheppard MN, Ho SY. Value and impact of necropsy in paediatric cardiology. *Heart*. 1996;75:626–631.
240. Helbing WA, Niezen RA, Le Cessie S, van der Geest RJ, Ottenkamp J, de Roos A. Right ventricular diastolic function in children with pulmonary regurgitation after repair of tetralogy of Fallot: volumetric evaluation by magnetic resonance velocity mapping. *J Am Coll Cardiol*. 1996;28:1827–1835. doi: 10.1016/S0735-1097(96)00387-7.
241. Apitz C, Latus H, Binder W, Uebing A, Seeger A, Bretschneider C, Sieverding L, Hofbeck M. Impact of restrictive physiology on intrinsic diastolic right ventricular function and lusitropy in children and adolescents after repair of tetralogy of Fallot. *Heart*. 2010;96:1837–1841. doi: 10.1136/hrt.2010.203190.
242. Chaturvedi RR, Shore DF, Lincoln C, Mumby S, Kemp M, Brierly J, Petros A, Gutteridge JM, Hooper J, Redington AN. Acute right ventricular restrictive physiology after repair of tetralogy of Fallot: association with myocardial injury and oxidative stress. *Circulation*. 1999;100:1540–1547.
243. Babu-Narayan SV, Uebing A, Davlouros PA, Kemp M, Davidson S, Dimopoulos K, Bayne S, Pennell DJ, Gibson DG, Flather M, Kilner PJ, Li W, Gatzoulis MA. Randomised trial of ramipril in repaired tetralogy of Fallot and pulmonary regurgitation: the APPROPRIATE study (Ace inhibitors for Potential PRevention Of the deleterious effects of Pulmonary Regurgitation In Adults with repaired TEtralogy of Fallot). *Int J Cardiol*. 2012;154:299–305. doi: 10.1016/j.ijcard.2010.09.057.
244. Brown ML, Dearani JA, Danielson GK, Cetta F, Connolly HM, Warnes CA, Li Z, Hodge DO, Driscoll DJ. Effect of operation for Ebstein anomaly on left ventricular function. *Am J Cardiol*. 2008;102:1724–1727. doi: 10.1016/j.amjcard.2008.08.018.
245. Geva T, Sandweiss BM, Gauvreau K, Lock JE, Powell AJ. Factors associated with impaired clinical status in long-term survivors of tetralogy of Fallot repair evaluated by magnetic resonance imaging. *J Am Coll Cardiol*. 2004;43:1068–1074. doi: 10.1016/j.jacc.2003.10.045.
246. Celermajer DS, Dodd SM, Greenwald SE, Wyse RK, Deanfield JE. Morbid anatomy in neonates with Ebstein's anomaly of the tricuspid valve: pathophysiologic and clinical implications. *J Am Coll Cardiol*. 1992;19:1049–1053.
247. Davos CH, Davlouros PA, Wensel R, Francis D, Davies LC, Kilner PJ, Coats AJ, Piepoli M, Gatzoulis MA. Global impairment of cardiac autonomic nervous activity late after repair of tetralogy of Fallot. *Circulation*. 2002;106(suppl 1):I69–I75.
248. Norozi K, Bahlmann J, Raab B, Alpers V, Arnhold JO, Kuehne T, Klimes K, Zoege M, Geyer S, Wessel A, Buchhorn R. A prospective, randomized, double-blind, placebo controlled trial of beta-blockade in patients who have undergone surgical correction of tetralogy of Fallot. *Cardiol Young*. 2007;17:372–379. doi: 10.1017/S1047951107000844.
249. Murphy JG, Gersh BJ, Mair DD, Fuster V, McGoon MD, Ilstrup DM, McGoon DC, Kirklin JW, Danielson GK. Long-term outcome in patients undergoing surgical repair of tetralogy of Fallot. *N Engl J Med*. 1993;329:593–599. doi: 10.1056/NEJM199308263290901.
250. Nollert G, Fischlein T, Bouterwek S, Böhmer C, Klinner W, Reichart B. Long-term survival in patients with repair of tetralogy of Fallot: 36-year follow-up of 490 survivors of the first year after surgical repair. *J Am Coll Cardiol*. 1997;30:1374–1383.
251. Gatzoulis MA, Balaji S, Webber SA, Siu SC, Hokanson JS, Poile C, Rosenthal M, Nakazawa M, Moller JH, Gillette PC, Webb GD, Redington AN. Risk factors for arrhythmia and sudden cardiac death late after repair of tetralogy of Fallot: a multicentre study. *Lancet*. 2000;356:975–981. doi: 10.1016/S0140-6736(00)02714-8.
252. Knauth AL, Gauvreau K, Powell AJ, Landzberg MJ, Walsh EP, Lock JE, del Nido PJ, Geva T. Ventricular size and function assessed by cardiac MRI predict major adverse clinical outcomes late after tetralogy of Fallot repair. *Heart*. 2008;94:211–216. doi: 10.1136/hrt.2006.104745.
253. Ghai A, Silversides C, Harris L, Webb GD, Siu SC, Therrien J. Left ventricular dysfunction is a risk factor for sudden cardiac death in adults late after repair of tetralogy of Fallot. *J Am Coll Cardiol*. 2002;40:1675–1680.
254. Khairy P, Landzberg MJ, Gatzoulis MA, Lucron H, Lambert J, Marçon F, Alexander ME, Walsh EP. Value of programmed ventricular stimulation after tetralogy of Fallot repair: a multicenter study. *Circulation*. 2004;109:1994–2000. doi: 10.1161/01.CIR.0000126495.11040.BD.
255. van der Hulst AE, Delgado V, Blom NA, van de Veire NR, Schalij MJ, Bax JJ, Roest AA, Holman ER. Cardiac resynchronization therapy in paediatric and congenital heart disease patients. *Eur Heart J*. 2011;32:2236–2246. doi: 10.1093/eurheartj/ehr093.
256. Dubin AM, Feinstein JA, Reddy VM, Hanley FL, Van Hare GF, Rosenthal DN. Electrical resynchronization: a novel therapy for the failing right ventricle. *Circulation*. 2003;107:2287–2289. doi: 10.1161/01.CIR.0000070930.33499.9F.
257. Thambo JB, Dos Santos P, De Guillebon M, Roubertie F, Labrousse L, Sacher F, Iriart X, Lafitte S, Ploux S, Jais P, Roques X, Haissaguerre M, Ritter P, Clementy J, Narayan SM, Bordachar P. Biventricular stimulation improves right and left ventricular function after tetralogy of Fallot repair: acute animal and clinical studies. *Heart Rhythm*. 2010;7:344–350. doi: 10.1016/j.hrthm.2009.11.019.
258. Kirsh JA, Stephenson EA, Redington AN. Images in cardiovascular medicine. Recovery of left ventricular systolic function after biventricular resynchronization pacing in a child with repaired tetralogy of Fallot and severe biventricular dysfunction. *Circulation*. 2006;113:e691–e692. doi: 10.1161/CIRCULATIONAHA.105.580126.
259. Everitt MD, Donaldson AE, Stehlik J, Kaza AK, Budge D, Alharethi R, Bullock EA, Kfoury AG, Yetman AT. Would access to device therapies improve transplant outcomes for adults with congenital heart disease? Analysis of the United Network for Organ Sharing (UNOS). *J Heart Lung Transplant*. 2011;30:395–401. doi: 10.1016/j.healun.2010.09.008.
260. Karamlou T, Hirsch J, Welke K, Ohye RG, Bove EL, Devaney EJ, Gajarski RJ. A United Network for Organ Sharing analysis of heart transplantation in adults with congenital heart disease: outcomes and factors associated with mortality and retransplantation. *J Thorac Cardiovasc Surg*. 2010;140:161–168. doi: 10.1016/j.jtcvs.2010.03.036.
261. Gelow JM, Song HK, Weiss JB, Mudd JO, Broberg CS. Organ allocation in adults with congenital heart disease listed for heart transplant: impact of ventricular assist devices. *J Heart Lung Transplant*. 2013;32:1059–1064. doi: 10.1016/j.healun.2013.06.024.
262. Haddad H, Isaac D, Legare JF, Pflugfelder P, Hendry P, Chan M, Cantin B, Giannetti N, Zieroth S, White M, Warnica W, Doucette K, Rao V, Dipchand A, Cantarovich M, Kostuk W, Cecere R, Charbonneau E, Ross H, Poirier N. Canadian Cardiovascular Society Consensus Conference update on cardiac transplantation 2008: executive summary. *Can J Cardiol*. 2009;25:197–205.
263. Ross H, Tinckam K, Rao V, West LJ. In praise of ventricular assist devices: mechanical bridge to virtual crossmatch for the sensitized patient. *J Heart Lung Transplant*. 2010;29:728–730. doi: 10.1016/j.healun.2010.02.006.
264. Kirk R, Dipchand AI, Edwards LB, Kucheryavaya AY, Benden C, Christie JD, Dobbles F, Rahmel AO, Stehlik J, Hertz MI; International Society for Heart and Lung Transplantation. The Registry of the International Society for Heart and Lung Transplantation: fifteenth pediatric heart transplantation report–2012. *J Heart Lung Transplant*. 2012;31:1065–1072. doi: 10.1016/j.healun.2012.08.001.
265. Inuzuka R, Diller GP, Borgia F, Benson L, Tay EL, Alonso-Gonzalez R, Silva M, Charalambides M, Swan L, Dimopoulos K, Gatzoulis MA. Comprehensive use of cardiopulmonary exercise testing identifies adults with congenital heart disease at increased mortality risk in the medium term. *Circulation*. 2012;125:250–259. doi: 10.1161/CIRCULATIONAHA.111.058719.
266. Fernandes SM, Alexander ME, Graham DA, Khairy P, Clair M, Rodriguez E, Pearson DD, Landzberg MJ, Rhodes J. Exercise testing identifies patients at increased risk for morbidity and mortality following Fontan surgery. *Congenit Heart Dis*. 2011;6:294–303. doi: 10.1111/j.1747-0803.2011.00500.x.
267. Radojevic J, Inuzuka R, Alonso-Gonzalez R, Borgia F, Giannakoulas G, Prapa M, Liodakis E, Li W, Swan L, Diller GP, Dimopoulos K, Gatzoulis MA. Peak oxygen uptake correlates with disease severity and predicts outcome in adult patients with Ebstein's anomaly of the tricuspid valve. *Int J Cardiol*. 2013;163:305–308. doi: 10.1016/j.ijcard.2011.06.047.

268. Giardini A, Hager A, Lammers AE, Derrick G, Müller J, Diller GP, Dimopoulos K, Odendaal D, Gargiulo G, Picchio FM, Gatzoulis MA. Ventilatory efficiency and aerobic capacity predict event-free survival in adults with atrial repair for complete transposition of the great arteries. *J Am Coll Cardiol*. 2009;53:1548–1555. doi: 10.1016/j.jacc.2009.02.005.
269. Davies RR, Russo MJ, Yang J, Quaegebeur JM, Mosca RS, Chen JM. Listing and transplanting adults with congenital heart disease. *Circulation*. 2011;123:759–767. doi: 10.1161/CIRCULATIONAHA.110.960260.
270. Mehra MR, Kobashigawa J, Starling R, Russell S, Uber PA, Parameshwar J, Mohacsi P, Augustine S, Aaronson K, Barr M. Listing criteria for heart transplantation: International Society for Heart and Lung Transplantation guidelines for the care of cardiac transplant candidates–2006. *J Heart Lung Transplant*. 2006;25:1024–1042. doi: 10.1016/j.healun.2006.06.008.
271. Nwakanma LU, Williams JA, Weiss ES, Russell SD, Baumgartner WA, Conte JV. Influence of pretransplant panel-reactive antibody on outcomes in 8,160 heart transplant recipients in recent era. *Ann Thorac Surg*. 2007;84:1556–1562. doi: 10.1016/j.athoracsur.2007.05.095.
272. Meyer SR, Campbell PM, Rutledge JM, Halpin AM, Hawkins LE, Lakey JR, Rebeyka IM, Ross DB. Use of an allograft patch in repair of hypoplastic left heart syndrome may complicate future transplantation. *Eur J Cardiothorac Surg*. 2005;27:554–560. doi: 10.1016/j.ejcts.2004.12.033.
273. Feingold B, Park SY, Comer DM, Bryce CL, Webber SA. Listing requirements for a prospective crossmatch in pediatric heart transplantation: analysis of Organ Procurement and Transplantation Network data from 1996 to 2009. *J Heart Lung Transplant*. 2012;31:1143–1144. doi: 10.1016/j.healun.2012.08.006.
274. Kfoury AG, Stehlik J, Renlund DG, Snow G, Seaman JT, Gilbert EM, Stringham JS, Long JW, Hammond ME. Impact of repetitive episodes of antibody-mediated or cellular rejection on cardiovascular mortality in cardiac transplant recipients: defining rejection patterns. *J Heart Lung Transplant*. 2006;25:1277–1282. doi: 10.1016/j.healun.2006.08.009.
275. Wu GW, Kobashigawa JA, Fishbein MC, Patel JK, Kittleson MM, Reed EF, Kiyosaki KK, Ardehali A. Asymptomatic antibody-mediated rejection after heart transplantation predicts poor outcomes. *J Heart Lung Transplant*. 2009;28:417–422. doi: 10.1016/j.healun.2009.01.015.
276. Stastny P, Lavingia B, Fixler DE, Yancy CW, Ring WS. Antibodies against donor human leukocyte antigens and the outcome of cardiac allografts in adults and children. *Transplantation*. 2007;84:738–745. doi: 10.1097/01.tp.0000281918.51138.3f.
277. Tambur AR, Pamboukian SV, Costanzo MR, Herrera ND, Dunlap S, Montpetit M, Heroux A. The presence of HLA-directed antibodies after heart transplantation is associated with poor allograft outcome. *Transplantation*. 2005;80:1019–1025.
278. Smith RN, Ueno T, Ito T, Tanaka K, Shea SP, Abdi R. Chemokines and chronic heart allograft rejection. *Transplantation*. 2007;84:442–444. doi: 10.1097/01.tp.0000277535.02541.30.
279. Patel ND, Weiss ES, Allen JG, Russell SD, Shah AS, Vricella LA, Conte JV. Heart transplantation for adults with congenital heart disease: analysis of the United Network For Organ Sharing database. *Ann Thorac Surg*. 2009;88:814–821. doi: 10.1016/j.athoracsur.2009.04.071.
280. Chen JM, Davies RR, Mital SR, Mercando ML, Addonizio LJ, Pinney SP, Hsu DT, Lamour JM, Quaegebeur JM, Mosca RS. Trends and outcomes in transplantation for complex congenital heart disease: 1984 to 2004. *Ann Thorac Surg*. 2004;78:1352–1361. doi: 10.1016/j.athoracsur.2004.04.012.
281. Wang A, Book WM, McConnell M, Lyle T, Rodby K, Mahle WT. Prevalence of hepatitis C infection in adult patients who underwent congenital heart surgery prior to screening in 1992. *Am J Cardiol*. 2007;100:1307–1309. doi: 10.1016/j.amjcard.2007.05.059.
282. Waddell TK, Bennett L, Kennedy R, Todd TR, Keshavjee SH. Heart-lung or lung transplantation for Eisenmenger syndrome. *J Heart Lung Transplant*. 2002;21:731–737.
283. Deleted in proof.
284. Canter CE, Shaddy RE, Bernstein D, Hsu DT, Chrisant MR, Kirklin JK, Kanter KR, Higgins RS, Blume ED, Rosenthal DN, Boucek MM, Uzark KC, Friedman AH, Friedman AH, Young JK. Indications for heart transplantation in pediatric heart disease: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young; the Councils on Clinical Cardiology, Cardiovascular Nursing, and Cardiovascular Surgery and Anesthesia; and the Quality of Care and Outcomes Research Interdisciplinary Working Group [published correction appears in *Circulation*. 2007;115:e385]. *Circulation*. 2007;115:658–676. doi: 10.1161/CIRCULATIONAHA.106.180449.
285. Michielon G, Parisi F, Squitieri C, Carotti A, Gagliardi G, Pasquini L, Di Donato RM. Orthotopic heart transplantation for congenital heart disease: An alternative for high-risk fontan candidates? *Circulation*. 2003;108(suppl 1):II140–149.
286. Chrisant MR, Naftel DC, Drummond-Webb J, Chinnock R, Canter CE, Boucek MM, Boucek RJ, Hallowell SC, Kirklin JK, Morrow WR; Pediatric Heart Transplant Study Group. Fate of infants with hypoplastic left heart syndrome listed for cardiac transplantation: a multicenter study. *J Heart Lung Transplant*. 2005;24:576–582. doi: 10.1016/j.healun.2004.01.019.
287. Jacobs JP, Quintessenza JA, Chai PJ, Lindberg HL, Asante-Korang A, McCormack J, Dadlani G, Boucek RJ. Rescue cardiac transplantation for failing staged palliation in patients with hypoplastic left heart syndrome. *Cardiol Young*. 2006;16:556–562. doi: 10.1017/S1047951106001223.
288. McHugh KE, Hillman DG, Gurka MJ, Gutgesell HP. Three-stage palliation of hypoplastic left heart syndrome in the University HealthSystem Consortium. *Congenit Heart Dis*. 2010;5:8–15. doi: 10.1111/j.1747-0803.2009.00367.x.
289. Ashburn DA, McCrindle BW, Tchervenkov CI, Jacobs ML, Lofland GK, Bove EL, Spray TL, Williams WG, Blackstone EH. Outcomes after the Norwood operation in neonates with critical aortic stenosis or aortic valve atresia. *J Thorac Cardiovasc Surg*. 2003;125:1070–1082. doi: 10.1067/mtc.2003.183.
290. Bernstein D, Naftel D, Chin C, Addonizio LJ, Gamberg P, Blume ED, Hsu D, Canter CE, Kirklin JK, Morrow WR; Pediatric Heart Transplant Study. Outcome of listing for cardiac transplantation for failed Fontan: a multi-institutional study. *Circulation*. 2006;114:273–280. doi: 10.1161/CIRCULATIONAHA.105.548016.
291. Petko M, Myung RJ, Wernovsky G, Cohen MI, Rychik J, Nicolson SC, Gaynor JW, Spray TL. Surgical reinterventions following the Fontan procedure. *Eur J Cardiothorac Surg*. 2003;24:255–259.
292. Carey JA, Hamilton JR, Hilton CJ, Dark JH, Forty J, Parry G, Hasan A. Orthotopic cardiac transplantation for the failing Fontan circulation. *Eur J Cardiothorac Surg*. 1998;14:7–13.
293. Gossett JG, Almond CS, Kirk R, Zangwill S, Richmond ME, Kantor PF, Tresler MA, Lenderman SM, Naftel DC, Matthews KL, Pahl E. Outcomes of cardiac transplantation in single-ventricle patients with plastic bronchitis: a multicenter study. *J Am Coll Cardiol*. 2013;61:985–986. doi: 10.1016/j.jacc.2012.10.042.
294. Ekman Joelsson BM, Sunnegårdh J, Hanseus K, Berggren H, Jonzon A, Jögi P, Lundell B. The outcome of children born with pulmonary atresia and intact ventricular septum in Sweden from 1980 to 1999. *Scand Cardiovasc J*. 2001;35:192–198.
295. Bull C, Kostelka M, Sorensen K, de Leval M. Outcome measures for the neonatal management of pulmonary atresia with intact ventricular septum. *J Thorac Cardiovasc Surg*. 1994;107:359–366.
296. Ashburn DA, Blackstone EH, Wells WJ, Jonas RA, Pigula FA, Manning PB, Lofland GK, Williams WG, McCrindle BW; Congenital Heart Surgeons Study Members. Determinants of mortality and type of repair in neonates with pulmonary atresia and intact ventricular septum. *J Thorac Cardiovasc Surg*. 2004;127:1000–1007. doi: 10.1016/j.jtcvs.2003.11.057.
297. Guleserian KJ, Armsby LB, Thiagarajan RR, del Nido PJ, Mayer JE Jr. Natural history of pulmonary atresia with intact ventricular septum and right-ventricle-dependent coronary circulation managed by the single-ventricle approach. *Ann Thorac Surg*. 2006;81:2250–2257. doi: 10.1016/j.athoracsur.2005.11.041.
298. Jahangiri M, Zurakowski D, Bichell D, Mayer JE, del Nido PJ, Jonas RA. Improved results with selective management in pulmonary atresia with intact ventricular septum. *J Thorac Cardiovasc Surg*. 1999;118:1046–1055. doi: 10.1016/S0022-5223(99)70100-5.
299. Rychik J, Levy H, Gaynor JW, DeCampli WM, Spray TL. Outcome after operations for pulmonary atresia with intact ventricular septum. *J Thorac Cardiovasc Surg*. 1998;116:924–931. doi: 10.1016/S0022-5223(98)70042-X.
300. Gilljam T, McCrindle BW, Smallhorn JF, Williams WG, Freedom RM. Outcomes of left atrial isomerism over a 28-year period at a single institution. *J Am Coll Cardiol*. 2000;36:908–916.
301. Hashmi A, Abu-Sulaiman R, McCrindle BW, Smallhorn JF, Williams WG, Freedom RM. Management and outcomes of right atrial isomerism: a 26-year experience. *J Am Coll Cardiol*. 1998;31:1120–1126.
302. Larsen RL, Eguchi JH, Mulla NF, Johnston JK, Fitts J, Kuhn MA, Razzouk AJ, Chinnock RE, Bailey LL. Usefulness of cardiac transplantation in children with visceral heterotaxy (asplenic and polysplenic syndromes and single right-sided spleen with levocardia) and comparison of results with cardiac transplantation in children with dilated cardiomyopathy. *Am J Cardiol*. 2002;89:1275–1279.

KEY WORDS: AHA Scientific Statements ■ congenital heart defects ■ Fontan procedure ■ heart failure ■ right ventricle ■ tetralogy of Fallot ■ transposition of the great vessels ■ ventricular remodeling