Am J Physiol Heart Circ Physiol 315: H1779–H1788, 2018.
First published September 21, 2018; doi:10.1152/ajpheart.00336.2018.

REVIEW | *Right Ventricular Physiology in Health and Disease*

Pathophysiology, adaptation, and imaging of the right ventricle in Fontan circulation

Matthew D. Files and Bhawna Arya

Seattle Children's Hospital, Seattle, Washington

Submitted 30 May 2018; accepted in final form 16 September 2018

Files MD, Arya B. Pathophysiology, adaptation and imaging of the right ventricle in Fontan circulation. *Am J Physiol Heart Circ Physiol* 315: H1779–H1788, 2018. First published September 21, 2018; doi:10.1152/ajpheart.00336.2018.—The Fontan procedure, which creates a total cavopulmonary anastomosis and represents the final stage of palliation for hypoplastic left heart syndrome, generates a unique circulation relying on a functionally single right ventricle (RV). The RV pumps blood in series around the systemic and pulmonary circulation, which requires adaptations to the abnormal volume and pressure loads. Here, we provide a complete review of RV adaptations as the RV assumes the role of the systemic ventricle, the progression of RV dysfunction to a distinct pattern of heart failure unique to this disease process, and the assessment and management strategies used to protect and rehabilitate the failing RV of Fontan circulation.

congenital heart disease; diastolic dysfunction; Fontan; hypoplastic left heart syndrome

INTRODUCTION

The fields of pediatric cardiology and congenital heart surgery encounter a heavy burden of pathophysiology of the right ventricle (RV). In no condition is this more clearly demonstrated than the longitudinal observation of the RV in hypoplastic left heart syndrome (HLHS) and other RV-dominant single ventricle defects. With the improved survival through staged surgical palliation, over 60% of children born with this spectrum of defects are expected to survive to adulthood (54), although healthy survival far into adult years is still within question. In this review, we examine the mechanisms that allow the RV to adapt to the role of the systemic pumping chamber, the physiological burden placed on the RV through staged palliation to Fontan circulation, methods to assess the RV, and medical therapy for the RV in this disease state. Additionally, we will review how the unique circulatory demands of Fontan circulation predispose patients to a pattern of heart failure distinct from typical congestive heart failure.

ANATOMY

In the spectrum of congenital malformations with a RV-dominant single ventricle defect, HLHS is by far the most prevalent. In the most commonly encountered form, the mitral and aortic valves are atretic and the left ventricular (LV) cavity is diminutive or nonexistent (Fig. 1*A*). In the fetal circulation, the RV provides all of the cardiac output through the pulmonary valve and ductus arteriosus, with the cerebral and coronary circulations perfused through retrograde aortic flow. There is compensatory RV dilation as it supplies all of the cardiac output, as opposed to 55–60% of the cardiac output in the typical fetal circulation. RV ejection fraction (EF) is increased, but total cardiac output is decreased relative to the cardiac output from the combined RV/LV in the normal fetal circulation (72). At birth, this circulation is dependent on patency of the arterial duct and shock ensues if the patency of the arterial duct closes. Additionally, the pulmonary vascular resistance falls dramatically in the first hours and days after birth. A pattern of excessive pulmonary blood flow at the expense of systemic perfusion develops in this precarious circulation, with a need for early neonatal intervention.

There are multiple other anatomic variations of RV-dominant single ventricle defects, each with prevalence lower than HLHS. An important distinction is the presence or absence of obstruction to the systemic outflow tract, which determines the first neonatal operation.

STAGED PALLIATION

Until the early 1980s, comfort care or cardiac transplant were the only options for management of HLHS, with the latter being unsuitable given the large discrepancy in the incidence of HLHS and the availability of neonatal heart donors. With the advent of the Norwood procedure (Fig. 1*B*) at Boston Children's Hospital, survival for these children has climbed, with the majority now expected to survive to adulthood (21, 55). The Norwood procedure remains a technically challenging neonatal operation; the goal is to repurpose the RV to pump to the systemic and pulmonary circulations in parallel. This is accomplished by directing the pulmonary valve to the systemic

Address for reprint requests and other correspondence: M. D. Files, Seattle Children's Hospital, 4800 Sand Point Ave. NE, Seattle, WA 98115 (e-mail: matthew.files@seattlechildrens.org).

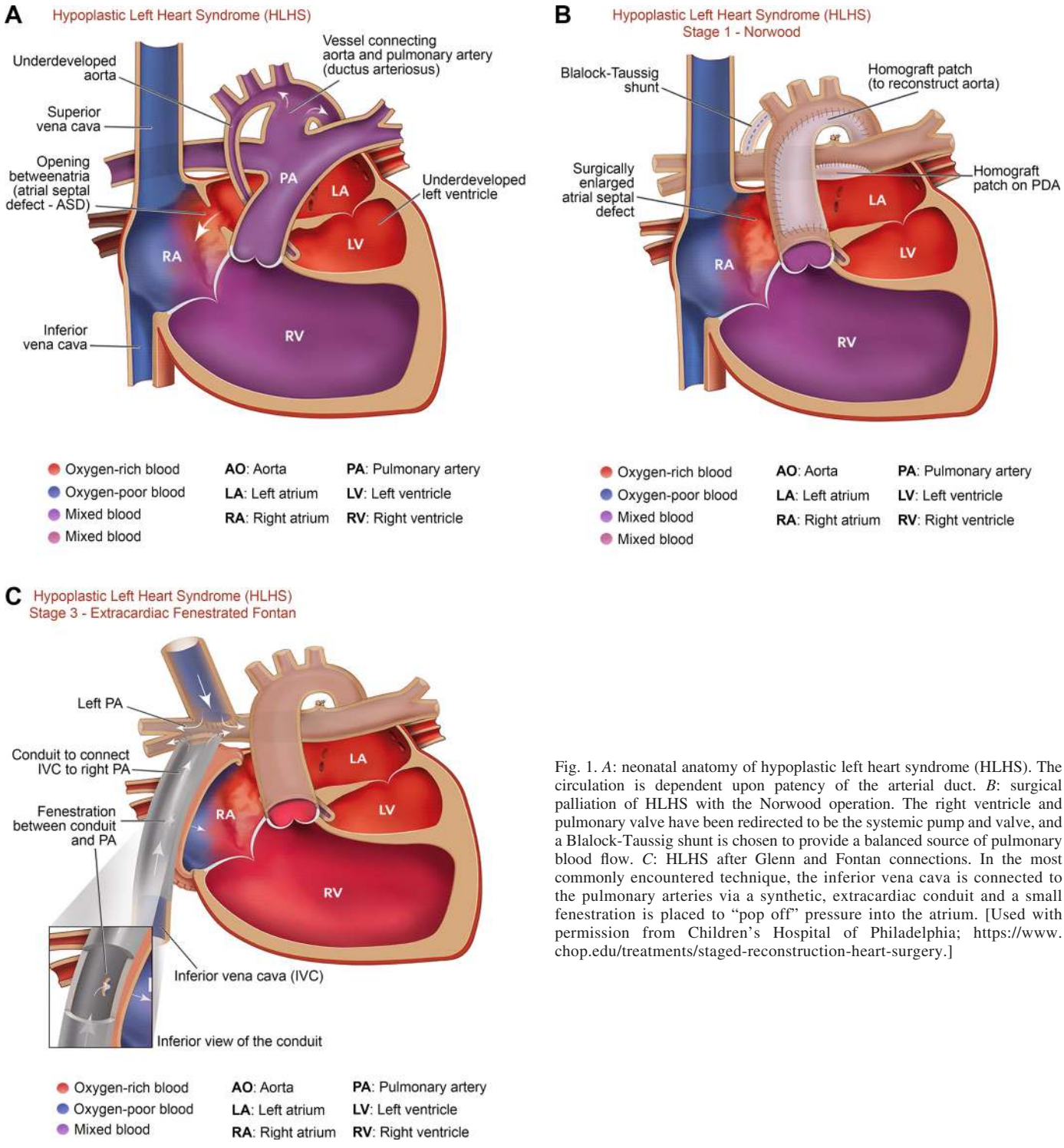

Fig. 1. *A*: neonatal anatomy of hypoplastic left heart syndrome (HLHS). The circulation is dependent upon patency of the arterial duct. *B*: surgical palliation of HLHS with the Norwood operation. The right ventricle and pulmonary valve have been redirected to be the systemic pump and valve, and a Blalock-Taussig shunt is chosen to provide a balanced source of pulmonary blood flow. *C*: HLHS after Glenn and Fontan connections. In the most commonly encountered technique, the inferior vena cava is connected to the pulmonary arteries via a synthetic, extracardiac conduit and a small fenestration is placed to "pop off" pressure into the atrium. [Used with permission from Children's Hospital of Philadelphia; https://www.chop.edu/treatments/staged-reconstruction-heart-surgery.]

outlet in a complex aortic arch reconstruction while providing a separate source of pulmonary blood flow (either a direct RV-pulmonary artery connection or an aortopulmonary shunt). Additionally, the coronary circulation must be placed in line with the neo-aorta to ensure adequate perfusion. Figure 2*B* shows the contrast of this univentricular circulation with normal biventricular circulation (Fig. 2*A*).

Although beyond the scope of this review, other RV-dominant single ventricle defects may require a different first stage palliation that does not require aortic arch reconstruction. In these cases, complications and outcomes are favorable relative to the Norwood operation.

The goals of the second and third stages of palliation are to sequentially reroute systemic venous blood directly into the pulmonary circulation, bypassing the heart. Around 3–6 mo of age, the superior cavopulmonary anastomosis or bidirectional Glenn operation connects the superior vena cava to the pulmonary artery and eliminates the source of pulmonary blood flow

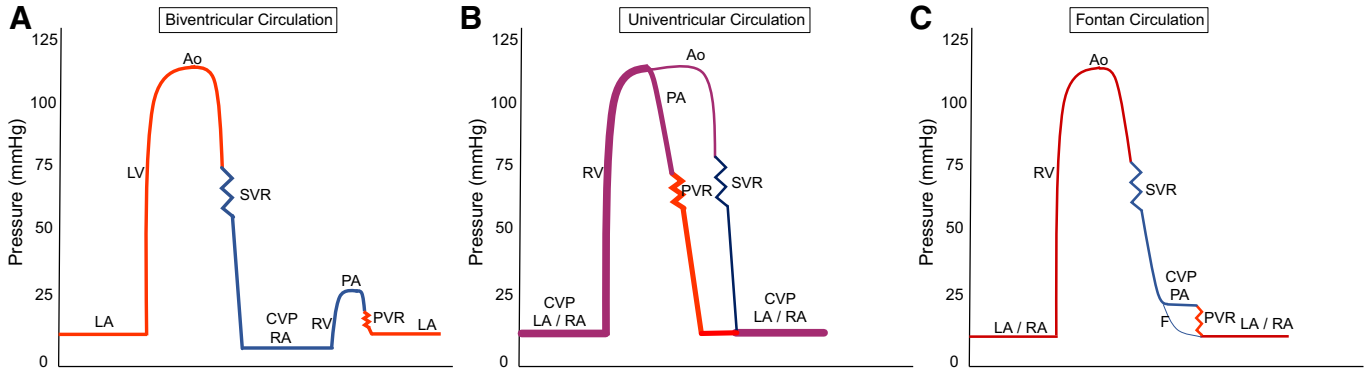

Fig. 2. Schematic highlighting the key features of a biventricular circulation (*A*), univentricular circulation (*B*), and Fontan circulation (*C*). In biventricular circulation, the ventricles pump to the systemic and pulmonary circulation in series. Note the low pressure (3–5 mmHg) that represents the central venous pressure of blood returning to the right atrium. In univentricular circulation, such as preoperative hypoplastic left heart syndrome as well as after the Norwood procedure, the single ventricle pumps to the aorta and pulmonary arteries in series. Typically there is excess pulmonary blood flow, and the right ventricle operates at systemic pressures and high volume load from the venous return from the pulmonary and systemic circulations. In the Fontan circulation, the single ventricle pumps to the systemic and pulmonary circulations in series, without a subpulmonary pump. One key feature is a striking increase in the central venous pressure. LA, left atrium; RA, right atrium; RV, right ventricle; Ao, aorta; PA, pulmonary artery; PVR, pulmonary vascular resistance; SVR, systemic vascular resistance; CVP, central venous pressure; F, Fontan.

from the stage 1 palliation. After this procedure, oxygen saturations are typically 80–85% due to continued mixing of pulmonary and systemic venous blood within the heart. Progressive cyanosis and exercise intolerance gradually develop in the subsequent years, due to developmental changes in cardiac output between the upper and lower body. These changes guide the timing of the final stage of palliation. In the Fontan operation, or total cavopulmonary anastomosis, the blood from the lower body is rerouted directly into the pulmonary circulation (Fig. 1*C*). The RV pumps oxygenated blood to the systemic circulation and then to the pulmonary circulation in series before the blood returns back to the heart (Fig. 2*C*). After Fontan completion, all of the systemic venous return enters the pulmonary circulation passively, without a pump, and oxygen saturations are typically mid-90s. Some right to left shunting still occurs at a surgically placed fenestration or small veno-venous collaterals.

HISTOLOGICAL AND MOLECULAR ADAPTATIONS OF THE SYSTEMIC RV

The RV myocardium has distinct embryological origins from the second heart field, whereas the LV originates from first heart field progenitors (17). This may partially explain the varied molecular response and histological makeup of the RV relative to the LV when subjected to pressure and volume load and why well-proven medical therapy for LV dysfunction fails to show benefit for RV failure.

The normal RV myocardial architecture has superficial circumferential fibers and deep longitudinal fibers with the majority of force contraction occurring longitudinally from the base to the apex. This is contrasted with the fibers of the LV, which contains obliquely oriented fibers in the superficial layer, which provides a component of twisting and torsion to LV ejection (29, 31). In normal postnatal development, RV hypertrophy regresses as pulmonary pressure declines, and the RV becomes thin walled relative to the LV. The mature RV is able to function well under a wide variety of preload conditions but is very sensitive to acute changes in afterload. Clinical RV failure complicates many disease states with a primary pulmonary insult (24). In contrast, the RV in HLHS remains both pressure and volume loaded, and the normal regression of hypertrophy does not occur.

On a histological and molecular level, it is not well understood how the systemic RV adapts to the chronic hemodynamic conditions of palliated HLHS. Histology studies have been skewed by selecting patients with end-stage heart failure (at the time of cardiac transplant), and, thus, there is a paucity of data about the "well-functioning systemic RV." Additionally, there are no animal models that fully capture the pathophysiology of HLHS, which further limits understanding of RV adaptation. Finally, comparisons to the most clinically and molecularly studied pattern of RV hypertrophy in adults [those with pulmonary artery hypertension (PAH)] are likely not the same adaptive processes as a patient with HLHS whose RV has always functioned at systemic pressures. Indeed, RV hypertrophy and adaptation in PAH very frequently results in systolic dysfunction within years of onset, yet the majority of teens and adults with HLHS have normal RV systolic function (5, 75). While the hypertrophied RV in PAH frequently shows an inadequate microvascular density and subsequent ischemia, ischemia is uncommon in HLHS (7, 77). On a microscopic and molecular level, there are differences between adaptive and maladaptive RV hypertrophy currently being explored, but the clinical distinction between adaptive and pathological processes is often difficult to discern (66).

Microscopic fibrosis may be found in the hearts of HLHS, which theoretically may be related to the wall stress during early volume loading and/or mismatch between myocardial oxygen supply and demand, and further contribute to systolic and diastolic performance (63, 65). Additionally, myocardial fiber disarray is occasionally found in the RV myocardium of HLHS, although this is not a consistent finding (10).

Similar to other forms of heart failure, immunohistochemical analyses of RV myocytes in HLHS reveals a pattern of preserved fetal gene expression (10). MicroRNA (miRNA) profiles of patients with HLHS with significant heart failure show a pattern that is not found in other forms of pediatric or adult heart failure. Furthermore, miRNA profiles can change

between the stages of palliation (71). Some of these unique miRNA profiles correlate with those found in a RV pressure-overload model. This suggests that some miRNA signaling pathways appear responsive to pressure, whereas others are sensitive to volume load. Further study is needed to identify the miRNA targets in the pathophysiology of this disease and to classify the molecular mechanisms that allow some RVs to serve as the systemic pumping chamber for decades while others fail.

While they do not fully characterize the physiology of HLHS, animal data of pressure and volume loading show a unique difference between the RV and LV. For example, the pressure-loaded RV upregulates the Wnt pathway, whereas the pressure-loaded LV downregulates the same pathway (74). Additionally pressure loading the RV upregulates multiple apoptosis pathways that are not upregulated with LV loading. The downstream effects of these pathways may explain why the RV is predisposed to maladaptive responses to pressure loading. The RV also differs in the metabolic response to acute pressure loading with inadequate adjustment of substrate utilization to balance the increased mitochondrial demand (35). Potential pharmacological manipulation of metabolic pathways may overcome this inadequate metabolic response. Additionally, the RV appears more sensitive than the LV to developing fibrosis and collagen deposition with volume loading (24, 51), which may explain the increased diastolic dysfunction seen in RV-dominant Fontan patients. Hopefully these newly explored molecular and metabolic differences between the RV and LV will lead to new therapeutic strategies for the pressure and volume loaded RV.

PHYSIOLOGICAL ADAPTIONS OF THE SINGLE RV DURING STAGED PALLIATION

After stage 1 palliation, the RV pumps to the systemic and pulmonary circulations in parallel (Fig. 2*B*), and small changes in the resistance to these circuits can drastically change the ratio of pulmonary and systemic blood flow. This fragile balance between the circulations partially explains the ongoing risk of mortality during Norwood hospitalization (~20–30%) (21, 56) and between hospital discharge and stage 2 palliation (~6–15%) (4, 68). The pressure and volume loaded state of the RV leads to progressive dilation over time (9, 40, 56). Frequently, RV dilation promotes significant geometric distortion of the RV, which can increase tricuspid regurgitation and promote a globular shape and dyssynchony (40). These maladaptive changes experienced by the RV during this high pressure, volume, and afterload state have led to the current strategy of an early second stage palliation.

"Unloading" the ventricle by removing the venous return from the upper body during the bidirectional Glenn operation reduces the RV volume and subsequent wall stress and afterload and prevents further deterioration in RV EF and in some cases increases RV EF (9, 53, 56). While conceptually attractive, the results of volume unloading have shown less promising for preserving or improving tricuspid regurgitation (37). There are still variable opinions regarding the optimal timing, but most centers perform the bidirectional Glenn operation between 3 and 6 mo, and the risk of postsurgical and interstage mortality declines relative to Norwood circulation (50).

The third stage, the Fontan operation, further reduces the preload to the ventricle. The systemic, systemic venous, and pulmonary circulations are now placed back in series, albeit without a subpulmonary pump (Figs. 1*C* and 2*C*). With sequential removal of the systemic venous inflow into the ventricle, there is a significant loss of preload relative to the initial Norwood circulation, and the ventricle exhibits a high ventricular mass-to-volume ratio, which can contribute to diastolic dysfunction (5, 67). To minimize the effect of this preload starved condition, surgeons now routinely place a small fenestration between the cavopulmonary anastomosis and the atrium to allow a small volume of residual right to left shunting.

A significant majority (81%) of RV-dominant Fontan patients demonstrate diastolic dysfunction (5), which may be a combination of a preload starved ventricle (clinically evident as an elevated mass-to-volume ratio), macro- and microscarring and fibrosis, and dyssynchronous relaxation (58, 61). Diastolic dysfunction has multiple effects (47). The clearest is an elevation in the end-diastolic pressure transmitted backward through the pulmonary circulation, which further raises central venous pressure. Additionally, diastolic relaxation is important in "pulling" blood through the pulmonary circuit and thus diastolic dysfunction and dyssynchony exacerbate the preload starved state of the ventricle. Finally, the interactions among the system vascular resistance, endothelial function (28), skeletal muscle function (14, 34), and venous capacitance (44) all have important considerations and possible modifications to Fontan circulation efficiency but remain poorly understood at this point.

LONGITUDINAL OBSERVATION OF FONTAN

Understanding palliation for HLHS into adulthood is limited given the relatively few patients who underwent the Norwood operation in the 1980s and 1990s. Patients with HLHS are just beginning to enter adulthood in large numbers. While the immediate surgical and medium-term (10 yr) outcomes after Fontan have steadily increased (26, 64), these patients remain at risk for a host of other cardiac and extracardiac problems. The RV often maintains normal systolic function; thus, RV systolic function is generally a poor predictor of Fontan-associated complications (5, 18). The RV mass and RV mass-to-volume remain significantly elevated throughout childhood (5, 22), suggesting that this preload starved state is not transient and that progressive RV hypertrophy is presumably ongoing due to high work requirements pumping through both circulations in series. Additionally, patients often have borderline or reduced cardiac output despite normal EF and fail to sufficiently increase cardiac output during exercise (1). The Fontan circulation is characterized by a poorly compliant ventricle, borderline cardiac output, and markedly elevated central venous pressures. It is this combination that explains the constellation of symptoms and pathophysiology referred to as Fontan failure. Important contributors to cardiac performance and morbidity in the long-term evaluation of Fontan circulation include atrioventricular synchrony, sinus node function, tricuspid valve function, and peripheral vascular function but are beyond the scope of this review.

RV AND LV DIFFERENCES IN FONTAN CIRCULATION

A cursory look confirms the speculation that a single LV should perform better than an RV since the LV was "built" to support the systemic circulation. RV-dominant single ventricle defects (the majority of which are HLHS and undergo the Norwood operation) have worse neonatal and early childhood mortality in multiple series relative to the outcomes of LV-dominant single ventricle defects. However, a high burden of this mortality and morbidity is concentrated at the time of the Norwood operation. In a series of over 3,000 Fontan patients, Redington et al. (65) analyzed the evidence for superiority in systolic performance, quality of life, and survival of the LV over the RV after Fontan palliation and found surprisingly little evidence to support that assumption. It is possible that this will change as more patients with HLHS reach adulthood (era effect), as these RV-dominant patients seem to have a higher incidence of diastolic dysfunction, Fontan failure, and worse exercise performance relative to their LV-dominant peers (5, 36). However, current evidence does support a remarkable ability of the RV to adapt to acting as the systemic pump in Fontan circulation.

FONTAN FAILURE

Similar to other forms of congenital heart disease, patients undergoing palliation for single ventricle defects through the Fontan operation are at risk for arrhythmias, ventricular dysfunction, valvar insufficiency, and embolus. A feature that is unique for Fontan patients is loosely categorized as "Fontan failure," which is a combination of diverse and multifactorial extra-cardiac manifestations of living with this chronic circulation. Diastolic dysfunction may be particularly deleterious in Fontan circulation, as elevation of RV diastolic pressure is transmitted to the atria and pulmonary veins, which further increases pulmonary and central venous pressures. Figure 2*C* shows the drastic increase in central venous pressure, which is in the low teens in healthy Fontan patients and can be significantly higher in those with diastolic dysfunction or elevated pulmonary resistance. The elevated central venous pressure leads to markedly increased lymphatic pressure and the combination leads to circulatory insufficiency. This explains many of the hallmark features of a failing Fontan circulation, including chronic pleural effusions, hepatic dysfunction, plastic bronchitis, and protein losing enteropathy. Each of these entities is rare in isolation, but collectively common, with freedom from Fontan failure declining as patients reach adulthood and beyond (5, 18, 60, 69). While treatment of some of these form of Fontan failure have improved (specific therapies for plastic bronchitis and protein losing enteropathy), the development of Fontan failure continues to carry a poor prognosis.

ASSESSMENT OF THE RV

Impaired RV function is associated with poor outcomes in HLHS (2), and the early detection of cardiac dysfunction is important for future management and prognosis. However, functional assessment of the RV-dominant single ventricle is challenging. The geometry and myocardial architecture of the RV are vastly different than the ellipsoid LV. The RV contracts in a longitudinal direction with a contractile wave moving sequentially from the tricuspid inflow into the RV body and finally through the infundibulum and outflow, ejecting the blood into the great artery, whereas the LV contraction is more circumferential with limited impact of longitudinal shortening (49). Thus, quantitative assessment of the LV cannot be extrapolated to evaluate the systemic RV of HLHS.

ECHOCARDIOGRAPHIC ASSESSMENT

Qualitative echocardiographic RV functional assessment, especially in complex congenital heart disease like HLHS, often results in misclassification of the RV dysfunction but continues to be used universally (8). Quantitative echocardiographic evaluation of the RV systolic and diastolic function is limited; however, some parameters are reasonable substitutes for the gold standard cardiac magnetic resonance imaging (CMR)-derived RV EF and catheterization-derived RV filling pressures, respectively. These can be used in the assessment of the systemic RV.

There are several echocardiographic measures for quantification of systolic RV function. Two-dimensional echocardiographic RV fractional area change is a reasonable substitute for RV EF. The area change between end systole and end diastole is measured from the RV-centric apical four-chamber view, with a RV fractional area change of $>35\%$ considered normal in adults (3). Tricuspid annular plane systolic excursion is an M-mode assessment for measuring lateral tricuspid annulus systolic longitudinal displacement from end diastole to end systole and is a parameter for evaluating RV longitudinal function. This is performed in an apical four-chamber view with an M-mode capturing RV free wall motion. It correlates well with RV EF when dysfunction is global; however, correlation is lower if there are RV regional wall motion abnormalities. Tricuspid annular plane systolic excursion is also influenced by tricuspid insufficiency and becomes less reliable as tricuspid valve function is impaired (42). Geometry-independent measures, such as RV myocardial performance index and RV contractility (dP/dt), can be used to overcome RV imaging difficulties (16).

Advanced echocardiographic technologies are promising for systolic RV functional assessment. The superior echocardiographic method for measuring RV EF is from three-dimensional echocardiographic end-systolic and end-diastolic volumes (41). Strain and strain rate are methods for measuring regional and global myocardial deformation or geometric and dimensional changes in the cardiac muscle. In the systemic RV, it can be measured from the apical four-chamber view using speckle-tracking echocardiography along the RV basal, mid, and apical free wall segments during end systole. Two- and three-chamber views can be used to obtain RV inferior and posterior wall longitudinal strain. Normal global strain values apply to the LV deformation in a two-ventricular heart and cannot be extrapolated to the systemic RV. In a strain study of postoperative patients with HLHS, adequate RV remodeling involved transition of RV mechanics from a predominantly longitudinal to a more circumferential contraction pattern (39, 59). More recently, three-dimensional strain methods have been proposed for simultaneous evaluation of RV volumes, RV EF, and mechanics (6). Further standardization and optimization of RV strain measurements in HLHS are necessary, but in

time they can be expected to become part of routine RV functional assessment.

In the majority of Fontan patients, systolic function is preserved or even hyperdynamic until late after the Fontan procedure (12) while abnormal early ventricular relaxation is present in up to 75% of Fontan patients (47, 58). Acute volume unloading associated with the Fontan procedure is associated with predictable changes in ventricular geometry and wall thickness; the sudden decrease in RV preload results in increased ventricular wall thickness that does not normalize over time. This leads to acute increase in the time constant of isovolumic relaxation (τ) secondary to elevated atrial and ventricular end-diastolic pressure and a reduction in early rapid filling [measured by transtricuspid Doppler flow (*E*)]. There is incoordinate ventricular wall segment motion with reciprocal outward motion of other segments during isovolumic relaxation. In the systemic RV in Fontan circulation, two-dimensional echocardiographic Doppler of the transtricuspid early filling velocity (*E*) and tissue Doppler early peak velocity of the tricuspid annulus (E') are decreased, whereas E/E' and isovolumic relaxation time are increased with decreased ventricular compliance (5, 13, 45, 47).

There are no established normal values in children or in patients with single ventricular physiology for the majority of systolic and diastolic echocardiographic measures. The values obtained are most useful in tracking changes in RV function within an individual patient longitudinally. When RV dysfunction is suspected by echocardiographic methods, advanced imaging or interventional modalities should be pursued to better quantify the dysfunction.

Evaluation of the tricuspid valve morphology and function is critical to understanding RV function. After Norwood palliation, the systemic RV must generate output more than two times higher than a normally developed heart (30). This results in myocardial hypertrophy, ventricular dilatation, and an interventricular septal shift leftward, which, in turn, causes tricuspid annular dilatation, papillary muscle displacement, and tricuspid valve leaflet tethering. Tricuspid valve dysfunction is often the result of RV deformation after Norwood palliation for HLHS. If it worsens without surgical correction, it is also a common cause for progressive RV dysfunction due to increased preload and dilation and reduction in cardiac output, which may influence coronary supply-demand mismatch (20, 73). The tricuspid valve tissue thickness, mobility, prolapse, and annular dimensions are observed by standard two-dimensional echocardiographic imaging. Severity of regurgitation is assessed using Doppler techniques (45).

CMR Imaging

CMR provides accurate assessment of RV geometry, function, and myocardial structure, making it the reference standard for quantification of RV volume, EF, and mass (46, 52). Where two-dimensional echocardiography underestimates RV volume by nearly 30% (45), CMR accounts for the unique geometry of the RV providing a more complete assessment (15). CMR postprocessing of RV volume calculates end-diastolic and end-systolic volumes using the sum of manually traced slices with measures to account for the gaps between slices. In HLHS, especially in the long-term followup of patients after Fontan, CMR provides objective and reproducible RV measures in the heterogeneous systemic RV (9). An elevated CMR-derived end-diastolic volume is independently associated with death and transplant (62). CMR indexes also play an important role in evaluation of medication efficacy for RV failure in this population (62, 76). RV myocardial strain can be evaluated by CMR, and the results are promising in subgroups of congenital heart disease such as tetralogy of Fallot; however, only preliminary data is available in the Fontan systemic RV. CMR is proving superior to catheterization for cardiac output and relative flow evaluation in single ventricle physiology, which is subject to multiple sources of pulmonary blood flow.

Myocardial delayed enhancement is a CMR technique for the identification of myocardial fibrosis and infarction. Late gadolinium enhancement correlates with the presence and extent of myocardial fibrosis in histological studies (38), and it is present in 28% of Fontan patients. An increase in late gadolinium enhancement is associated with lower EF, increased end-diastolic volume and increased mass (63). CMR usually requires general anesthesia or sedation in younger children and requires a high level of cardiac imaging expertise. It is also expensive, not portable, and not compatible with many pace-making systems, making its utility limited compared with echocardiography. In situations where CMR is contraindicated or unsuccessful, cardiac computed tomography imaging could provide the information required for decision making.

Still, CMR has quickly become the gold standard for noninvasive evaluation when concerns arise regarding anatomic or functional complications in Fontan patients. It provides important predictive data for adverse clinical outcomes and can directly aid in surgical planning.

Cardiac Catheterization

Cardiac catheter-derived hemodynamic evaluation and cineangiography remain the gold standard practice in the lifelong management of patients with single ventricles (70). RV end-diastolic pressure provides important information about diastolic function. An elevated end-diastolic pressure is characterized by a stiff RV with decreased compliance and impaired relaxation. Direct transcatheter pressure measurements give insight to RV preload (Fontan circuit mean pressure and transpulmonary gradient) and afterload (aortic arch peak gradient). Additionally, angiograms (Fig. 3) provide excellent resolution of pulmonary artery, cavopulmonary connections, and aortic reconstruction, which instruct transcatheter versus surgical interventions to improve RV function and Fontan circulation.

Stress Hemodynamics

Finally, stress hemodynamics have recently been studies in the Fontan population using dobutamine stress CMR techniques (61). Preliminary data demonstrated a slower increase in cardiac index compared with normal with initiation of dobutamine. At high doses of dobutamine, cardiac index continued to rise in the normal heart but not in Fontan patients. This blunted rise in cardiac index was directly related to a fall in end-diastolic volume during stress, suggesting that limited preload contributes to exercise intolerance.

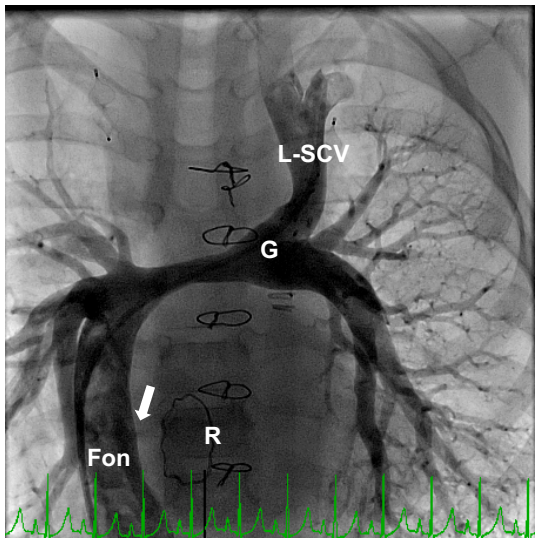

Fig. 3. Angiogram of a patient with hypoplastic left heart syndrome with a left superior vena cava (L-SVC). Contrast is injected into the L-SVC and fills both branch pulmonary arteries as well as refluxes down the Fontan pathway (Fon), with a small blush of contrast filling the atrium showing the fenestration (white arrow). There is hypoplasia of the central pulmonary arteries, which were successfully treated with stenting during this procedure. Also seen is a tricuspid annuloplasty ring (R), which improved significant tricuspid regurgitation at the time of the Fontan operation.

MEDICAL THERAPY

What medical therapies are available to help the RV adapt to the unique physiological conditions placed by staged palliation in Fontan circulation? Unfortunately, standard heart failure therapies are not clearly beneficial, as the ventricular pump function is frequently not the underlying abnormality. Additionally, there is a paucity of well-studied medical therapy for this disease. A significant majority of patients with HLHS are treated with angiotensin-converting enzymes (ACE) inhibitors (78), likely secondary to the high levels of evidence showing benefit for other forms of heart failure. It is theoretically attractive to lower the systemic vascular resistance that the systemic RV has to pump against. Despite lack of evidence proving a benefit of ACE inhibitors in surgical outcomes (23), exercise capacity (43), ventricular remodeling, and heart failure classification (33), this practice is still widespread. Expert consensus recommends ACE inhibitors for a systemic RV with systolic dysfunction (32) but not routinely for all Fontan patients.

Two large retrospective studies of patients with HLHS have recently shown an impressive reduction in mortality between the first and second staged operations for patients treated with digoxin (11, 57). This association was found after removal of patients with arrhythmias and adjustment for multiple confounders. However, given the retrospective nature of these studies, understanding the mechanism for benefit is not possible. Proposed mechanisms include treating occult arrhythmias, an increase in the vagal tone, or mild inotropic improvement in systolic function. In the brief time since these publications, this practice has become widespread, which may preclude having equipoise for a prospective, randomized investigation into the mechanism and to effectively prove causality. It is unclear if digoxin has a clinical benefit outside of this narrow timeframe for patients with HLHS.

While not focused on improving RV function, it is theoretically attractive to specifically target pulmonary vascular resistance as a mechanism to improve Fontan circulation. Indeed, pulmonary vascular resistance serves as a bottleneck in Fontan circulation, particularly during times of increased metabolic demand or exercise (25). The lack of a subpulmonary pump prevents the significant increase of flow through the pulmonary circulation and medications to lower pulmonary vascular resistance may improve the abnormal exercise response seen in Fontan patients. Short-term studies of placebo-controlled trials of sildenafil have shown improvements in echocardiographic measures and exercise performance in Fontan patients (27). Currently, the Pediatric Heart Network is conducting a randomized controlled trial of longer-term use of a novel phosphodiesterase-5 inhibitor, udenafil, in 400 Fontan patients, with results expected in 2019.

There are emerging therapies for some of the noncardiac manifestations of Fontan failure; however, we continue to have few therapies that have been shown to be beneficial for treating a systemic RV and no specific medications that have been shown to reverse diastolic dysfunction for this group of patients.

While beyond the scope of this review, aggressive surgical and catheter-based intervention is essential in preserving myocardial function and optimizing the circulation. Attention to features that promote ventricular dilation (tricuspid regurgitation, high aortopulmonary collateral burden) and increase afterload (recurrent coarctation, pulmonary artery hypoplasia) is part of the lifelong surveillance required for these patients.

SUMMARY

The adaptations of the systemic RV in Fontan circulation create a unique quandary for the management and survival of these patients for their lifetime. As we gain an improved understanding of RV mechanics, molecular pathways, and metabolic response to pressure and volume loading, we also improve our diagnostic capabilities. Efforts must now be focused on medical and surgical therapies targeted at modifying the early incoordinate RV relaxation and hindering the late progression of myocardial stiffness in this subgroup.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

M.F. and B.A. conceived and designed research; M.F. prepared figures; M.F. and B.A. drafted manuscript; M.F. and B.A. edited and revised manuscript; M.F. and B.A. approved final version of manuscript.

REFERENCES

1. **Ait Ali L, Cadoni A, Rossi G, Keilberg P, Passino C, Festa P.** Effective cardiac index and systemic-pulmonary collaterals evaluated by cardiac magnetic resonance late after Fontan palliation. *Am J Cardiol* 119: 2069–2072, 2017. doi:10.1016/j.amjcard.2017.03.040.
2. **Altmann K, Printz BF, Solowiejczyk DE, Gersony WM, Quaegebeur J, Apfel HD.** Two-dimensional echocardiographic assessment of right ventricular function as a predictor of outcome in hypoplastic left heart syndrome. *Am J Cardiol* 86: 964–968, 2000. doi:10.1016/S0002-9149(00)01131-0.
3. **Anavekar NS, Gerson D, Skali H, Kwong RY, Yucel EK, Solomon SD.** Two-dimensional assessment of right ventricular function: an echocardiographic-MRI correlative study. *Echocardiography* 24: 452–456, 2007. doi:10.1111/j.1540-8175.2007.00424.x.

4. **Anderson JB, Beekman RH 3rd, Kugler JD, Rosenthal GL, Jenkins KJ, Klitzner TS, Martin GR, Neish SR, Brown DW, Mangeot C, King E, Peterson LE, Provost L, Lannon C; National Pediatric Cardiology Quality Improvement Collaborative.** Improvement in interstage survival in a National Pediatric Cardiology Learning Network. *Circ Cardiovasc Qual Outcomes* 8: 428–436, 2015. doi:10.1161/CIRCOUTCOMES.115.001956.
5. **Anderson PA, Sleeper LA, Mahony L, Colan SD, Atz AM, Breitbart RE, Gersony WM, Gallagher D, Geva T, Margossian R, McCrindle BW, Paridon S, Schwartz M, Stylianou M, Williams RV, Clark BJ 3rd; Pediatric Heart Network Investigators.** Contemporary outcomes after the Fontan procedure: a Pediatric Heart Network multicenter study. *J Am Coll Cardiol* 52: 85–98, 2008. doi:10.1016/j.jacc.2008.01.074.
6. **Atsumi A, Seo Y, Ishizu T, Nakamura A, Enomoto Y, Harimura Y, Okazaki T, Abe Y, Aonuma K.** Right ventricular deformation analyses using a three-dimensional speckle-tracking echocardiographic system specialized for the right ventricle. *J Am Soc Echocardiogr* 29: 402–411.e2, 2016. doi:10.1016/j.echo.2015.12.014.
7. **Baffa JM, Chen SL, Guttenberg ME, Norwood WI, Weinberg PM.** Coronary artery abnormalities and right ventricular histology in hypoplastic left heart syndrome. *J Am Coll Cardiol* 20: 350–358, 1992. doi:10.1016/0735-1097(92)90101-R.
8. **Bellsham-Revell HR, Simpson JM, Miller OI, Bell AJ.** Subjective evaluation of right ventricular systolic function in hypoplastic left heart syndrome: how accurate is it? *J Am Soc Echocardiogr* 26: 52–56, 2013. doi:10.1016/j.echo.2012.09.020.
9. **Bellsham-Revell HR, Tibby SM, Bell AJ, Witter T, Simpson J, Beerbaum P, Anderson D, Austin CB, Greil GF, Razavi R.** Serial magnetic resonance imaging in hypoplastic left heart syndrome gives valuable insight into ventricular and vascular adaptation. *J Am Coll Cardiol* 61: 561–570, 2013. doi:10.1016/j.jacc.2012.11.016.
10. **Bohlmeyer TJ, Helmke S, Ge S, Lynch J, Brodsky G, Sederberg JH 2nd, Robertson AD, Minobe W, Bristow MR, Perryman MB.** Hypoplastic left heart syndrome myocytes are differentiated but possess a unique phenotype. *Cardiovasc Pathol* 12: 23–31, 2003. doi:10.1016/S1054-8807(02)00127-8.
11. **Brown DW, Mangeot C, Anderson JB, Peterson LE, King EC, Lihn SL, Neish SR, Fleishman C, Phelps C, Hanke S, Beekman RH 3rd, Lannon CM; National Pediatric Cardiology Quality Improvement Collaborative.** Digoxin use is associated with reduced interstage mortality in patients with no history of arrhythmia after stage i palliation for single ventricle heart disease. *J Am Heart Assoc* 5: 5, 2016. doi:10.1161/JAHA.115.002376.
12. **Cheung MM, Smallhorn JF, McCrindle BW, Van Arsdell GS, Redington AN.** Non-invasive assessment of ventricular force-frequency relations in the univentricular circulation by tissue Doppler echocardiography: a novel method of assessing myocardial performance in congenital heart disease. *Heart* 91: 1338–1342, 2005. doi:10.1136/hrt.2004.048207.
13. **Cheung YF, Penny DJ, Redington AN.** Serial assessment of left ventricular diastolic function after Fontan procedure. *Heart* 83: 420–424, 2000. doi:10.1136/heart.83.4.420.
14. **Cordina R, O'Meagher S, Gould H, Rae C, Kemp G, Pasco JA, Celermajer DS, Singh N.** Skeletal muscle abnormalities and exercise capacity in adults with a Fontan circulation. [Erratum in *Heart* 99: 1788, 2013.] *Heart* 99: 1530–1534, 2013. doi:10.1136/heartjnl-2013-304249.
15. **Crean AM, Maredia N, Ballard G, Menezes R, Wharton G, Forster J, Greenwood JP, Thomson JD.** 3D Echo systematically underestimates right ventricular volumes compared to cardiovascular magnetic resonance in adult congenital heart disease patients with moderate or severe RV dilatation. *J Cardiovasc Magn Reson* 13: 78, 2011. doi:10.1186/1532-429X-13-78.
16. **Dallaire F, Slorach C, Hui W, Sarkola T, Friedberg MK, Bradley TJ, Jaeggi E, Dragulescu A, Har RL, Cherney DZ, Mertens L.** Reference values for pulse wave Doppler and tissue Doppler imaging in pediatric echocardiography. *Circ Cardiovasc Imaging* 8: e002167, 2015. doi:10.1161/CIRCIMAGING.114.002167.
17. **Delgado-Olguin P.** Embryological origins: how does the right ventricle form. In: *Right Ventricular Physiology, Adaptation and Failure In Congenital and Acquired Heart Disease*, edited by Redington AN. New York: Springer, 2017, p. 1–17.
18. **Elder RW, McCabe NM, Veledar E, Kogon BE, Jokhadar M, Rodriguez FH 3rd, McConnell ME, Book WM.** Risk factors for major adverse events late after Fontan palliation. *Congenit Heart Dis* 10: 159–168, 2015. doi:10.1111/chd.12212.
20. **Elmi M, Hickey EJ, Williams WG, Van Arsdell G, Caldarone CA, McCrindle BW.** Long-term tricuspid valve function after Norwood operation. *J Thorac Cardiovasc Surg* 142: 1341–1347.e4, 2011. doi:10.1016/j.jtcvs.2010.11.065.
21. **Feinstein JA, Benson DW, Dubin AM, Cohen MS, Maxey DM, Mahle WT, Pahl E, Villafañe J, Bhatt AB, Peng LF, Johnson BA, Marsden AL, Daniels CJ, Rudd NA, Caldarone CA, Mussatto KA, Morales DL, Ivy DD, Gaynor JW, Tweddell JS, Deal BJ, Furck AK, Rosenthal GL, Ohye RG, Ghanayem NS, Cheatham JP, Tworetzky W, Martin GR.** Hypoplastic left heart syndrome: current considerations and expectations. *J Am Coll Cardiol* 59, *Suppl*: S1–S42, 2012. doi:10.1016/j.jacc.2011.09.022.
22. **Fogel MA, Weinberg PM, Chin AJ, Fellows KE, Hoffman EA.** Late ventricular geometry and performance changes of functional single ventricle throughout staged Fontan reconstruction assessed by magnetic resonance imaging. *J Am Coll Cardiol* 28: 212–221, 1996. doi:10.1016/0735-1097(96)00111-8.
23. **François K, Bové T, De Groote K, Panzer J, Vandekerckhove K, Suys B, De Wolf D, Van Nooten G.** Pleural effusions, water balance mediators and the influence of lisinopril after completion Fontan procedures. *Eur J Cardiothorac Surg* 36: 57–62, 2009. doi:10.1016/j.ejcts.2009.02.059.
24. **Friedberg MK, Redington AN.** Right versus left ventricular failure: differences, similarities, and interactions. *Circulation* 129: 1033–1044, 2014. doi:10.1161/CIRCULATIONAHA.113.001375.
25. **Gewillig M, Brown SC, Eyskens B, Heying R, Ganame J, Budts W, La Gerche A, Gorenflo M.** The Fontan circulation: who controls cardiac output? *Interact Cardiovasc Thorac Surg* 10: 428–433, 2010. doi:10.1510/icvts.2009.218594.
26. **Giannico S, Hammad F, Amodeo A, Michielon G, Drago F, Turchetta A, Di Donato R, Sanders SP.** Clinical outcome of 193 extracardiac Fontan patients: the first 15 years. *J Am Coll Cardiol* 47: 2065–2073, 2006. doi:10.1016/j.jacc.2005.12.065.
27. **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* 123: 1185–1193, 2011. doi:10.1161/CIRCULATIONAHA.110.981746.
28. **Goldstein BH, Urbina EM, Khoury PR, Gao Z, Amos MA, Mays WA, Redington AN, Marino BS.** Endothelial function and arterial stiffness relate to functional outcomes in adolescent and young adult fontan survivors. *J Am Heart Assoc* 5: 5, 2016. doi:10.1161/JAHA.116.004258.
29. **Haddad F, Hunt SA, Rosenthal DN, Murphy DJ.** Right ventricular function in cardiovascular disease, part I: Anatomy, physiology, aging, and functional assessment of the right ventricle. *Circulation* 117: 1436–1448, 2008. doi:10.1161/CIRCULATIONAHA.107.653576.
30. **Hijazi ZM, Fahey JT, Kleinman CS, Kopf GS, Hellenbrand WE.** Hemodynamic evaluation before and after closure of fenestrated Fontan. An acute study of changes in oxygen delivery. *Circulation* 86: 196–202, 1992. doi:10.1161/01.CIR.86.1.196.
31. **Ho SY, Nihoyannopoulos P.** Anatomy, echocardiography, and normal right ventricular dimensions. *Heart* 92, *Suppl* 1: i2–i13, 2006. doi:10.1136/hrt.2005.077875.
32. **Hsu DT, Pearson GD.** Heart failure in children: part II: diagnosis, treatment, and future directions. *Circ Heart Fail* 2: 490–498, 2009. doi:10.1161/CIRCHEARTFAILURE.109.856229.
33. **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.** Enalapril does not improve growth or ventricular function in infants with single ventricle: a multicenter clinical trial. *Circulation* 120: S560–S561, 2009.
34. **Inai K, Saita Y, Takeda S, Nakazawa M, Kimura H.** Skeletal muscle hemodynamics and endothelial function in patients after Fontan operation. *Am J Cardiol* 93: 792–797, 2004. doi:10.1016/j.amjcard.2003.11.062.
35. **Kajimoto M, Nuri M, Isern NG, Robillard-Frayne I, Des Rosiers C, Portman MA.** Metabolic response of the immature right ventricle to acute pressure overloading. *J Am Heart Assoc* 7: 7, 2018. doi:10.1161/JAHA.118.008570.
36. **Kaneko S, Khoo NS, Smallhorn JF, Tham EB.** Single right ventricles have impaired systolic and diastolic function compared to those of left ventricular morphology. *J Am Soc Echocardiogr* 25: 1222–1230, 2012. doi:10.1016/j.echo.2012.08.005.

37. **Kasnar-Samprec J, Kühn A, Hörer J, Vogt M, Cleuziou J, Lange R, Schreiber C.** Unloading of right ventricle by bidirectional superior cavopulmonary anastomosis in hypoplastic left heart syndrome patients promotes remodeling of systemic right ventricle but does not improve tricuspid regurgitation. *J Thorac Cardiovasc Surg* 144: 1102–1109, 2012. doi:10.1016/j.jtcvs.2012.08.012.
38. **Kehr E, Sono M, Chugh SS, Jerosch-Herold M.** Gadolinium-enhanced magnetic resonance imaging for detection and quantification of fibrosis in human myocardium in vitro. *Int J Cardiovasc Imaging* 24: 61–68, 2008. doi:10.1007/s10554-007-9223-y.
39. **Khoo NS, Smallhorn JF, Kaneko S, Kutty S, Altamirano L, Tham EB.** The assessment of atrial function in single ventricle hearts from birth to Fontan: a speckle-tracking study by using strain and strain rate. *J Am Soc Echocardiogr* 26: 756–764, 2013. doi:10.1016/j.echo.2013.04.005.
40. **Khoo NS, Smallhorn JF, Kaneko S, Myers K, Kutty S, Tham EB.** Novel insights into RV adaptation and function in hypoplastic left heart syndrome between the first 2 stages of surgical palliation. *JACC Cardiovasc Imaging* 4: 128–137, 2011. doi:10.1016/j.jcmg.2010.09.022.
41. **Khoo NS, Young A, Occleshaw C, Cowan B, Zeng ISL, Gentles TL.** Assessments of right ventricular volume and function using three-dimensional echocardiography in older children and adults with congenital heart disease: comparison with cardiac magnetic resonance imaging. *J Am Soc Echocardiogr* 22: 1279–1288, 2009. doi:10.1016/j.echo.2009.08.011.
42. **Koestenberger M, Nagel B, Avian A, Ravekes W, Sorantin E, Cvirn G, Beran E, Halb V, Gamillscheg A.** Systolic right ventricular function in children and young adults with pulmonary artery hypertension secondary to congenital heart disease and tetralogy of Fallot: tricuspid annular plane systolic excursion (TAPSE) and magnetic resonance imaging data. *Congenit Heart Dis* 7: 250–258, 2012. doi:10.1111/j.1747-0803.2012.00655.x.
43. **Kouatli AA, Garcia JA, Zellers TM, Weinstein EM, Mahony L.** Enalapril does not enhance exercise capacity in patients after Fontan procedure. *Circulation* 96: 1507–1512, 1997. doi:10.1161/01.CIR.96.5.1507.
44. **Kurishima C, Saiki H, Masutani S, Senzaki H.** Tailored therapy for aggressive dilatation of systemic veins and arteries may result in improved long-term Fontan circulation. *J Thorac Cardiovasc Surg* 150: 1367–1370, 2015. doi:10.1016/j.jtcvs.2015.08.002.
45. **Kutty S, Rathod RH, Danford DA, Celermajer DS.** Role of imaging in the evaluation of single ventricle with the Fontan palliation. *Heart* 102: 174–183, 2016. doi:10.1136/heartjnl-2015-308298.
46. **Lai WW, Gauvreau K, Rivera ES, Saleeb S, Powell AJ, Geva T.** Accuracy of guideline recommendations for two-dimensional quantification of the right ventricle by echocardiography. *Int J Cardiovasc Imaging* 24: 691–698, 2008. doi:10.1007/s10554-008-9314-4.
47. **Margossian R, Sleeper LA, Pearson GD, Barker PC, Mertens L, Quartermain MD, Su JT, Shirali G, Chen S, Colan SD; Pediatric Heart Network Investigators.** Assessment of diastolic function in single-ventricle patients after the Fontan procedure. *J Am Soc Echocardiogr* 29: 1066–1073, 2016. doi:10.1016/j.echo.2016.07.016.
49. **Mertens LL, Friedberg MK.** Imaging the right ventricle–current state of the art. *Nat Rev Cardiol* 7: 551–563, 2010. doi:10.1038/nrcardio.2010.118.
50. **Meza JM, Hickey EJ, Blackstone EH, Jaquiss RDB, Anderson BR, Williams WG, Cai S, Van Arsdell GS, Karamlou T, McCrindle BW.** The optimal timing of stage 2 palliation for hypoplastic left heart syndrome: an analysis of the Pediatric Heart Network Single Ventricle Reconstruction Trial Public Data Set. *Circulation* 136: 1737–1748, 2017. doi:10.1161/CIRCULATIONAHA.117.028481.
51. **Modesti PA, Vanni S, Bertolozzi I, Cecioni I, Lumachi C, Perna AM, Boddi M, Gensini GF.** Different growth factor activation in the right and left ventricles in experimental volume overload. *Hypertension* 43: 101–108, 2004. doi:10.1161/01.HYP.0000104720.76179.18.
52. **Mooij CF, de Wit CJ, Graham DA, Powell AJ, Geva T.** Reproducibility of MRI measurements of right ventricular size and function in patients with normal and dilated ventricles. *J Magn Reson Imaging* 28: 67–73, 2008. doi:10.1002/jmri.21407.
53. **Newburger JW, Sleeper LA, Frommelt PC, Pearson GD, Mahle WT, Chen S, Dunbar-Masterson C, Mital S, Williams IA, Ghanayem NS, Goldberg CS, Jacobs JP, Krawczeski CD, Lewis AB, Pasquali SK, Pizarro C, Gruber PJ, Atz AM, Khaikin S, Gaynor JW, Ohye RG; Pediatric Heart Network Investigators.** Transplantation-free survival and interventions at 3 years in the single ventricle reconstruction trial. *Circulation* 129: 2013–2020, 2014. doi:10.1161/CIRCULATIONAHA.113.006191.
54. **Newburger JW, Sleeper LA, Gaynor JW, Hollenbeck-Pringle D, Frommelt PC, Li JS, Mahle WT, Williams IA, Atz AM, Burns KM, Chen S, Cnota J, Dunbar-Masterson C, Ghanayem NS, Goldberg CS, Jacobs JP, Lewis AB, Mital S, Pizarro C, Eckhauser A, Stark P, Ohye RG; Pediatric Heart Network Investigators.** Transplant-free survival and interventions at 6 years in the single ventricle reconstruction trial. *Circulation* 137: 2246–2253, 2018. doi:10.1161/CIRCULATIONAHA.117.029375.
55. **Norwood WI, Lang P, Casteneda AR, Campbell DN.** Experience with operations for hypoplastic left heart syndrome. *J Thorac Cardiovasc Surg* 82: 511–519, 1981.
56. **Ohye RG, Sleeper LA, Mahony L, Newburger JW, Pearson GD, Lu M, Goldberg CS, Tabbutt S, Frommelt PC, Ghanayem NS, Laussen PC, Rhodes JF, Lewis AB, Mital S, Ravishankar C, Williams IA, Dunbar-Masterson C, Atz AM, Colan S, Minich LL, Pizarro C, Kanter KR, Jaggers J, Jacobs JP, Krawczeski CD, Pike N, McCrindle BW, Virzi L, Gaynor JW; Pediatric Heart Network Investigators.** Comparison of shunt types in the Norwood procedure for single-ventricle lesions. *N Engl J Med* 362: 1980–1992, 2010. doi:10.1056/NEJMoa0912461.
57. **Oster ME, Kelleman M, McCracken C, Ohye RG, Mahle WT.** Association of digoxin with interstage mortality: results from the Pediatric Heart Network Single Ventricle Reconstruction Trial Public Use Dataset. *J Am Heart Assoc* 5: 5, 2016. doi:10.1161/JAHA.115.002566.
58. **Penny DJ, Redington AN.** Angiographic demonstration of incoordinate motion of the ventricular wall after the Fontan operation. *Br Heart J* 66: 456–459, 1991. doi:10.1136/hrt.66.6.456.
59. **Pettersen E, Helle-Valle T, Edvardsen T, Lindberg H, Smith HJ, Smevik B, Smiseth OA, Andersen K.** Contraction pattern of the systemic right ventricle shift from longitudinal to circumferential shortening and absent global ventricular torsion. *J Am Coll Cardiol* 49: 2450–2456, 2007. doi:10.1016/j.jacc.2007.02.062.
60. **Poh CL, Zannino D, D'Udekem Y.** Life after surviving fontan surgery: a meta-analysis of the incidence and predictors of late death. *Heart Lung Circ* 26: S404, 2017. doi:10.1016/j.hlc.2017.03.145.
61. **Pushparajah K, Wong JK, Bellsham-Revell HR, Hussain T, Valverde I, Bell A, Tzifa A, Greil G, Simpson JM, Kutty S, Razavi R.** Magnetic resonance imaging catheter stress haemodynamics post-Fontan in hypoplastic left heart syndrome. *Eur Heart J Cardiovasc Imaging* 17: 644–651, 2016. doi:10.1093/ehjci/jev178.
62. **Rathod RH, Prakash A, Kim YY, Germanakis IE, Powell AJ, Gauvreau K, Geva T.** Cardiac magnetic resonance parameters predict transplantation-free survival in patients with fontan circulation. *Circ Cardiovasc Imaging* 7: 502–509, 2014. doi:10.1161/CIRCIMAGING.113.001473.
63. **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* 55: 1721–1728, 2010. doi:10.1016/j.jacc.2009.12.036.
64. **Ravishankar C, Gerstenberger E, Sleeper LA, Atz AM, Affolter JT, Bradley TJ, Gaynor JW, Goldstein BH, Henderson HT, Jacobs JP, Lewis AB, Dunbar-Masterson C, Menon SC, Pemberton VL, Petit CJ, Pike NA, Pizarro C, Schumacher KR, Williams IA, Newburger JW; Pediatric Heart Network Investigators.** Factors affecting Fontan length of stay: results from the Single Ventricle Reconstruction Trial. *J Thorac Cardiovasc Surg* 151: 669–675.e1, 2016. doi:10.1016/j.jtcvs.2015.09.061.
65. **Redington AN.** Single right ventricular function and failure in the Fontan circulation. In: *Right Ventricular Physiology, Adaptation and Failure in Congenital and Acquired Heart Disease*, edited by Redington AN. New York: Springer, 2017, p. 185–192.
66. **Ryan JJ, Archer SL.** The right ventricle in pulmonary arterial hypertension: disorders of metabolism, angiogenesis and adrenergic signaling in right ventricular failure. *Circ Res* 115: 176–188, 2014. doi:10.1161/CIRCRESAHA.113.301129.
67. **Rychik J, Jacobs ML, Norwood WI Jr.** Acute changes in left ventricular geometry after volume reduction operation. *Ann Thorac Surg* 60: 1267–1274, 1995. doi:10.1016/0003-4975(95)00704-O.
68. **Schidlow DN, Gauvreau K, Patel M, Uzark K, Brown DW.** Site of interstage care, resource utilization, and interstage mortality: a report from the NPC-QIC registry. *Pediatr Cardiol* 36: 126–131, 2015. doi:10.1007/s00246-014-0974-7.

69. **Schwartz I, McCracken CE, Petit CJ, Sachdeva R.** Late outcomes after the Fontan procedure in patients with single ventricle: a meta-analysis. *Heart* 104: 1508–1514, 2018. doi:10.1136/heartjnl-2017-312807.
70. **Stumper O, Penford G.** Catheter hemodynamic assessment of the univentricular circulation. *Ann Pediatr Cardiol* 10: 167–174, 2017. doi:10.4103/apc.APC_160_16.
71. **Sucharov CC, Sucharov J, Karimpour-Fard A, Nunley K, Stauffer BL, Miyamoto SD.** Micro-RNA expression in hypoplastic left heart syndrome. *J Card Fail* 21: 83–88, 2015. doi:10.1016/j.cardfail.2014.09.013.
72. **Szwast A, Tian Z, McCann M, Donaghue D, Rychik J.** Right ventricular performance in the fetus with hypoplastic left heart syndrome. *Ann Thorac Surg* 87: 1214–1219, 2009. doi:10.1016/j.athoracsur.2008.11.032.
73. **Takahashi K, Inage A, Rebeyka IM, Ross DB, Thompson RB, Mackie AS, Smallhorn JF.** Real-time 3-dimensional echocardiography provides new insight into mechanisms of tricuspid valve regurgitation in patients with hypoplastic left heart syndrome. *Circulation* 120: 1091–1098, 2009. doi:10.1161/CIRCULATIONAHA.108.809566.
74. **Urashima T, Zhao M, Wagner R, Fajardo G, Farahani S, Quertermous T, Bernstein D.** Molecular and physiological characterization of RV remodeling in a murine model of pulmonary stenosis. *Am J Physiol Heart Circ Physiol* 295: H1351–H1368, 2008. doi:10.1152/ajpheart.91526.2007.
75. **van de Veerdonk MC, Kind T, Marcus JT, Mauritz GJ, Heymans MW, Bogaard HJ, Boonstra A, Marques KM, Westerhof N, Vonk-Noordegraaf A.** Progressive right ventricular dysfunction in patients with pulmonary arterial hypertension responding to therapy. *J Am Coll Cardiol* 58: 2511–2519, 2011. doi:10.1016/j.jacc.2011.06.068.
76. **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* 127: 322–330, 2013. doi:10.1161/CIRCULATIONAHA.112.135392.
77. **Voelkel NF.** How does the pressure-overloaded right ventricle adapt and why does it fail? Macro-and micro-molecular perspectives. In: *Right Ventricular Physiology, Adaptation and Failure in Congenital and Acquired Heart Disease*, edited by Redington AN. New York: Springer, 2017, p. 19–27.
78. **Wernovsky G, Ghanayem N, Ohye RG, Bacha EA, Jacobs JP, Gaynor JW, Tabbutt S.** Hypoplastic left heart syndrome: consensus and controversies in 2007. *Cardiol Young* 17, *Suppl* 2: 75–86, 2007. doi:10.1017/S1047951107001187.