

AHA SCIENTIFIC STATEMENT

Evaluation and Management of the Child and Adult With Fontan Circulation

A Scientific Statement From the American Heart Association

ABSTRACT: It has been 50 years since Francis Fontan pioneered the operation that today bears his name. Initially designed for patients with tricuspid atresia, this procedure is now offered for a vast array of congenital cardiac lesions when a circulation with 2 ventricles cannot be achieved. As a result of technical advances and improvements in patient selection and perioperative management, survival has steadily increased, and it is estimated that patients operated on today may hope for a 30-year survival of >80%. Up to 70 000 patients may be alive worldwide today with Fontan circulation, and this population is expected to double in the next 20 years. In the absence of a subpulmonary ventricle, Fontan circulation is characterized by chronically elevated systemic venous pressures and decreased cardiac output. The addition of this acquired abnormal circulation to innate abnormalities associated with single-ventricle congenital heart disease exposes these patients to a variety of complications. Circulatory failure, ventricular dysfunction, atrioventricular valve regurgitation, arrhythmia, protein-losing enteropathy, and plastic bronchitis are potential complications of the Fontan circulation. Abnormalities in body composition, bone structure, and growth have been detected. Liver fibrosis and renal dysfunction are common and may progress over time. Cognitive, neuropsychological, and behavioral deficits are highly prevalent. As a testimony to the success of the current strategy of care, the proportion of adults with Fontan circulation is increasing. Healthcare providers are ill-prepared to tackle these challenges, as well as specific needs such as contraception and pregnancy in female patients. The role of therapies such as cardiovascular drugs to prevent and treat complications, heart transplantation, and mechanical circulatory support remains undetermined. There is a clear need for consensus on how best to follow up patients with Fontan circulation and to treat their complications. This American Heart Association statement summarizes the current state of knowledge on the Fontan circulation and its consequences. A proposed surveillance testing toolkit provides recommendations for a range of acceptable approaches to follow-up care for the patient with Fontan circulation. Gaps in knowledge and areas for future focus of investigation are highlighted, with the objective of laying the groundwork for creating a normal quality and duration of life for these unique individuals.

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As ever-greater numbers of patients with single-ventricle types of congenital heart disease (CHD) survive, this unique population will require continued lifelong medical care, with important personal, societal, and financial impact. The Fontan palliation was introduced in 1968¹ and improved the survival of patients with all types of single-ventricle anatomy, including those with underdeveloped or absent right or left ventricles.² The worldwide population of patients with Fontan circulation grew to an estimated 50 000 to 70 000 patients in 2018, with 40% of patients >18 years of age.³ The current estimate of 30-year survival after surgical Fontan completion is ≈85%.⁴⁻⁷ Despite this remarkable improvement in survival, ensuring these patients a normal quality and duration of life is not currently a reality as multiple organ system dysfunction progresses.

Many alterations in the general health of patients with Fontan circulation are related to the biophysics and physiology of their cardiac anatomy and surgery, in addition to psychosocial, neurocognitive, and mental health challenges, which are just being recognized. The hallmark of the Fontan circulation is a sustained, abnormally elevated central venous pressure combined with decreased cardiac output, especially during periods of increased demands, resulting in a cascade of physiological consequences. Clinical hazards faced by patients include progressive fatigue, heart failure, arrhythmias, and end-organ complications such as liver disease, in addition to anxiety and concern about their condition and future. Whereas multiple reports exist characterizing the condition of these patients, there is an important unmet need in the medical community for a more complete understanding of the pathophysiology, origins, and mechanisms of the development of end-organ consequences.⁸ Evidence-based treatment strategies and preventive management schema are limited, with a need for more widespread consensus within the healthcare community as to how best to serially monitor and manage these patients.

WHY IS THERE A NEED FOR A STATEMENT?

Because patients with Fontan circulation are surviving into adulthood in greater numbers, their management is affected by a relative scarcity of medical knowledge of the pathophysiological origin and optimal care for their unique condition. Potential complications involve not only the heart but also multiple organ systems, including the liver, lungs, brain, bones, and lymphatic system. The end-organ consequences of the Fontan circulation are ubiquitous and usually progressive. Appropriate medical care for these patients requires coordinated input from pediatric and adult congenital cardiologists, as

well as multiple subspecialists, many of whom are not familiar with the physiology or the end-organ consequences of the Fontan circulation. A focused effort to increase our knowledge about patients surviving single-ventricle palliative surgeries is therefore critically important at this time.

In a synthesis of the best current evidence and expertise into a single unified source, this American Heart Association (AHA) statement outlines the fundamental cardiovascular and extracardiac physiological challenges faced by the patient with Fontan circulation, defines our current understanding of the end-organ consequences, highlights knowledge gaps in need of further investigational research, and provides a rationale to support diagnostic and therapeutic best practices that will benefit this population as it continues to increase in number and age over the coming years.

SURGICAL CONSIDERATIONS

The Fontan circulation is based on the premise that a subpulmonary ventricular pump is not compulsory for venous return to cross the pulmonary vascular bed. Rather, pulmonary blood flow, and thus preload to the single ventricle, can be driven by moderately elevated central venous pressure when pulmonary vascular resistance is low enough to permit adequate forward flow under these hemodynamic circumstances. The evolution of the surgical techniques to achieve this unique circulation began with animal studies in the 1940s and culminated in the successful treatment of 2 patients with tricuspid atresia reported in 1971 by Francis Fontan and colleagues⁹ and the pioneering work by Guillermo Kreutzer and colleagues² reported in 1973.

Since then, the Fontan procedure has undergone numerous refinements. The initial use of homograft valves was abandoned because of early calcification and pathway obstruction.¹⁰ Modifications such as the atrioventricular and atriopulmonary connections that attempted to harness the contractile power of a small right ventricle or the right atrium have been abandoned for total cavopulmonary types of connection. These more recent modifications eliminate massive atrial dilation and the associated energy losses and stasis.^{11,12} To further bypass the right atrium completely, Marcelletti and colleagues¹³ introduced a valveless extracardiac conduit between the inferior vena cava and the branch pulmonary artery (extracardiac total cavopulmonary connection [TCPC]; Figure 1) to obviate suture lines within the atrium. Without clear evidence as to which is superior, both lateral tunnel and extracardiac TCPCs are performed by surgeons today according to personal and institutional preferences. Although technically TCPC can be completed as a single-stage operation, because of the survival

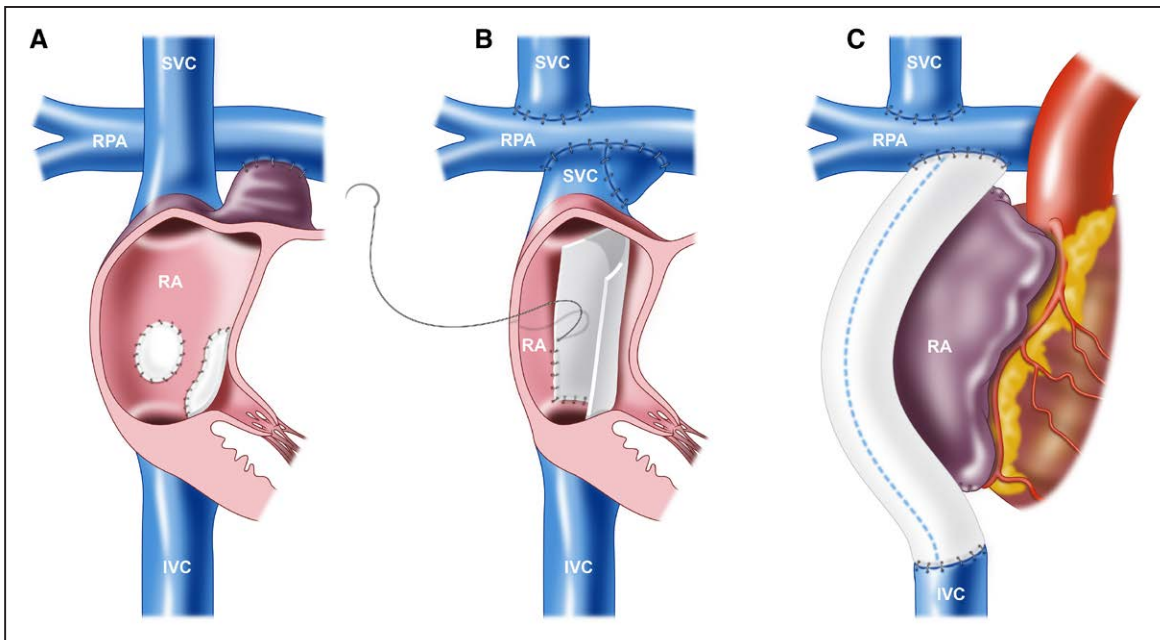


Figure 1. Various techniques of the Fontan procedure.

A, Atriopulmonary connection. **B,** Lateral tunnel total cavopulmonary connection (TCPC). **C,** Extracardiac conduit TCPC. IVC indicates inferior vena cava; RA, right atrium; RPA, right pulmonary artery; and SVC, superior vena cava.

benefits initially demonstrated with staged palliation in hypoplastic left heart syndrome, nearly all Fontan procedures are currently performed in planned stages with a transitional superior cavopulmonary connection (either the bidirectional Glenn or hemi-Fontan connection).¹⁴

A further landmark in the evolution of the Fontan procedure was the introduction of a fenestration between the systemic venous return and the pulmonary venous atrium, which creates a controlled right-to-left shunt. Because fenestration augments ventricular preload and partially offloads systemic hypertension, some centers have routinely adopted fenestration for all Fontan procedures, whereas others have used it only in high-risk patients. The primary clinical benefit of a fenestration appears to be in reducing the amount and duration of pleural drainage after the Fontan procedure, thus decreasing the duration of hospital stay. Some centers proceed with planned anticipatory fenestration closure by interventional catheterization during late follow-up.¹⁵

Considerable investigative efforts have been devoted to discovering ways to further improve surgical technique and to optimize the circulation. Collaborating with engineers in Milan, Italy, Marc de Leval and coworkers¹⁶ used computational fluid dynamics to conceptualize the most optimal cavopulmonary connections to limit flow disturbance and to minimize power loss. Investigations have now demonstrated that the routine use of an 18- to 20-mm conduit for extracardiac TCPC with the avoidance of flow competition between the superior and inferior venous pathways can

lead to the lowest power loss; thus, this conduit is a favorable construct.^{17,18} Through computational fluid dynamics modeling, a new modification using a Y graft to route the inferior venous return has been proposed to minimize power loss with the additional benefit of evenly distributing the hepatic venous flow to the lungs and thereby reducing the impetus for the development of pulmonary arteriovenous malformations (PAVMs).¹⁹ However, clinical results with this Y-graft Fontan have been mixed.²⁰ Innovative combined surgical/interventional catheterization or hybrid procedures for Fontan completion have been proposed but adopted in only a few centers.²¹

While there is no standardized age or weight for proceeding from a superior cavopulmonary circulation to Fontan completion, most centers currently proceed when a patient is 2 to 4 years of age. However, the optimal age at surgery is now being reconsidered in some centers.^{22,23} Preoperative investigations have traditionally included a combination of echocardiography, cardiac catheterization, and computed tomography or cardiac magnetic resonance. However, with improved early surgical outcomes and better postoperative management, a more patient-specific algorithm has been adopted. In low-risk patients with acceptable ventricular and atrioventricular valve function and absence of residual lesions such as aortic or pulmonary arterial obstruction, some centers now proceed with a Fontan procedure on the basis of an assessment with echocardiography and cardiac magnetic resonance only. Cardiac catheterization can be replaced with

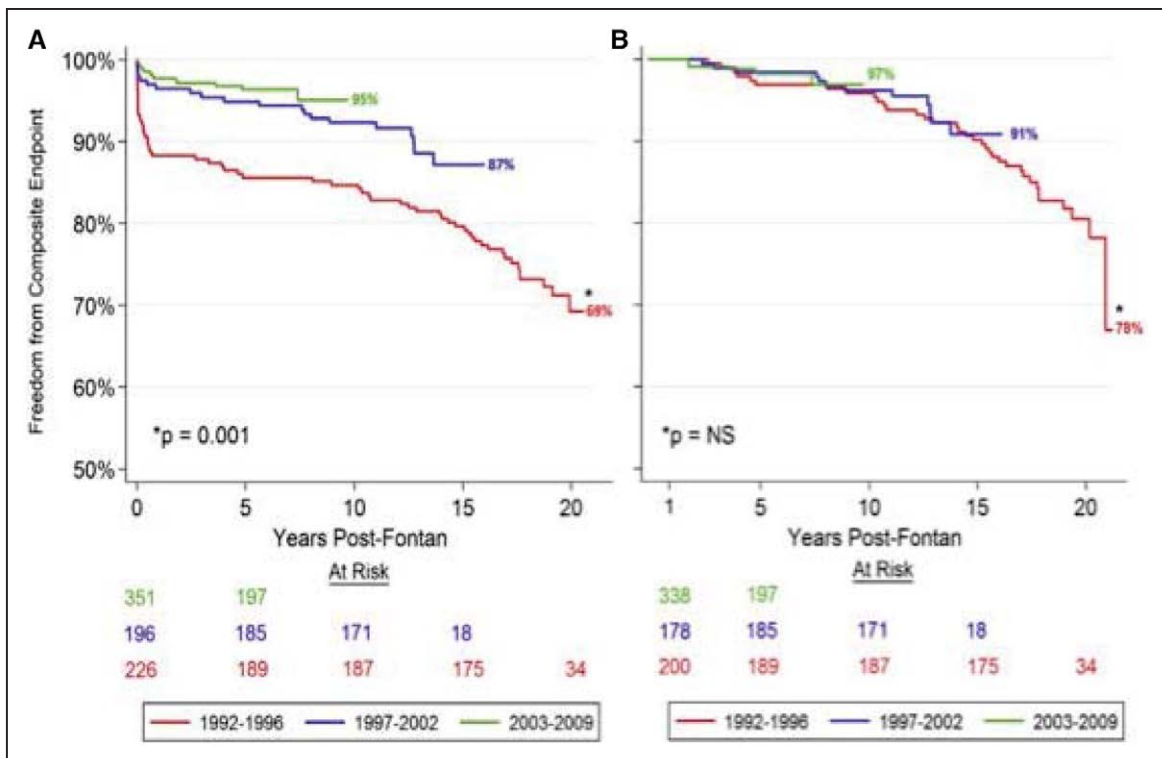


Figure 2. Impact of surgical era on transplantation-free survival after the Fontan operation.

A, All patients and **(B)** conditional transplantation-free survival to 1 year. Reprinted from Downing et al⁷ with permission from The American Association for Thoracic Surgery. Copyright © 2017, The American Association for Thoracic Surgery.

an internal jugular line to measure the superior vena cava pressure.²⁴

Many of the so-called Ten Commandments of requisite anatomic and physiological criteria for Fontan suitability published in 1978 by Choussat et al²⁵ have been overturned or revised.²⁶ Some of the unmodifiable characteristics, including chronic lung disease with pulmonary hypertension, severe ventricular systolic or diastolic dysfunction, and recalcitrant pulmonary vein stenosis, may result in a patient being unsuitable for a Fontan procedure. Other risk factors are now considered potentially modifiable. Moderate to severe atrioventricular or semilunar valve regurgitation may require repair or replacement, and branch pulmonary artery stenosis or hypoplasia can be improved by arterioplasty or stenting. Consideration may be given to placement of steroid-eluting epicardial leads at the time of the Fontan procedure in patients with preoperative atrial arrhythmias or underlying sinus or junctional bradycardia because the transvenous route for placement of pacemaker leads can be problematic.²⁷

The short-term and medium-term outcomes after the Fontan procedure are excellent in the current era (Figure 2), with operative mortality approaching 1% and reported transplantation-free survival of 95% and 90% at 5 and 10 years, respectively.^{4,7,28,29} It is now estimated that the 30-year outcome of those

undergoing the Fontan procedure today will be 85% survival.³ Advances in surgical techniques and perioperative care, including the adaptation of a staged protocol for univentricular palliation and better patient selection, have undoubtedly contributed to this remarkable success. Conversely, because the spectrum of ventricular hypoplasia is wide, efforts are currently underway to design creative surgical options in select patients for whom a relatively high-risk biventricular repair may be possible. Long-term outcomes for complex biventricular repairs will need to be compared with those for Fontan circulation, as outlined in this statement.

SURVIVAL OUTCOMES

The Fontan operation is approaching its fifth decade.¹ The estimation of long-term outcomes of this population spans up to 35 years, with the ANZFR (Australia and New Zealand Fontan Registry) reporting a 62% survival over that time frame.³⁰ Large variations in survival outcomes have been reported in the literature. These variations can readily be explained by the impact of era, surgical techniques, heterogeneity of physiological features in different forms of a single ventricle, and indications for surgery. The early experience with the Fontan procedure was characterized by evolution of the cavopulmonary connection type. The early atrio-

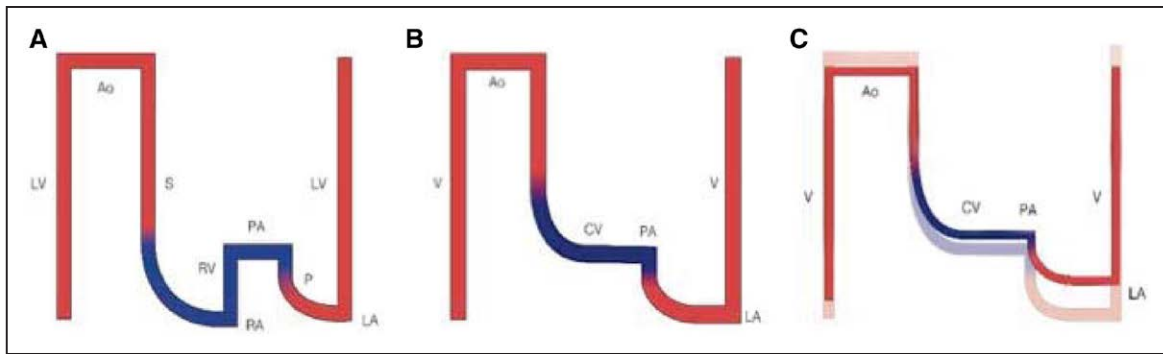


Figure 3. Scheme of normal cardiovascular circulation and Fontan circulation at early and late stages.

A, Normal biventricular circulation. The pulmonary circulation (P) is connected in series to the systemic circulation (S). The right ventricle (RV) ensures that the right atrial pressure remains lower than the left atrial pressure and delivers the driving force to the blood to overcome pulmonary impedance. **B**, Fontan circuit. The caval veins are directly connected to the pulmonary artery (PA); systemic venous pressures are markedly elevated. **C**, Fontan circuit late (superimposed on early Fontan circuit). With time, a negative spiral ensues: Pulmonary resistance increases, resulting in a further increase in caval vein (CV) congestion but even more in reduced flow and ventricular stretch, which itself increases ventricular filling pressure. Line thickness reflects output; color reflects oxygen saturation. Ao indicates aorta; LA, left atrium; LV, left ventricle; and V, single ventricle. Reprinted from Gewillig and Brown.⁴⁵ Copyright © 2016, BMJ Publishing Group Ltd and the British Cardiovascular Society. This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

pulmonary Fontan technique has been shown to be associated with worse long-term outcomes than the more recent versions of the operation, including the lateral tunnel and the extracardiac conduit.³¹ Likewise, the earlier Bjork modification, which consisted of placement of a conduit between the right atrial and the right hypoplastic ventricular chamber, also has been associated with worse survival. A report from the Mayo Clinic, where the Bjork modification was pioneered, describes a 30-year survival of 43%, in a population that includes these patients. In contrast, the ANZFR, which excludes the Bjork modification and includes an experience that started a decade later, reports a survival of 70% over the same era.^{6,30} Today, the estimates of 20-year survival for survivors of the Fontan procedure vary between 61% and 85%.⁴⁻⁷ An examination of the survival curves shows that there does not seem to be a sudden or sharp decline in the survival of this population, without acceleration in mortality.³ The attrition is remarkably constant, and the outcomes of the contemporary techniques of Fontan—the lateral tunnel and the extracardiac conduit—are superior to those observed with the first forms of Fontan. We may therefore be in a position to predict that the population operated on today is likely to have reasonably good survival of ≈85% at 30 years.³

We are also more aware of factors affecting outcomes. Having a single right ventricle supporting the Fontan circulation and, in particular, having hypoplastic left heart syndrome, does not adversely affect early survival to this stage, although patients with a hypoplastic left heart seem to be at higher risk for more complications.^{7,32-34} Male sex, presence of a common atrioventricular valve (AVV), older age at Fontan operation, elevated preoperative and early postoperative pulmonary artery pressures, concomitant surgery at the time of the

Fontan, and prolonged pleural effusions after Fontan completion have all been associated with worse late survival.^{5,6,35-38} Patients developing late complications such as protein-losing enteropathy (PLE), thromboembolic events, or arrhythmias and those with a ventricular pacemaker will have a worse survival.^{8,39-42} Although survival of this population has improved, the burden of associated physiological constraints and morbidities has remained, with up to 50% having a major adverse event before reaching adulthood.³³

An evaluation of survival of a population with Fontan circulation should also now include the impact of cardiac transplantation. Large variation has been observed across centers worldwide in terms of access to heart transplantation.^{43,44} In a recent report from the Pediatric Heart Network, the proportion of survivors having transplantation within 15 years of the Fontan varied from 0% and 21% across centers.⁴⁴ In a population-based study in Australia and New Zealand, the overall rate of transplantation for this population remains low at <3 % of patients.⁴³

PHYSIOLOGICAL LIMITATIONS

The Fontan circulation is characterized by the absence of an adequate subpulmonary ventricle. Essentially, the caval veins are connected without a pumping ventricle to the pulmonary arteries.^{45,46} The cavopulmonary connection effectively creates an upstream flow restriction across the pulmonary circulation, which dominates the circulation.⁴⁷ The pulmonary circulation is interposed between the venous return of the body and the systemic ventricle, thereby imposing a precardiac flow limitation to the systemic venous system, causing upstream congestion and decreased downstream flow (Figure 3).

These 2 features, elevated systemic venous pressure and chronically decreased output, are the root cause of the majority of the pathological impairments of the Fontan circulation.

The Venous Pathway

The normal subpulmonary ventricle (normally the right ventricle) keeps systemic venous and right atrial pressures low at rest and during exertion, accelerates pulmonary flow in a pulsatile manner, and increases cardiac output by both heart rate and augmented stroke volume. Pulmonary pressures can normally increase up to 50 mm Hg (or even more) during exercise, leading to recruitment of lung vessels.⁴⁸ The normal subpulmonary ventricle will also allow some compensation in disease states such as pulmonary pathway obstruction or any lung disease that may result in increased pulmonary vascular resistance. The absence of a subpulmonary ventricle results in increased venous pressure at rest and at exercise, with a greater dependency on the skeletal and respiratory muscle pumps for preload augmentation during exercise. In addition, lack of pulsatility and marked attenuation of the normal high-pressure high-flow pulmonary arterial circulation during exercise occur. Consequently, there is less recruitment of collapsible pulmonary vessels, especially at low exercise levels. This results in diminished ventricular preload, with decreased volume-induced ventricular stretch downstream during exercise.

Excessive flow restriction in this passive flow system can occur at any level of the Fontan circuit or the lungs: the Fontan venous connections; the pulmonary arteries; the pulmonary capillary network, including precapillary sphincters; the pulmonary veins; or the venoatrial connection. These impediments include, but are not limited to, stenosis, hypoplasia, distortion, vasoconstriction, pulmonary vascular disease, loss or exclusion of large vessels or microvessels, turbulence or competitive flow collision, flow mismatch, and obstruction by external compression. Impediment at any level of this circuit can profoundly affect cardiac output in Fontan circulation, to a greater degree than in a 2-ventricle circulation.

The Ventricle

From even before birth, the single ventricle is subject to abnormal hemodynamic demands and morphological abnormalities that can predispose to systolic or diastolic dysfunction.⁴⁹ Palliation of the single ventricle with an aortopulmonary shunt or pulmonary artery band in the neonatal period results in increased ventricular volume load, a condition caused by the presence of pulmonary and systemic circulations existing in parallel, with mix-

ing within the single ventricle. Valvular regurgitation (atrioventricular or semilunar) can also add to the hemodynamic stress on the myocardium. As a result of intracardiac mixing, arterial oxygen saturation is low, and the myocardium is subject to a chronically hypoxic environment. A significant proportion of patients with a single ventricle have either morphological right or indeterminate anatomy.⁵⁰ However, even in those with single left ventricle, normal geometry as in a 2-ventricle system is not preserved. Myocardial fiber arrangement in the single ventricle is often disturbed and myocardial fibrosis is present. As a consequence, ventricular energetics and the mechanics of contraction can be deranged, with ventricular systolic and diastolic dyssynchrony possible.^{51,52}

At the time when the Fontan procedure is performed, the ventricle commonly evolves from being volume overloaded, overgrown, and overstretched to volume deprived with a smaller cavity and increased wall thickness.^{49,53} In the short term, this can create a ventricular mass-to-volume mismatch that can deleteriously influence both systolic and diastolic function. Shifting volume load and ventricular mass ratios early in the course of surgical reconstruction may also carry long-term implications for ventricular mechanics.⁵⁴

During exercise, individuals with a normal heart increase their stroke volume by 20% to 50%; in contrast, such an exercise-induced increase may be completely absent in patients with Fontan circulation, most likely as a result of preload restriction.⁴⁸ Chronic volume deprivation with lack of fiber stretch is known to decrease contractility and to increase muscle stiffness, resulting in increasing filling pressures.⁵⁵ Moreover, abnormal ventriculo-vascular coupling may further compound ventricular stiffness.^{56,57}

The Lungs

Throughout the first years of life for the child with a single ventricle, the pulmonary vasculature is subjected to multiple alterations likely to affect growth and function. During fetal life, pulmonary flow is altered from normal, and pulmonary vascular development can be affected. Neonatal palliation will frequently result in further alterations (usually an increase) in pulmonary blood flow, whereas the staged cavopulmonary connections will decrease pulmonary blood flow. Flow distribution to the lungs may not be uniform. As a result, acquired hypoplasia or vascular disease of the pulmonary vascular bed may occur. Stenosis resulting from ductal constriction, abnormal connections, or surgical scarring can further compromise the pulmonary architecture. The Fontan circulation itself imposes multiple abnormal physiological features onto the pulmonary vasculature such as chronically decreased volume of flow, minimally to mildly desaturated bronchial flow, increased

aortopulmonary collateral flow, suboptimal mixing of inferior and superior caval flow streams, endothelial dysfunction, absence of pulsatility, and absence of episodic high flow and high pressure, as is normally seen during exercise, all required for exercise-associated vessel recruitment and vasodilation. In combination, these factors contribute to a burden of pulmonary vascular trauma, resulting in an elevated and increasing pulmonary vascular resistance, which can itself contribute to Fontan circulatory failure.^{58,59}

CIRCULATORY FAILURE AND VENTRICULAR DYSFUNCTION

Heart Failure

A well-accepted definition of heart failure is the inability of the heart to meet resting and exercise demands at low filling pressures. By such a definition, essentially all patients with Fontan circulation have a physiological form of chronic heart failure from the first day after the operation, yet we know that this circulation sufficiently sustains life for decades. The defining thresholds for characterizing failure in a patient with Fontan circulation differ from other cardiovascular conditions. Within the context of physiological failures inherent in the Fontan circulation, some patients develop classic heart failure symptoms such as fluid retention and exercise intolerance. The consequences of progressive heart failure in the patient with Fontan circulation are substantial and result in cardiac and noncardiac morbidities that affect long-term survival and quality of life.

An important distinction to make is the presence of 2 categories of heart failure in the patient with Fontan circulation with a single ventricle: the classic ventricular pump failure phenomenon with its clinical manifestations and Fontan circulatory failure, which is unique as a physiological consequence of chronically elevated systemic venous pressure and low cardiac output. In other words, symptoms of heart failure may exist despite reasonable ventricular performance of the single ventricle, simply as a consequence of venous hypertension and its end-organ consequences inherent in the pathophysiology of every patient with Fontan circulation.

Within 15 years of the introduction of the first Fontan procedure, early survival improved markedly; however, a 1%/y continuous hazard for failure was present throughout the follow-up period.⁶⁰ A recent report of patients who underwent the atriopulmonary Fontan indicates that only 45% of patients remain free of death, heart transplantation, or New York Heart Association class III to VI heart failure over a 28-year follow-up period.⁶¹ Evidence suggests that long-term survival has improved in patients who have undergone the lateral tunnel or extracardiac conduit. However, circulatory

failure remains an important cause of death in this population.³¹ Clinical heart failure signs and symptoms are among the leading causes of hospital admission in the Fontan population, and once such heart failure is apparent, it is a strong predictor for worse outcomes.^{44,62} In a report from the Dutch CONCOR registry, mortality in the patient with Fontan circulation admitted with heart failure was 24% at 1 year and 35% at 3 years from presentation.⁶³

Systolic or diastolic dysfunction is the underlying cause of circulatory failure in the general population, and the diagnosis and treatment of affected individuals are focused primarily on measures that evaluate and improve myocardial performance.⁶⁴ In contrast, the causes of heart failure in the Fontan population are substantially more heterogeneous and complex. They result in varying phenotypes of heart failure that may represent complex interactions among variables such as systolic and diastolic ventricular performance, structural cardiac or valvular abnormalities, rhythm disorders, and the pathophysiology of passive venous flow through the pulmonary circulation.⁶⁵

Ventricular Function

Systolic ventricular function is relatively preserved in the first decades after the Fontan procedure⁵⁰ but declines over time.⁴⁴ In the presence of atrial arrhythmias, ventricular dysfunction can improve once rhythm control is achieved.⁶⁶ Systolic ventricular dysfunction is present in 40% to 60% of patients with Fontan circulation undergoing evaluation for heart transplantation.^{67,68} These patients often have the manifestations of chronic low cardiac output, including exercise intolerance, poor somatic growth, and fatigue. Systolic ventricular dysfunction can be difficult to assess in the patient with Fontan circulation with a non-left ventricular systemic ventricle because normal values of functional indexes for the right ventricle or the univentricular heart are not uniformly agreed on or readily available. Cardiac magnetic resonance imaging (MRI) is a standard and reliable means for providing serial information on ventricular performance, valvular function, and flow data in the patient with a single ventricle after Fontan.⁶⁹ Although 2-dimensional echocardiography is limited in its ability to evaluate a morphologically abnormal ventricle, fair correlation was demonstrated between the 2-dimensional echocardiographic and cardiac MRI determinations of ejection fraction in a large multicenter study.⁷⁰ Thus, 2-dimensional echocardiography may be adequate to monitor serial changes in ventricular function on a more frequent basis and may complement the application of serial cardiac MRI.

Similar to the adult noncongenital heart failure population, a substantial number of patients with Fontan circulation have evidence of heart failure with preserved

Table 1. Key Points: Heart Failure and Ventricular Dysfunction

Symptoms of heart failure include poor somatic growth, fluid retention including ascites, and exercise intolerance.
Heart failure can be related to systolic ventricular dysfunction, with important diastolic ventricular dysfunction increasing with age, although symptomatic circulatory failure may occur independently of ventricular function.
Potential contributors to heart failure include ventricular dysfunction, atrial tachycardia, valvar regurgitation, and volume-loading shunts.

ejection fraction. These patients manifest the signs and symptoms of venous congestion and its attendant consequences such as ascites, PLE, and liver cirrhosis, and they may exhibit growth failure as an indicator of low cardiac output.^{67,68} Diastolic dysfunction can be difficult to assess noninvasively in the single-ventricle population because of the lack of normal values for systemic right ventricles and univentricular hearts. Estimates of pressure-volume loop relationships indicate evidence for diastolic dysfunction early in the postoperative period after the Fontan operation.⁷¹ A volume challenge can often elicit “occult” diastolic dysfunction late after Fontan, highlighting the sensitivity of the single-ventricle heart to volume loads.^{72,73}

Ventricular performance can be gauged through functional assessments such as exercise performance. Baseline exercise performance in patients with Fontan circulation is significantly impaired, with a mean maximal peak oxygen consumption of 60% predicted.^{74,75} In a large multicenter study, no relationship was found between ejection fraction and exercise performance, whereas a lower resting oxygen saturation, lower oxygen pulse, and chronotropic incompetence were associated with worse exercise performance, highlighting the importance of factors other than systolic ventricular function on exercise capacity.⁷⁵ Key take-away points for heart failure and ventricular dysfunction are listed in Table 1.

CYANOSIS

The purpose of the Fontan operation is to separate the systemic from the pulmonic venous blood returns, yet some mixing still occurs. Systemic arterial oxygen saturation at rest in room air rarely achieves levels >95% and is commonly in the 90% to 95% range. There are a number of reasons for this mild degree of arterial oxygen desaturation. First, markedly deoxygenated coronary sinus vein blood typically drains into the pulmonary venous chamber and mixes with pulmonary venous blood. Second, nonpulsatile pulmonary arterial blood flow tends to gravitate to lower segments of the lung, whereas pulmonary aeration favors upper segments, resulting in a ventilation-perfusion mismatch. Third, a fenestration in the systemic venous pathway placed at the time of the Fontan operation may remain

patent and persist for years, with variable degrees of right-to-left shunting.^{76,77} Similarly, small communications between the high-pressure systemic venous and lower-pressure pulmonary venous chambers may develop over time, either within the heart or through extracardiac venous collaterals.^{78,79} With exercise, arterial oxygen saturation often drops to <90% because each of the mechanisms for cyanosis may become exaggerated with activity and the relative magnitude of desaturated lower extremity venous return increases.

Some patients with Fontan circulation demonstrate notably low arterial oxygen saturations (<90%) at rest. This can be caused by the presence of a fenestration or the development of veno-venous collaterals with right-to-left shunting. Veno-venous collaterals may naturally form as a “pop-off” under conditions of normally anticipated systemic venous congestion and pulmonary artery pressure (10–15 mmHg) or secondary to the development of unusually elevated pulmonary arterial pressures (>15 mmHg).⁸⁰ Effective catheter-based techniques are available to close such communications and to improve oxygen saturation.⁸¹ However, this may come at the expense of increased impedance to venous return, diminished cardiac output, and decreased oxygen delivery,^{82,83} all of which can negatively affect end-organ function and patient well-being.⁸⁴ Decisions must therefore be made on an individual case-by-case basis as to the merits of fenestration closure or veno-venous collateral occlusion, weighing the tradeoff of cyanosis against the potential for deleterious hemodynamic effects.

Patients with Fontan circulation, notably those with heterotaxy syndrome, may develop PAVMs with intrapulmonary shunting and progressive cyanosis.⁸⁵ This is believed to result from the absence of an essential hepatic factor reaching the pulmonary vascular bed, a circulating agent that mitigates the development of PAVM. The precise nature or biochemical makeup of this agent is currently unknown, but it may also be the missing agent in conditions such as hepatopulmonary syndrome and hereditary hemorrhagic telangiectasia.⁸⁶ Preferential shunting of hepatic venous effluent away from one lung, as present in some forms of heterotaxy syndrome with venous anomalies, can lead to the development of PAVMs, whereas re-establishing hepatic venous effluent flow to the affected lung can result in resolution.^{87–89} Creation of a brachial or axillary arteriovenous fistula may also deliver the hepatic factor to an affected lung and resolve PAVMs.⁹⁰ MRI-derived computational fluid dynamic studies can be helpful in designing cavopulmonary connections that allow equitable hepatic venous effluent flow between the lungs to prevent PAVMs and in designing surgical venous re-routing strategies to treat this condition.^{91,92}

Because of the mild cyanosis seen in most patients with Fontan circulation, hemoglobin levels are

typically elevated. Normal or low hemoglobin values, although perhaps well tolerated in the patient with normal circulation, may be inadequate for the patient with Fontan circulation. Hemoglobin production is essential as a proper compensatory response to the mild cyanosis seen. Hence, maintenance of good iron stores is important.⁹³ An increased hemoglobin level increases blood viscosity and indicates the need for maintenance of proper fluid intake and hydration at all times.

AVV REGURGITATION

Significant AVV regurgitation in patients with univentricular hearts was historically a contraindication for staged single-ventricle palliation.^{25,94} More frequently, AVV regurgitation develops insidiously during follow-up at any stage of single-ventricle palliation. A continuous decline in AVV function in patients with Fontan circulation with the passing of time has been reported in a subset of patients with Fontan circulation.⁹⁵ Significant AVV regurgitation can eventually compromise the functioning of the Fontan circulation as a result of volume overload, ventricular dilatation, reduced ventricular contractility, and increased postcapillary and central venous pressures. Mechanisms of AVV regurgitation in a univentricular heart are multifactorial and include prior volume overload with a systemic-to-pulmonary shunt, annular dilation, and abnormal chordae and papillary muscles.^{96,97} Changes in loading conditions at different stages of surgery may lead to dysfunction of chordae and valvular apparatus, structures that may be inherently abnormal and prone to dysfunction from the very start. The tricuspid valve as the systemic AVV appears to be more prone to functional regurgitation than the mitral valve, with further dysfunction potential in those with a common AVV.⁹⁸ Reduced ventricular function is also associated with the development of AVV regurgitation.

Medical management of patients with Fontan circulation with AVV regurgitation may include afterload reduction and diuretic therapy. These agents may be helpful, but a strong evidence base for their use is lacking. Afterload reduction therapy is often used empirically in patients with a single ventricle before Fontan at various stages of palliation, but there are no data from prospective studies to support the use of these agents. In a multicenter randomized trial, enalapril administration in infants with a single ventricle did not improve somatic growth, ventricular function, or severity of heart failure.⁹⁹ Similarly, there are no data to support the use of afterload reduction to treat AVV regurgitation. Diuretics may be beneficial for patients with Fontan circulation with features of volume overload, but these agents should be used with caution because they can decrease cardiac output.

Table 2. Key Points: AVV Regurgitation

Significant AVV regurgitation may be related to structural valvar abnormalities, particularly of the tricuspid valve, annular dilatation, or reduced ventricular contractility.
Moderate or greater AVV regurgitation is a significant risk factor for long-term mortality after Fontan surgery.
Diuretics and afterload-reducing medications for AVV regurgitation require careful monitoring to avoid preload depletion.

AVV indicates atrioventricular valve.

Application of volume-unloading staged procedures and various AVV repair techniques during the staged palliation made Fontan completion among those patients achievable. Despite continued improvement in outcomes for patients at higher risk, AVV repair remains a significant risk factor for long-term mortality after the Fontan procedure.¹⁰⁰

Debate has been ongoing on the best timing of AVV repair in patients with a univentricular heart and on the need for AVV repair in patients with mild regurgitation. Valve repair in cases of moderate or severe regurgitation either at the time of planned surgery or between stages seems beneficial to prevent deterioration of ventricular function. Whereas surgical feasibility is well established and a variety of techniques have been described, few studies have investigated the midterm and long-term outcomes after AVV repair in patients with single-ventricle heart disease.^{101,102} Despite the known negative influence of AVV regurgitation on outcomes, recent studies have reported improved outcomes for patients with a single ventricle with successful AVV repair and good ventricular function.¹⁰³ Key take-away points for AVV regurgitation are listed in Table 2.

ARRHYTHMIAS

Each anatomic substrate of single-ventricle CHD and each type of surgical modification of the Fontan operation may pose its own arrhythmia-producing challenge. The various suture lines of any of the surgical techniques interfere with atrial conduction. The negative impact of the development of tachycardia on outcomes for patients with Fontan circulation has been most clearly demonstrated for adults with atriopulmonary repairs. Among a series of 321 adult patients, those with prior atriopulmonary repairs and receiving diuretics who developed atrial tachycardia had a 6-fold increase in death or transplantation and 6-year mortality of >40%.⁶² Patients with Fontan circulation with atrial tachycardia are more likely to develop right atrial thrombus, heart failure, and ventricular dysfunction and to require hospitalization.^{104–108}

Traditionally, sinus node dysfunction and atrial tachycardia have been attributed to injury to the sinus node or its arterial supply, atrial suture lines, atrial dilatation, and hypertrophy related to elevated atrial pressures.¹⁰⁹

Table 3. Prevalence of Arrhythmias and Pacemaker Placement

Arrhythmia	Atriopulmonary	Lateral Tunnel	Extracardiac Connection
Sinus node dysfunction, %	30–62	18–44	15–44
Supraventricular tachycardia, %	60–80	7–33	5–15
Pacemaker, %	11–23	5–55	3–27
Automated implantable cardioverter-defibrillator, %	1.4		
Ventricular tachycardia or sudden death, % (%/y)	2–10 (0.15–0.2)		

Important causes of late arrhythmia include the underlying genetics of the congenital defect with associated altered atrial tissue organization and programmed cell apoptosis, as well as the effects of neonatal cyanosis and cardiopulmonary bypass with injury to atrial and ventricular tissues, resulting in fibrosis and altered conduction properties. The method of reporting of the existence of arrhythmia varies significantly and is associated with the method of detection, which may include patient self-reporting, the need for intervention to terminate tachycardia or to implant a pacemaker, resting ECG, 24-hour ambulatory rhythm monitoring, or device interrogation. Finally, follow-up for >10 years after surgery is needed to assess the arrhythmia impact of one type of Fontan procedure versus another.

Table 3 summarizes the prevalence of various arrhythmias and pacemaker placement in different types of Fontan surgeries in studies reporting follow-up beyond 5 years.^{5,6,31,104,105,110–124} Contemporary surgical outcomes appear to have improved tachycardia outcomes.^{5,31,115} However, the duration of follow-up may not be adequate to make this conclusion because the median postoperative interval preceding the development of atrial tachycardia is 9 to 14 years and the time-related risk increases steadily thereafter.^{116,119,125} In the Australia/New Zealand study of 1006 patients, which reported a median follow-up of ≈10 years, supraventricular tachycardia was present in 10% of patients.⁵ In 2 large studies of adults with predominantly atriopulmonary repairs and follow-up extending from 15 to 30 years, freedom from supraventricular tachycardia at 25 years was ≈45%.^{116,117} Nonsustained and, less frequently, sustained ventricular tachycardia and sudden death are reported in 2% to 12% of patients; the time-related risk of sudden death appears to be 0.15%/y to 0.2%/y.^{5,6,110,118,124} The reported prevalence of implantation of defibrillators for secondary prevention is 1.4% to 2% of patients.^{5,44,118}

Risk factors for the late development of arrhythmias can be summarized from the previous studies and include older age at the time of primary Fontan,

atriopulmonary-type repair, preoperative and early postoperative tachycardia, moderate or greater AVV regurgitation, and longer follow-up.^{5,101,116,117,123} Male sex, right atrial isomerism, and loss of sinus rhythm during follow-up are reported risk factors for arrhythmia in some studies.^{111,117,118,126–128}

Assessing the importance of sinus rhythm and chronotropic incompetence, or the ability to appropriately increase the sinus rate with exertion, can be difficult.^{120,129} Sinus node dysfunction is common and is associated with longer follow-up, the atriopulmonary technique, and the later development of atrial tachycardia. Autonomic control of heart rate is impaired in patients with Fontan circulation, with lower heart rate variability and depressed baroreflex sensitivity.^{130,131} The increase in heart rate with exertion is an important means of augmenting cardiac output during periods of increased demand, and impaired responses have been reported in 62% of patients with Fontan circulation, the highest prevalence among adults with CHD.⁶² A combination of decreased heart reserve and peak oxygen consumption on exercise testing, or chronotropic incompetence, identifies patients at increased risk for early mortality.^{62,132–135} These studies emphasize the importance of serial exercise testing in older patients with Fontan circulation and highlight a potential role for consideration of early atrial rate-responsive pacing to augment the heart rate response to exertion.

Some surgical studies have reported that the presence of a pacemaker is a risk factor for death, transplantation, or Fontan failure.^{61,136} The Pediatric Heart Network has serially evaluated a cohort of young patients with Fontan surgeries, largely total cavopulmonary repairs.^{44,114,137} Pacemakers were required in 13% of patients, and pacing was reported to be associated with lower quality-of-life scores and lower ventricular ejection fraction, with no differences found in exercise performance.¹³⁷ The indication for pacing (sinus bradycardia or atrioventricular block, congenital or postsurgical) and the type of pacing (atrial, ventricular, or dual chamber) are not reported or analyzed separately. Pacing without atrioventricular synchrony and rate optimization and pacing only the ventricle can be expected to negatively affect hemodynamic status in the patient with a single ventricle.¹³⁸

Therapies for atrial tachycardia include antiarrhythmic medications, catheter ablation, atrial antibradycardia and antitachycardia pacing, and Fontan conversion with arrhythmia surgery.¹³⁹ Patients with Fontan circulation presenting with arrhythmias are recommended to undergo assessment of associated hemodynamic abnormalities, with interventional therapy as indicated, in addition to anticoagulation; termination of tachycardia expeditiously is recommended.^{140,141} The use of antiarrhythmic medications, including β -blockers, sotalol,

Table 4. Key Points: Arrhythmias

Atrial tachycardia develops in >50% of patients late after Fontan, although current surgical techniques may reduce this incidence.
Development of atrial tachycardia in patients with Fontan repairs is associated with significant morbidity, including heart failure and atrial thrombosis, and requires urgent and aggressive therapy.
Ventricular pacing may negatively affect cardiac output and lower quality-of-life scores.

dofetilide, and amiodarone, is associated with a high recurrence of atrial tachycardia and, in 1 study, an increased risk of adverse events compared with ablation or surgery.¹⁴² Flecainide should be used with caution in patients with structural heart disease, and long-term use of amiodarone is associated with thyroid dysfunction.¹⁴¹ Catheter ablation of atrial reentry tachycardia in patients with atriopulmonary Fontan is associated with acute success rates of 54% to 94%, lower than in other forms of heart disease, and early recurrence of atrial tachycardia in ≈50% of patients.^{143–147}

In the more contemporary lateral tunnel and extracardiac repairs, focal atrial tachycardia is present in at least 10% to 15% of patients with atrial tachycardia and is amenable to catheter ablation, although vascular access may be challenging.^{147–149} In patients with atriopulmonary Fontan repairs, atrial tachycardia is most commonly associated with marked atrial dilatation and hypertrophy, with impaired hemodynamics. An approach consisting of a Fontan conversion to an extracardiac Fontan combined with arrhythmia surgery has been shown to reduce arrhythmia recurrence and to improve hemodynamic status.^{125,139,150–155} In patients with Fontan surgeries undergoing intracardiac reoperations, surgical ablation for atrial tachycardia is recommended in the most recent guidelines and consensus statements.^{140,141} Currently, high-risk older patients presenting with significant arrhythmias and ascites, significant AVV regurgitation, or advanced ventricular dysfunction are likely to be considered for heart transplantation rather than Fontan conversion surgery.^{125,155,156}

Future directions for reducing the incidence of arrhythmias include prophylactic interventions at the time of Fontan surgery, which may include placement of isthmus or right atrial cryoablative lesions, or atrial antibradycardia pacing lead implantation.^{157–161} Early and prompt intervention for residual hemodynamic issues is essential to limit hypertrophy and ventricular dysfunction.^{140,141} Obesity contributes to the development of atrial fibrillation and diastolic dysfunction and represents a modifiable risk factor to improve outcomes.^{162,163} Regular physical exercise may have a positive impact on autonomic nervous function, heart rate reserve, and, in turn, arrhythmia propensity and outcome, although this is speculative.^{120,131} Key take-away points for arrhythmias are listed in Table 4.

PLE AND PLASTIC BRONCHITIS

Protein-Losing Enteropathy

PLE is the abnormal loss of serum proteins into the intestinal lumen. It occurs in 5% to 12% of individuals after Fontan palliation.^{39,44,164} Morbidity stemming from the disease is marked, and although improved in the current era, mortality remains high.^{164–166}

The pathophysiology of PLE remains incompletely characterized, but several factors appear to contribute in varying combinations for each individual case. Recent investigation into lymphatic anatomy and function in patients with PLE has revealed an increase in abnormal lymphatic vessels throughout the intestinal tract.¹⁶⁷ Lymphatic congestion, likely present in every patient with Fontan circulation, can lead to overflow or leak of these channels, resulting in spillage of lymph-rich material into the low-pressure intestinal tract and thus enteric protein loss. Lymphatic leak may be worsened by several factors, including the degree of pressure elevation in the systemic veins into which the lymphatic vessels must drain.^{167,168} Variability in the anatomic configuration of the lymphatic system may predispose to intestinal or bronchial lymphatic leakage when chronic venous congestion is present. For example, some individuals may have lymphatic channels and decompression pathways that run adjacent to the gut lumen or airway and, when in the presence of elevated venous pressure and lymphatic congestion, manifest spillage into these low-pressure passages. This may explain why only select patients with similar degrees of venous hypertension develop PLE or plastic bronchitis (PB) and others do not. Exaggeration of elevated pressure secondary to anatomic obstruction or cardiac dysfunction can accentuate the problem of luminal protein loss.^{164,169} Altered intestinal mucosal perfusion may also play a role. Chronically limited cardiac output demonstrated in patients with Fontan circulation can result in a state of persistently elevated systemic vascular resistance with redistribution of blood flow, along the lines of chronic heart failure. A selective increase in mesenteric vascular resistance may be present as part of flow redistribution. Increased mesenteric vascular resistance has been demonstrated in patients with Fontan circulation and is also increased in those with PLE.¹⁷⁰ Furthermore, chronically low cardiac output leads to a proinflammatory state that may alter enterocyte membrane permeability, predisposing to PLE.¹⁷¹ Finally, a subset of patients with PLE have diminished HSPGs (heparan sulfate proteoglycans), a protein present in the enterocyte membrane that normally assists in enteral protein trafficking, and its absence can result in protein leakage.¹⁷² The overall result of these derangements is leakage or spillover of the intestinal lymphatics and loss of protein into the intestinal lumen. As a result of protein loss, serum oncotic pressure decreases, leading to systemic

edema. When the intestinal wall becomes edematous, malabsorption occurs, and protein loss can worsen, leading to a vicious cycle of intestinal symptoms and edema often referred to as a PLE flare. These sporadic periods of worsening PLE often follow a viral infection, further suggesting that inflammation plays a role in bowel wall leak in this condition.

PLE often persists as a chronic condition for extended periods of months to years. Subclinical PLE may also exist with low levels of enteric protein loss that may not manifest as ostensible tissue edema but may nevertheless contribute to perturbations in somatic growth and development of abnormalities in the coagulation cascade, processes that depend on proper protein balance. Transient PLE has been identified in select patients with spontaneous remission and periods of wellness for extended periods of time. However, when sustained PLE is present, complications from chronic protein loss lead to significant systemic morbidity. Chronic diffuse edema leads to symptoms of abdominal and extremity swelling, as well as diminished tissue integrity and difficulty in wound healing.¹⁷³ Coagulation abnormalities result from dysregulation of clotting mechanisms (eg, factor loss or altered production), with an increased risk for thromboembolic complications above and beyond the already increased risk present in every patient with Fontan circulation. Bone density can be profoundly diminished as a consequence of chronic hypocalcemia secondary to low levels of albumin, an essential protein for calcium transport.¹⁷⁴ Linear growth failure occurs frequently.¹⁷³ Immune abnormalities, including low immunoglobulin levels and lymphopenia with profoundly low CD4 T-cell counts, are typically present. Individuals with PLE have a greater likelihood and increased persistence of cutaneous virally mediated processes such as warts and molluscum contagiosum.^{175,176} Emerging data suggest that lymphopenia may be present in a substantial number of patients with Fontan circulation without clinically overt PLE and that lymphopenia worsens with greater duration from the Fontan operation. The process of chronic low-level lymphocyte loss resulting from enteric lymphatic congestion and intestinal spillage may explain this finding. Gastrointestinal bleeding can also occur in PLE, with resulting anemia worsening the clinical symptoms.¹⁷⁷

The gold standard test to diagnose PLE is an elevated α -1 antitrypsin clearance in a 24-hour stool collection.¹⁷⁸ Given the challenges in collecting adequate specimen samples for this test, it is also acceptable to base a PLE diagnosis on an elevated α -1 antitrypsin level in a single stool sample together with the presence of serum hypoalbuminemia and symptoms of edema without another identified cause. Tracking serum albumin periodically may detect laboratory-based subclinical albumin loss, act as a marker for subtle deterioration of hemodynamics and strain on a congested lymphatic

system, and gauge nutritional status before the onset of full-blown clinical PLE. After a confirmed PLE diagnosis, evaluation for potentially correctable derangements in the Fontan circulation should be undertaken with appropriate assessments.

At this time, treatment of PLE is primarily symptomatic. Heart transplantation has been reported to be an effective strategy in several reports. However, the ravages of long-standing PLE can lead to chronically ill, poorly nourished, frail individuals, a common picture for those with PLE. These patients are often poor candidates for transplantation and may not survive the wait for an organ. The mainstay of symptomatic treatment is aimed at decreasing fluid overload, with aggressive diuresis often augmented by intravenous albumin replacement to replenish oncotic pressure and to drive fluid out of tissue and into the vascular space. Even after a flare is resolved, most individuals will require ongoing maintenance diuretics, and some will require ongoing long-term albumin replacement.¹⁷³ In addition to being useful for sparing renal potassium losses with diuresis, spironolactone may improve symptoms via improved natriuresis or as an anti-inflammatory agent and is often included in a maintenance regimen.^{179,180} Dietary modifications, including a high-protein, low-fat diet with a greater-than-normal proportion of medium-chain triglycerides, may be considered as an adjunct to symptomatic therapy,¹⁸¹ although diet alone is typically insufficient to overcome the process. Diarrhea may be present primarily as a result of intestinal lymphatic leak or secondary to gut microbial overgrowth, with loperamide therapy anecdotally reported as helpful.¹⁸² Intravenous immunoglobulin may be administered to raise oncotic pressure in addition to replacing chronically low serum immunoglobulin. Although there are reports of PLE remission associated with intravenous immunoglobulin administration,¹⁸³ this response to treatment is not widespread. Enteral corticosteroids, most often oral controlled-release budesonide, have been demonstrated to help maintain serum albumin levels and to decrease symptoms.^{184,185} Although helpful in select patients, steroid therapy can result in cushingoid features, hypertension, dyslipidemia, and suppression of the adrenocortical axis and may contribute to poor growth, poor tissue integrity, and bone demineralization. A strategy of a time-limited course of high-dose steroids with weaning to low maintenance levels can be considered. Phosphodiesterase-5 inhibitors can be used to lower Fontan pathway pressures and to decrease mesenteric vascular resistance, thereby potentially increasing normal lymphatic drainage and improving tissue perfusion, but their efficacy in PLE is not well established.¹⁸⁶ Exogenous unfractionated heparin, either intravenous or subcutaneous, has been reported to induce remission, perhaps in the select subset of individuals with PLE complicated by abnormal or absent cell membrane

heparin sulfate proteoglycan. A trial of heparin therapy may therefore be considered, but as with other therapies, if improvement of the disease state is not achieved in the time span of weeks to months, it should be discontinued.^{187,188} Dopamine infusion appears to induce remission of protein loss in a small series of patients bridged to transplantation.¹⁸⁹

Invasive procedures may provide the best opportunity for true disease improvement and should be considered on a case-by-case basis. Some individuals with PLE improve with transcatheter fenestration creation, which reduces impedance to forward venous flow at the expense of increased cyanosis resulting from right-to-left shunting.^{169,190} Lymphatic interventional procedures aimed at interrupting lympho-intestinal connections originating from the liver have achieved remission in a small number of patients with PLE and appear promising.¹⁶⁷ Surgical innominate vein exclusion with rerouting of the innominate vein and the thoracic ductal return directly to the low-pressure pulmonary venous atrium has resulted in remission of PLE at the expense of increased cyanosis.¹⁹¹ Lymphatic pathway drainage-altering therapies may prove to be safe and effective strategies for management of PLE as these procedures evolve and more experience is broadly achieved. Currently, such therapies are most commonly considered in the patient with PLE deemed at high risk or thought not to be a candidate for heart transplantation. To date, only orthotopic heart transplantation has been demonstrated to consistently and effectively treat PLE, with the tradeoff of a relatively high, but in most cases acceptable, risk of mortality.¹⁹² The precise timing of referral for invasive procedures such as fenestration creation, catheter-based lymphatic intervention, surgical thoracic duct rerouting, and heart transplantation remains a challenge when balanced against the potential efficacy of medical management.

Plastic Bronchitis

PB is a disease characterized by the production of thick, tenacious casts within the airway lumen. It is reported to occur in <5% of individuals with Fontan circulation, although the prevalence of subclinical PB may be higher.^{166,193} It confers significant morbidity, most often chronic cough and hypoxemia, with expectoration of proteinaceous casts and increased risk of mortality.¹⁹⁴ Fontan-associated PB is believed to be caused by the spillage of protein-rich lymph through lymphatic-to-bronchial communications.^{195–197} Both PLE and PB may be considered part of the clinical spectrum of lymphatic insufficiency associated with chronically elevated venous pressure. Lymphatic system overflow and congestion are in search of natural decompression. In select patients, perhaps related to an individual's unique lymphatic vascular architecture, lymph decompresses into the airway lumen, causing PB. In PB, an airway inflammatory re-

action, precipitated either via a concurrent respiratory infection or secondary to individual abnormalities of inflammatory response, results in fibrin cross-linking within the lymph, causing it to coagulate into a rubbery, solid cast.¹⁹⁸ Bronchial casts can partially or completely obstruct the airway in which it forms and in severe cases may lead to severe hypoxemia, asphyxiation, and death.

PB is diagnosed after production of an airway cast either by patient expectoration or via bronchoscopic removal. Although not diagnostic, symptoms of chronic cough, wheezing, or respiratory symptoms not responsive to bronchodilator therapy in a patient with Fontan circulation may prompt consideration of possible PB. Imaging with MRI T2-weighted techniques that allow visualization of high-water-content structures may help define patterns of lymphatic vascular architecture within the chest or abdomen either before or shortly after the Fontan operation that may be more highly associated with PB or PLE.¹⁹⁹

Initial treatment should target symptomatic therapies aimed at airway clearance. However, a vigorous investigation of the state of the Fontan circulation is warranted to rule out cardiovascular anatomic considerations. Similar to PLE, pulmonary vasodilator therapy and diuretic treatment, particularly with aldosterone inhibition, can be helpful.²⁰⁰ Treatment with bronchodilators and aggressive chest physiotherapy should be started for any patient regularly producing casts.^{200,201} Anti-inflammatory therapy with inhaled steroids may be considered, although the effectiveness of this therapy is unclear.²⁰² Therapy with mucolytics such as dornase- α or N-acetylcysteine has been reported to be efficacious in improving cast mobilization in small series and may be considered.²⁰¹ Nebulized and inhaled tissue plasminogen activator therapy can be very effective in clearing obstructive airway material in acutely symptomatic individuals because it targets the fibrin cross-links that lead to cast formation.^{203,204} Long-term therapy with tissue plasminogen activator for cast prevention has also been reported.²⁰⁰ In addition to medical therapy, dietary modifications that decrease lymphatic flow such as a low-fat diet have been associated with symptomatic improvement or resolution in some patients.²⁰⁵ Any significant hypoxemia, respiratory distress, or shock in a patient with PB should be treated with urgent bronchoscopy with the goal of clearing the obstructed airway.²⁰⁶ Until recently, the most effective therapy for PB was heart transplantation and elimination of the Fontan circulation. Survival after heart transplantation for PB is relatively favorable and commonly results in disease remission.²⁰⁷ Currently, catheter-based intervention to embolize and eliminate lympho-bronchial airway communications has resulted in durable remission of the disease with excellent outcomes, including low morbidity and mortality.¹⁹⁷ Catheter-based occlusion of lymphatic leaks in PB can be lifesaving; however, such

Table 5. List of Management Strategies and Potential Treatments for PLE and PB After the Fontan Operation

Condition	Strategy	Objective
Diagnostic evaluation		
PLE and PB	Cardiac imaging (echocardiography, MRI, or CT) and cardiac catheterization	Identify anatomic problems and measure hemodynamics (eg, cardiac output, central venous pressure)
PLE and PB	Lymphatic imaging* (T2-weighted MRI, lymphangiography)	Characterize state of lymphatic vasculature
		Identify possible decompression channels into gut or airway lumen
PLE and PB	ECG and Holter monitoring	Identify hemodynamically important arrhythmia
Medical management		
PLE and PB	Diuretics	Reduce venous and lymphatic congestion
		Treat peripheral edema and ascites (PLE)
PLE and PB	Aldosterone inhibition	May have direct effects on lymphatic decongestion
		May improve ventricular function and treat heart failure
PLE and PB	Pulmonary vasodilators (phosphodiesterase-5 inhibitors, endothelin-1 inhibitors)	Lower impedance to forward systemic venous flow through the pulmonary vascular circuit, thereby reducing lymphatic congestion
PLE	Heparin	Reduce intestinal membrane permeability
		Reduce intestinal inflammation
PLE	Corticosteroid (oral controlled-release budesonide)	Reduce intestinal inflammation and stabilize cell membranes
		Restore integrity to intestinal permeability barrier
PB	Aerosolized tissue plasminogen activator	Break down bronchial casts to ease expectoration or to reduce production
Interventional/surgical management		
PB	Thoracic duct ligation	Redirect lymphatic drainage away from airway lumen decompression channels
PLE and PB	Cardiac pacing	Maintain appropriate heart rate and cardiac output in conditions of heart block or sick sinus node disease
PLE and PB	Fontan baffle fenestration	Lower impedance to forward systemic venous flow
		May increase cardiac output and oxygen delivery but at expense of cyanosis
PLE and PB	Catheter-based lymphatic intervention	Identify pathways of lymphatic decompression into gut lumen or airway and allow potential occlusion of abnormal decompression channels

(Continued)

Table 5. Continued

Condition	Strategy	Objective
PLE	Surgical rerouting of innominate vein/thoracic duct to left atrium	Eliminate impedance to lymphatic drainage
		Decompress lymphatic system into low-pressure atrium but at the expense of cyanosis
PLE and PB	Fontan takedown to Glenn or shunt state	Alter hemodynamics to reduce lower body systemic venous pressure and to reduce lymphatic congestion
PLE and PB	Heart transplantation	Alter hemodynamics by reducing systemic venous hypertension and improving cardiac output

CT indicates computed tomography; MRI, magnetic resonance imaging; PB, plastic bronchitis; and PLE, protein-losing enteropathy.

*Evolving technology with limited application at this point but with anticipated expansion of use.

interventions do not influence the underlying deleterious pathophysiology of the Fontan circulation. Therapies targeting venous and lymphatic decongestion with diuretics and pulmonary vasodilators are often still necessary to optimize the circulation in hopes of preventing recurrence. Table 5 lists the various management and treatment strategies for PLE and PB. Key take-away points for PLE and PB are listed in Table 6.

LIVER FIBROSIS AND CIRRHOSIS

Liver fibrosis and cirrhosis are growing concerns for the patient with Fontan circulation. Liver injury resulting from cardiac dysfunction has long been recognized, with the earliest documentation occurring in 1833.²⁰⁸

Cardiac failure with circulatory congestion typically manifests as centrilobular hepatic congestion and necrosis, with activation of inflammation in some cases.²⁰⁹ Over time, particularly if within the context of repeated insults, fibrosis may progress to cardiac cirrhosis. Liver involvement in patients with Fontan circulation was brought into prominence after the description of chronic passive congestion, cardiac cirrhosis, hepatocellular carcinoma (HCC), and hepatic adenoma in a series of 9 postmortem patients, all of whom had Fontan-associated liver disease (FALD).²¹⁰ Abnormalities of the liver

Table 6. Key Points: PLE and PB

PLE and PB are clinical manifestations of chronic venous congestion-induced lymphatic insufficiency with a host of potentially life-threatening consequences.
PLE may lead to edema and ascites, growth failure, decreased bone density, coagulation abnormalities, and lymphopenia and results in increased risk of death.
Treatment strategies for PLE and PB include symptomatic management, attempts at improvement of circulatory hemodynamics, manipulation of the lymphatic system, and cardiac transplantation.

PB indicates plastic bronchitis; and PLE, protein-losing enteropathy.

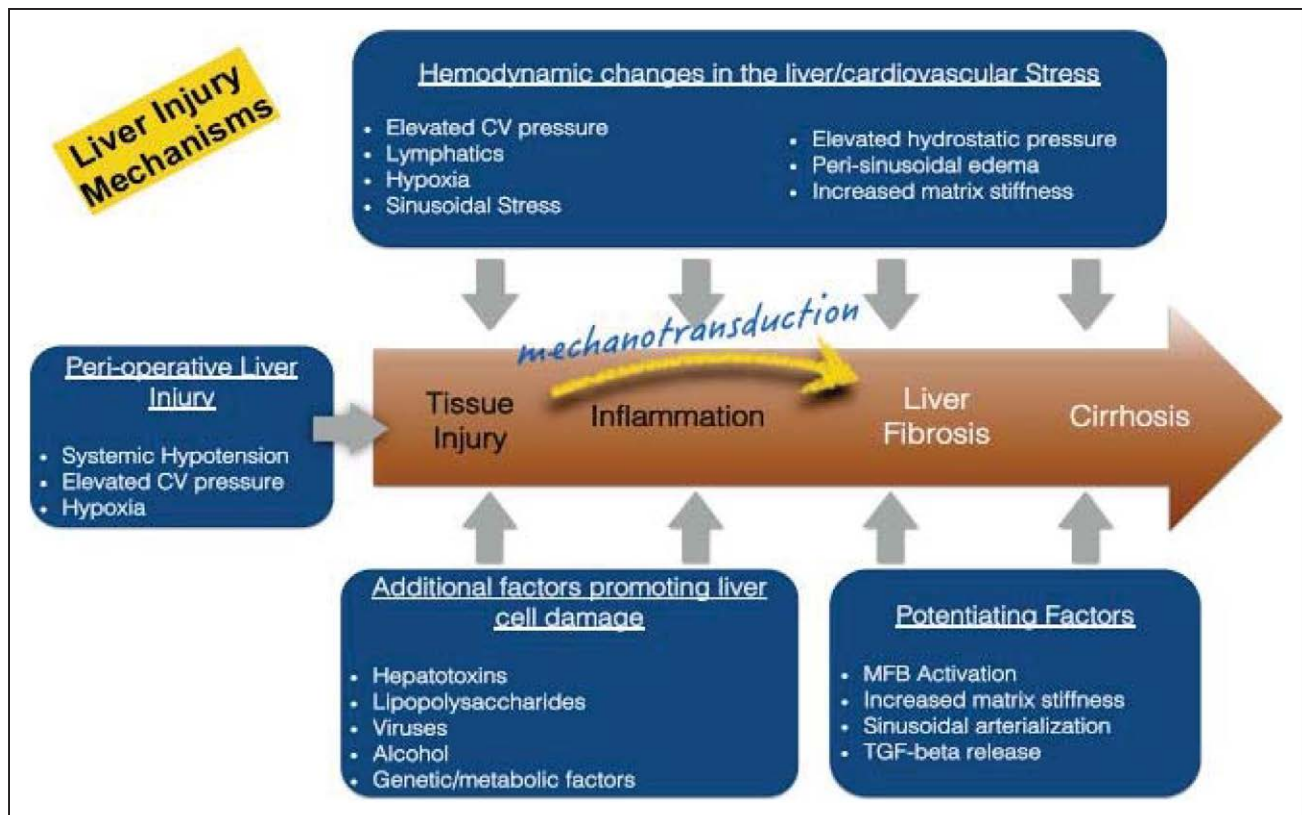


Figure 4. Potential mechanisms of liver injury associated with the Fontan circulation.

Hydrodynamic stressors include elevated central venous (CV) pressure, causing sinusoidal stress and dilation, and abnormal lymphatic load. Perioperative factors around the time of Fontan surgery include a sudden increase in venous pressure and any additional perioperative hypoxia. Myofibroblast activation (MFB) occurs as a result of sinusoidal stretch, and hypoxia signaling molecules such as transforming growth factor (TGF)- β and hypoxia-inducible factor 1 act as promoters for profibrotic signaling.

can be seen early within the first 5 years after Fontan operation.²¹¹ Findings from elective surveillance liver biopsy indicate that all patients with Fontan circulation have some degree of liver fibrosis present and that the severity is related mostly to increasing age at biopsy and increasing time from Fontan operation.²¹²

Pathogenesis

FALD is in part, if not predominantly, related to hepatic flow characteristics unique to the Fontan circulation.²¹³ Infradiaphragmatic hemodynamics change profoundly from the moment the Fontan circulation is installed. Venous pressures rise; lymphatic overflow and congestion ensue; and cardiac output decreases from baseline. Exertional stress exaggerates these phenomena with precipitous increases in central venous pressures to levels ≥ 25 mmHg when the individual is awake and active.^{214,215} The earliest manifestations of these profound hemodynamic changes are reflected in the universal acute increase in liver stiffness. Hepatic stiffness persists during late follow-up in the vast majority.²¹⁶ The high central venous pressures mimic hepatic venous outlet obstruction, giving rise to arterialization of hepatic blood flow through the so-called hepatic arterial buffer response.

The arterial buffer response has long been recognized as an intricate regulatory mechanism through which overall hepatic blood inflow is maintained through autoregulation of the 2 hepatic inflows: hepatic arterial flow (normally contributing $\geq 25\%$ of inflow) and portal venous flow (normally $\approx 75\%$ of hepatic inflow).^{217,218} Hypervascular nodules within the body of the liver are seen frequently during late follow-up but do not necessarily correlate with worse FALD.²¹⁹ Increased volume of hepatic venous return is associated with a greater degree of fibrosis.²²⁰ This may be a consequence of hepatic arterialization associated with worsening fibrosis, thus leading to increased venous return.

A number of potential mechanisms may contribute to the development of this unique condition, FALD.²²¹ Figure 4 demonstrates some of the mechanisms for the development of liver fibrosis in the patient with Fontan circulation.

Manifestations of FALD

Biological Parameters

Mild elevations in liver enzymes such as ALT (alanine aminotransferase) and AST (aspartate aminotransferase) are very common soon after the Fontan

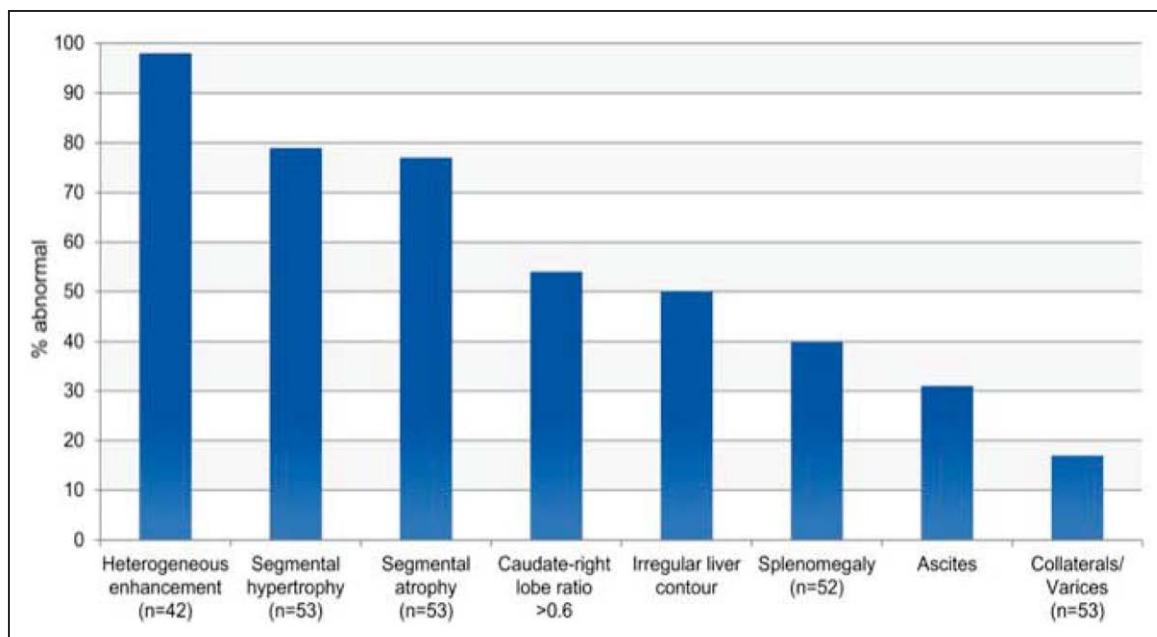


Figure 5. Findings on abdominal imaging (n=54) in the adult with Fontan circulation.

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operation without any major ostensible evidence of clinical impact on hepatic synthetic or metabolic dysfunction. In a review of late follow-up, 84% of patients with Fontan circulation demonstrated at least 1 serological liver abnormality, elevated GGT (γ -glutamyl transferase) being the most common and the dominant abnormality in 70% of these cases.²²² Of note, in addition to the liver, increased GGT may reflect overall antioxidant inadequacy and increased oxidative stress and may prove to be a biomarker of general instability in cardiovascular disease.²²³ Over time, there is progressive elevation of predominantly GGT and bilirubin. GGT, for example, increases in 80% of individuals over a 4-year follow-up period. Total bilirubin levels also increase with age. A rise in prothrombin time and international normalized ratio may be seen, as well as a decrease in platelet count, consistent with increased portal venous pressure and splenic consumption.

Imaging Features

Abdominal imaging, in particular as patients transition into the adolescent and adult years, is important in the patient with Fontan circulation.²²⁴ In a study of adults at a median of 26 years of age, hepatic imaging was abnormal in all patients, with a wide spectrum of findings (Figure 5).²²⁵ Ultrasound is relatively insensitive for detecting fibrotic changes, although it is able to provide hemodynamic information and gross structural information, which can be important in the serial evaluation of patients. Ultrasound identifies increased liver volumes in the early phases of congestive hep-

topathy or diminished volumes associated with relative caudate lobe hypertrophy as fibrosis progresses to cirrhosis. As central venous pressures or trans-hepatic resistance increases, ultrasound can characterize a number of important findings: the presence or absence of anterograde portal venous flow, enlargement of the hepatic artery as arterIALIZATION of hepatic flow begins, and changes in celiac and mesenteric flow resistances from Doppler tracings.

Experience is growing in defining the utility of elastography in the evaluation of the degree of FALD present.²²⁶ This promises to be a valuable tool for serial evaluation of the progression of hepatic stiffness over time.²²⁷ Acoustic tissue imaging with application of elastography methodology provides additional ultrastructural information on liver stiffness.²²⁸ Shear-wave velocity in patients with Fontan circulation is $\approx 2.2 \pm 0.38$ m/s compared with a normal value of 1.1 ± 0.29 m/s. MRI liver elastography is also available and can provide detailed characterization of liver stiffness and additional structural information.²²⁹

Liver stiffness reflects the combination of liver fibrosis, venous congestion, and altered liver compliance patterns, all of which are present in FALD. Hence, distinguishing between these contributing factors can be a challenge.²³⁰ Hydration status influenced elastography measures of liver stiffness in a porcine model.²³¹ Nevertheless, the composite measure of both processes, namely hepatic vascular congestion and liver tissue scarring, may prove to be of clinical value in the longitudinal characterization of FALD.

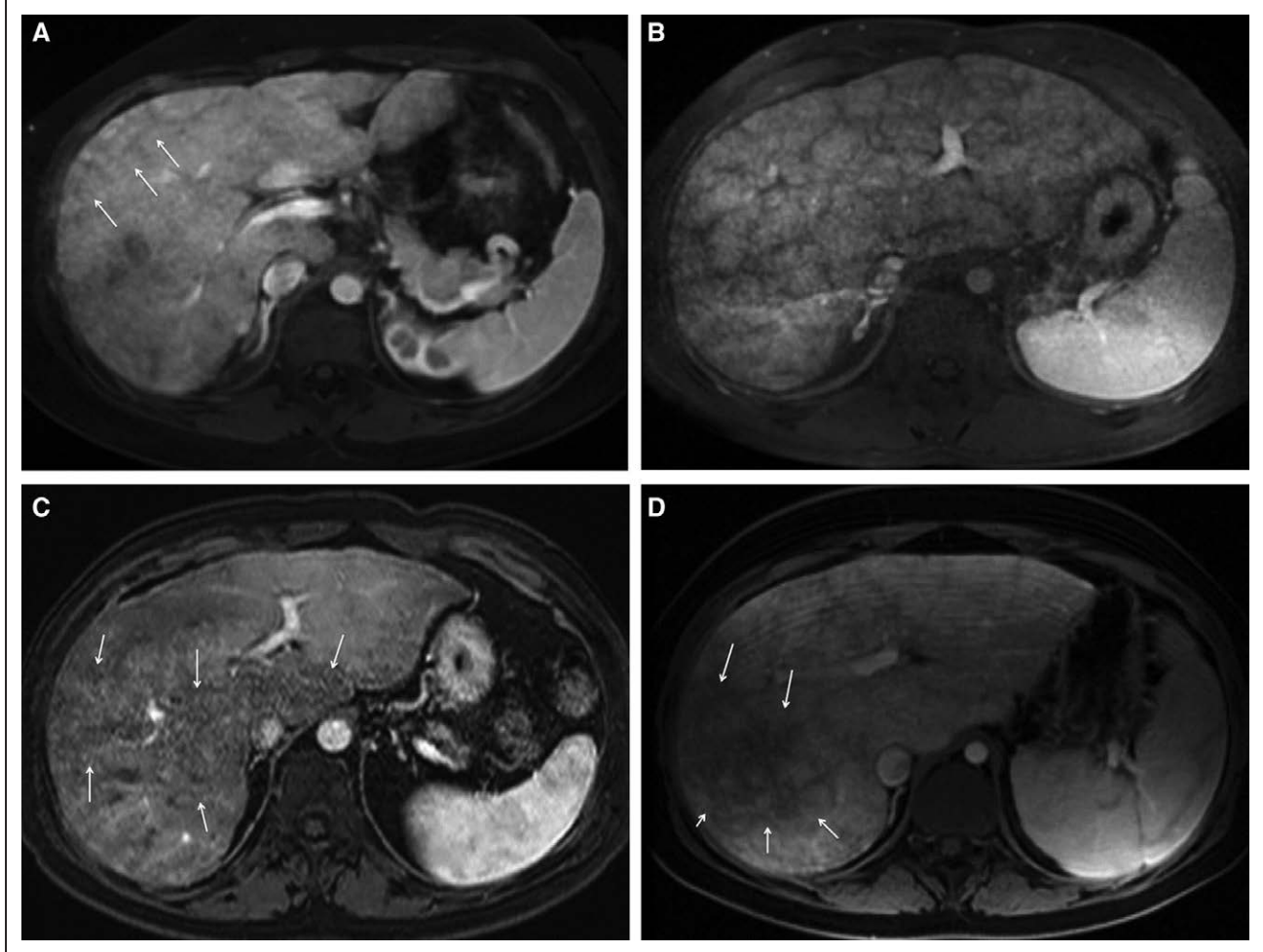


Figure 6. Abnormal magnetic resonance imaging (MRI) liver enhancement patterns.

A, Portal venous phase after contrast MRI shows relatively mild peripheral reticular enhancement (arrows). **B**, Diffuse peripheral and central reticular enhancement pattern seen in more advanced congestive hepatopathy. **C**, Poorly defined areas of “cloud-like” enhancement (arrows) in the right hepatic lobe with relative sparing of the left lobe. **D**, Severe enhancement abnormality with larger areas of focally diminished enhancement in the right hepatic lobe (arrows), suggesting greater congestion combined with fibrosis in this area.

Computed tomography and MRI provide complementary, detailed, and accurate information about liver morphology and structure and vascular enhancement patterns.^{232,233} The liver is imaged in multiple consecutive time phases after contrast injection. This yields information on early enhancement in the arterial, portal venous, and late venous phases. Enhancement patterns are demonstrated in Figure 6. Enhancement characteristics of hepatic nodules are particularly useful in advanced cross-sectional imaging. Arterially hyperenhancing nodules, for example, usually represent focal nodular hyperplasia. On the other hand, HCC appears to be hypoenhanced in the hepatic phase; that is, late at ≈ 20 minutes after contrast injection. New and exciting trends in MRI that offer promising prospects to further liver characterization in FALD include T1 and T2 imaging, diffusion-weighted imaging, and metabolic imaging that incorporates hepatocellular function such as gadonexate disodium hepatocyte-specific agents.²³⁴

Histological Changes

In a report of liver biopsies performed as part of a surveillance program in 67 patients with Fontan circulation at mean age of 17 ± 4.5 years, some degree of liver fibrosis and scarring was seen in all.²¹² A wide spectrum of histological changes is associated with FALD (Table 7). Various degrees of liver fibrosis can be seen on Masson trichrome staining (Figure 7). A variety of liver fibrosis scoring systems exist, developed primarily to grade various liver conditions unrelated to the unique pathophysiology of the Fontan circulation. Recently, a more objective quantification of fibrotic load that uses Sirius red staining of collagen has been proposed. This approach is promising in that it may help standardization of histological grading, which will allow comparative analyses to be applied more widely (Figure 8).²³⁵ Liver fibrosis is known to be reversible in some instances. It is unlikely, however, when greater degrees of collagen cross-linkage have occurred; that is, a maturation and strengthening of the collagen

Table 7. Spectrum of Histological Findings on Liver Biopsy in the Patient With Fontan Circulation

Histological Features	Prevalence of Feature, %
Any bridging fibrosis	45
Central vein to vein bridging fibrosis	30
Central vein to portal tract fibrosis	37
Portal to portal tract fibrosis	10
Bile ductular reaction	24
Cholestasis	1
Lobular inflammation	1
Portal inflammation	15
Hepatocellular damage/necrosis	4
Steatosis	7

matrix that can be detected histologically by orcein positivity. The notion of discovering mechanisms for impairing or halting the progression of histological change in FALD or the potential for reverse remodeling when hemodynamic normality has been restored is of great interest.

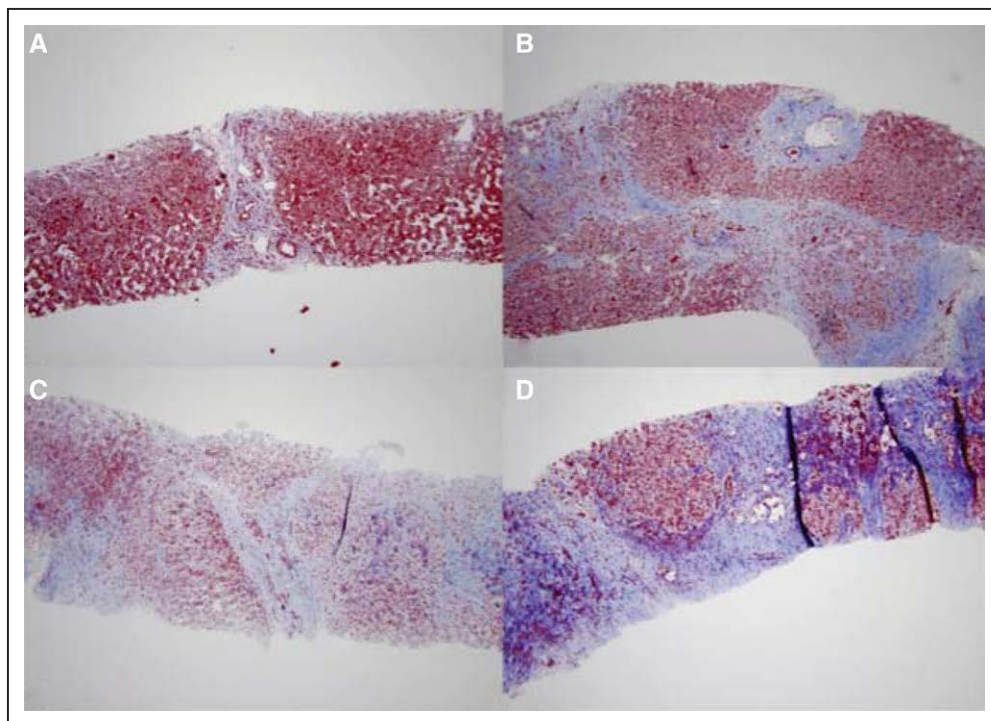
Hepatocellular Carcinoma

The most extreme manifestation of liver injury associated with the Fontan circulation is the development of HCC. This phenomenon occurs in addition to an

overall increased risk of cancer in general in adult patients with repaired complex CHD.²³⁶ In a report of 33 patients diagnosed with HCC after a Fontan operation at a median of 30 years of age (range, 12–52 years), the prevalence was documented to be $\approx 1.3\%$.²³⁷ The prognosis, similar to HCC in other contexts, remains quite poor, with more than half of affected patients dying within 2 years of diagnosis. Those who are detected while asymptomatic appear to have a better prognosis because their treatment options are broader. The association of HCC with cirrhosis and varying degrees of fibrosis needs confirmation in patients with Fontan circulation. The question of whether HCC risk is increased with increasing severity of fibrosis in FALD or whether other factors come into play is unclear. HCC has been observed in patients as young as 12 years of age. Advanced treatment strategies include local resection, chemoembolization, radiofrequency ablation, heart-liver transplantation, or a palliative care approach.²³⁸

Clinical Impact of FALD

Liver disease in patients with Fontan circulation is most frequently indolent. Although fortunately quite rare, decompensated cirrhosis may indeed occur with manifestations of encephalopathy, variceal bleed, and portal gastropathy and enteropathy.²³⁹ Most often, however, there is a variable degree of fibrosis and compensated

**Figure 7.** Masson trichrome staining of liver specimens from patients with Fontan circulation.

A, Mild (stage 1 of 5) fibrosis surrounding a portal tract. Mild sinusoidal dilation is also seen within the hepatic lobule (Masson trichrome stain). **B**, More extensive (stage 3 of 5) fibrosis with broad septa throughout the biopsy core (Masson trichrome stain). **C**, Advanced (stage 4 of 5) portal fibrosis with septa formation and evolving regenerative nodule (Masson trichrome stain). **D**, Thick bands of fibrosis and regenerative nodules consistent with cirrhosis (stage 5 of 5; Masson trichrome stain). Reprinted from Wu et al²²⁵ with permission from The American Association for Thoracic Surgery. Copyright © 2016, The American Association for Thoracic Surgery.

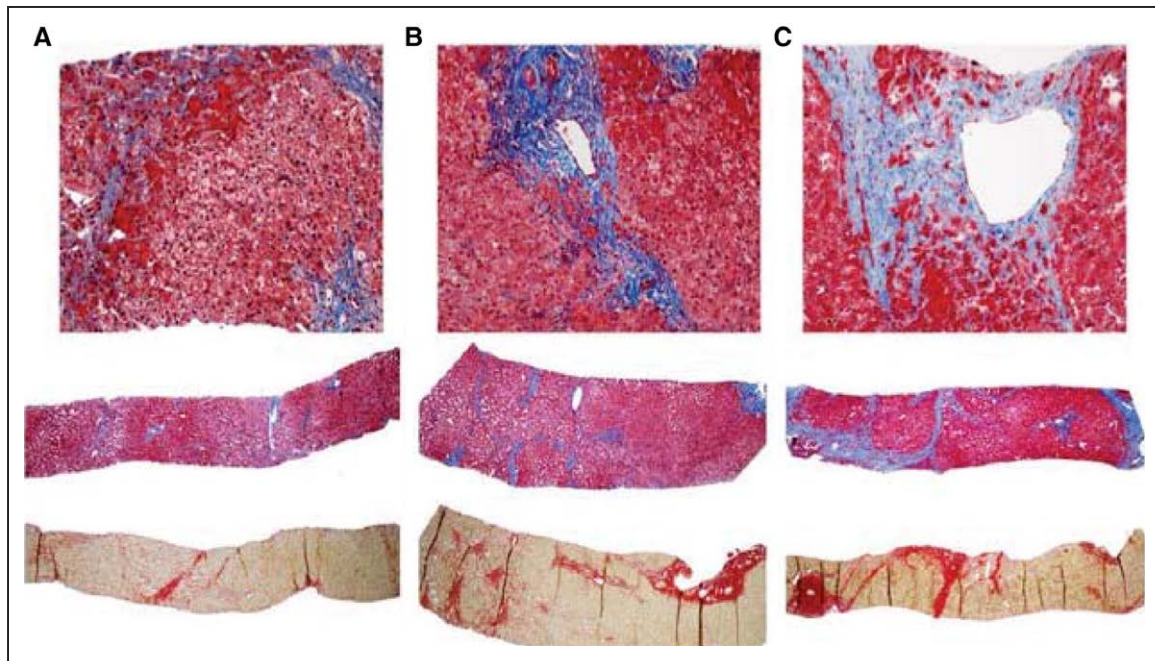


Figure 8. Three examples of histopathological fibrosis scoring of Masson trichrome stains (top 2 images, ≈ 200 and ≈ 40 Å) and quantitative Sirius red percent collagen deposition (CD; bottom, ≈ 40 Å).

A, Case shows mild to moderate central vein expansion and mild delicate perisinusoidal fibrosis (congestive hepatic fibrosis score [CHFS], 2A; sinusoidal fibrosis [SF], 2) and minimal portal fibrosis (METAVIR histologic score, F1) with less percent CD than average for all cases at 18.2%. **B**, In comparison, this case shows more portal fibrosis with bridging (METAVIR histologic score, F3) with about the same amount of centrilobular fibrosis (CHFS, 2B; SF, 2). The percent CD is much higher at 37.3%. **C**, This case shows pericentral scarring with portal-portal, central-central, and portal-central bridging fibrosis (METAVIR histologic score, F3; CHFS, 3) with minimal sinusoidal dilation and high percent CD at 41.2%. Reprinted from Surrey et al²³⁵ with permission from Elsevier. Copyright © 2016, Elsevier.

cirrhosis. An uncoupling exists between structural/morphological features observed on imaging and histology and liver functional status as defined by synthetic function of the liver. Therefore, imaging features do not necessarily predict immediate clinical outcomes. Thus, clinical decision-making is difficult because critical or functional reserve of the liver cannot currently be accurately ascertained and may be quite satisfactory despite imaging assessment and histological findings. This lack of data becomes especially relevant when major surgical procedures such as revision surgery to the Fontan circuit or cardiac transplantation are being planned. Under these circumstances, clinicians lean heavily on blunt tools that do not directly predict surgical outcomes and are not specific to FALD. These tools may include, for example, the VAST (varices, ascites, splenomegaly, or thrombocytopenia) score, the MELD-XI (Model for End-Stage Liver Disease Excluding INR [international normalized ratio]) score, the Child-Turcotte-Pugh score, or liver damage scores.^{240–242} More work is required in this area to develop Fontan circulation–specific tools to predict the impact of FALD on surgical outcomes.

Proposed Therapeutic Approaches

All patients with Fontan circulation should undergo regular hepatic screening with assessments that are age dependent and may include laboratory serum screening

and imaging (see the Surveillance Strategies: Proposed Schema of How to Monitor the Patient With Fontan Circulation section). Serum α -fetoprotein is a valuable early biomarker for conversion from liver fibrosis to carcinoma and may be incorporated into a regular screening scheme in older patients. A marked or sudden increase in abnormalities of liver parameters should prompt hemodynamic assessment. All potentially important hemodynamic derangements such as significant AVV regurgitation, pathway obstruction, diastolic dysfunction, pulmonary vascular disease, or aortic arch obstruction should be carefully evaluated for possible interventional approaches. Creative surgical strategies such as hepatic vein exclusion, although potentially of short-term promise, are hitherto unproven as a good long-term tactic and may carry adverse consequences such as cyanosis. The use of pharmacological agents such as pulmonary vasodilator therapy, vascular decongestant agents such as diuretics, or antifibrotic therapies such as aldosterone inhibition or angiotensin-converting enzyme (ACE) inhibition is theoretically of potential benefit but as of yet is unproven to prevent the development or to halt the progression of FALD. Considering the ubiquity of FALD, evidence for progression with age, and overall growing concern, study of these strategies is warranted.

General liver preventive health should be advised to all patients with Fontan circulation. These include

Table 8. Key Points: Liver Disease

Variable degrees of hepatomegaly, hepatic congestion, and liver fibrosis are common and may lead to cirrhosis, with elevations of bilirubin and liver enzymes typical.
Patients with Fontan circulation should be counseled about avoiding hepatotoxins and adverse lifestyle, which may exacerbate the likelihood of liver disease.
An increased risk of late hepatocellular carcinoma is recognized, indicating the importance of long-term liver surveillance.

avoidance of liver toxins when possible, including alcohol and high-dose acetaminophen. The risks and benefits of potential hepatotoxic drugs such as amiodarone should be weighed carefully. Patients with Fontan circulation should be strongly advised to be vaccinated for hepatitis B, to avoid smoking, and to prevent overweight/obesity.²⁴³ End-stage hepatic disease with liver cirrhosis is generally associated with diminished systemic vascular resistance, although this has not been extensively studied in the Fontan circulation. Nevertheless, agents that lower systemic vascular resistance (eg, milrinone, dobutamine) should be used with caution because they may be ineffective or potentially harmful in the critically ill patient with cirrhosis. Liver cirrhosis and end-stage disease may profoundly influence liver performance, leading to an increase in serum ammonia and a decrease in circulating albumin because hepatic clearance and synthetic function are affected. Key take-away points for FALD are listed in Table 8.

RENAL DYSFUNCTION

The kidneys receive a substantial proportion ($\approx 20\%$ – 25%) of cardiac output at rest. Therefore, the circulatory abnormalities common in the patient with Fontan circulation will eventually affect the renal system.²⁴⁴ Other factors may contribute to renal dysfunction in patients with Fontan circulation. These may accrue in a cumulative manner and include multiple exposures to nephrotoxic medications, cardiopulmonary bypass runs (inflammation), intravenous iodinated contrast agents, and long-standing cyanosis resulting in cyanotic nephropathy.^{244–246} Cardiac surgery–associated acute kidney injury is well documented in children and adults after Fontan palliation and revision surgery and can be secondary to prolonged cardiopulmonary bypass times, resulting in hemoglobinuria, perioperative low cardiac output, and systemic hypotension.^{247–249} In adults who underwent Fontan revision, a higher preoperative creatinine level has been associated with a greater risk of decline in renal function postoperatively.²⁵⁰ Postoperative acute kidney injury occurs in up to 40% of children undergoing Fontan surgery and is associated with longer intensive care unit and overall hospital stay.²⁵¹ However, the long-term effects of postoperative acute kidney injury on renal function later in life remain unclear.

Chronic kidney disease or renal dysfunction is evident after the Fontan operation once patients reach adolescence and early adulthood, and it often goes undetected. Measured renal function (glomerular filtration rate), as opposed to estimated glomerular filtration rate (eGFR), reveals abnormality in nearly 50%, with one-third of patients >18 years of age demonstrating albuminuria.²⁵² In a younger cohort of children, abnormal renal function detected from eGFR as opposed to direct measures is evident in 10% of patients, which may likely reflect an underestimation of the degree of dysfunction.²⁵³

Studies focusing on long-term renal function and biomarkers for surveillance in the patient with Fontan circulation are limited.^{250,253–257} Consensus is lacking on which circulating and urine biomarkers are optimal to evaluate renal dysfunction as part of routine clinical surveillance. Decreased eGFR is associated with a poorer prognosis in the general adult CHD population.²⁴⁴ The presence of chronic kidney disease is often calculated with the MDRD (Modification of Diet in Renal Disease) equation,²⁵⁸ the Cockcroft-Gault equation,²⁵⁹ or the Chronic Kidney Disease Epidemiology Collaboration formula.²⁶⁰ The MDRD equation is well validated and adjusts for age-related changes in creatinine and cystatin C, with an eGFR >90 mL \cdot min $^{-1}$ \cdot 1.73 m $^{-2}$ considered normal for adults.²⁵⁸ Conversely, the Schwartz and CKiD (Chronic Kidney Disease in Children) formulas are used for children <18 years of age.²⁶¹ Cystatin C, a protein encoded by CST3, is gaining recognition as a biomarker for renal and cardiovascular disease.²⁵⁶ Equations that include measurements of cystatin C may better predict outcomes compared with creatinine-based eGFR because of the reduced muscle mass noted in the Fontan population.^{253,256} However, further studies are needed to assess the accuracy and prognostic significance of different eGFRs in the Fontan population, especially in the presence of significant liver disease, which may alter levels of cystatin C.

Proteinuria and microalbuminuria are well-recognized markers of chronic glomerular injury. An increased prevalence of proteinuria and microalbuminuria is reported in cyanotic CHD.^{262,263} The prevalence is 10% to 37% in patients with Fontan circulation.^{6,255,264} Despite the lack of evidence supporting the use of ACE inhibitors in patients with Fontan circulation, some investigators noted the use of ACE inhibitors to be associated with a possible renal protective effect, with no patients with proteinuria among those on ACE inhibitors compared with 43% with proteinuria in those patients not on ACE inhibitors.²⁵⁴ Whether proteinuria and microalbuminuria are associated with adverse outcomes, as in other populations, remains unclear.

The renal resistive index is an area of growing interest as a marker for heart failure severity and end-organ damage in adult CHD.^{265,266} This sonographic index is

Table 9. Key Points: Renal Dysfunction

Renal dysfunction is present in at least 10% of younger patients with Fontan circulation, with increasing prevalence in adolescence and adulthood.
Decreased GFR, proteinuria, and albuminuria appear to develop and progress over time.
Impaired renal function may often go unnoticed and should be evaluated in the older patient, in particular before invasive procedures or before anesthesia is administered.

GFR indicates glomerular filtration rate.

used to assess renal arterial disease by measuring the peak systolic and end-diastolic velocity with a calculated index normal value of 0.60.²⁶⁶ A study identified that a high renal resistive index (≥ 0.81) reflects heart failure severity, hepatic and renal function (24-hour creatine clearance), glucose intolerance, and overall mortality in 280 patients with Fontan circulation.²⁶⁶ This noninvasively measured renal resistive index may be a useful biomarker to assess potential end-organ sequelae associated with Fontan physiology.

Serum biomarkers such as creatinine, blood urea nitrogen, and cystatin C are the measures that can be used for regular renal surveillance. Other studies have reported the use of urine biomarkers such as albumin-to-creatinine ratio, KIM-1 (kidney injury molecule 1), NGAL (neutrophil gelatinase-associated lipocalin), and NAG (N-acetyl-glucosaminidase), which may be useful to further distinguish the type of renal dysfunction such as tubulointerstitial injury.^{256,267} With the increased incidence of renal dysfunction and its unclear impact later in life, monitoring for renal dysfunction through assessments such as blood laboratory evaluations (eg, cystatin C) and assessments for proteinuria in early adolescence is reasonable, with nephrology consultation in the face of early evidence of chronic kidney disease.

Renal protective measures should be advised for all patients with Fontan circulation. These include recognition of the importance of staying hydrated, keeping blood pressure and blood sugar levels under control, avoiding smoking and excessive sodium intake, and preventing overweight/obesity. If chronic kidney disease develops, avoiding prolonged use of nonsteroidal anti-inflammatory drugs and minimizing contrast dye exposure are required because they can further impair renal function. Key take-away points for renal dysfunction are listed in Table 9.

SOMATIC GROWTH, BONE HEALTH, AND PHYSICAL DEVELOPMENT

The musculoskeletal system is crucially important to long-term health in children who have undergone the Fontan operation. Although many patients are within normal limits for height and weight, deficits in linear height have been associated with diminished function-

al health status.²⁶⁸ Abnormalities in body composition, bone structure, and growth factors are present in children and adolescents after the Fontan operation.^{269–271} Little is known about the specific pathophysiological mechanism of how Fontan circulatory physiology affects this important and dynamic system, on top of what may be an abnormal substrate either from a genetic blueprint perspective or as additive to early factors present before the Fontan operation.

Lean muscle mass is known to be abnormally low in children and adolescents with Fontan physiology and is associated with decreased exercise performance.^{270,272} Vitamin D levels are also abnormally low, and in those with vitamin D deficiency, deficits in lean muscle mass are more profound.^{270,273} It is not known whether there is something unique about the Fontan circulation that affects the absorption of vitamin D, although one may speculate that alterations in gut circulation may affect essential element and vitamin absorption. Differences in renal perfusion and microcirculation that are present in the Fontan circulation may also affect vitamin D production in the kidney. Understanding the impact of the Fontan operation on vitamin D levels may have implications for simple therapies such as the timing of supplementation to help promote long-term muscle and bone development and to improve strength and physical functioning.

Normal development of cortical bone structure in childhood and adolescence is critical to the lifelong health of the musculoskeletal system. In healthy children, cortical bone thickness increases in association with the increase in lean muscle mass that occurs during normal growth and pubertal development.^{274,275} Any reduction in the development of cortical bone thickness places children at risk for lifelong osteopenia and associated complications such as an increased likelihood of bone fracture.²⁷⁶ Although linear growth delay has been well described in children who have undergone Fontan palliation,^{268,277,278} bone structure itself is abnormal in children and adolescents with Fontan physiology.²⁶⁹ In a cohort of 43 patients, virtually all measures of bone health were below the mean value for an age- and sex-matched control cohort. The deficits in periosteal circumference and cortical area persisted even after adjustment for muscle mass deficits, suggesting that altered bone structure, although exacerbated by muscle deficits, is itself a consequence of the Fontan circulation. In a physiological milieu characterized by low cardiac output and elevated central venous pressure, it may not be surprising that bone structure is abnormal, but a recognition of the timing of the abnormality would provide an opportunity to design an intervention to increase bone health before bone structure is set in late adolescence.

In a large series, the bone health of 210 patients with Fontan circulation presenting to a multidisciplinary spe-

cialized Fontan clinic was characterized.²⁷⁹ The mean age was 11.8±4.8 years; 90 were female; and 25 had evidence of PLE. Patients underwent dual-energy x-ray absorptiometry (Hologic, Inc, Bedford, MA) for evaluation of bone mineral density and laboratory blood tests to measure parathyroid hormone and vitamin D 25-OH levels. For patients with Fontan circulation without PLE, the mean height z score, bone mineral density z scores for height-adjusted whole body less head, and bone mineral density z scores for height-adjusted lumbar spine were all significantly lower than normal ($z=-0.65$, -1.18 , and -0.22 , respectively). For those 25 patients with PLE, z score values were even more dramatically diminished ($z=-1.99$, -2.4 , and -1.29 , respectively). Furthermore, parathyroid hormone values were abnormally elevated (>52 pg/mL) in 48% of subjects, and vitamin D was profoundly low (<20 ng/mL) in 15%. Height-adjusted whole body less head bone mineral density z scores correlated inversely with parathyroid hormone levels ($P<0.01$). These findings suggest that secondary hyperparathyroidism is common in children with Fontan circulation, perhaps related to the postulated alterations in calcium metabolism resulting from changes in renal perfusion or poor absorption at the gut level. Secondary hyperparathyroidism is a factor that may contribute to bone demineralization and poor growth in children with Fontan circulation. As is now recognized in adults with heart failure, parathyroid hormone itself may prove to be a valuable biomarker of heart failure and may be helpful in prognosticating outcomes in those with Fontan circulation.²⁸⁰

An additional finding of importance in the Fontan population is the relationship between the mediators of growth hormone and the degree of heart failure as characterized by circulating levels of serum BNP (brain natriuretic peptide).²⁷¹ In a cohort of 41 children and young adults with Fontan physiology, a significant negative association was noted between both IGF-1 (insulin-like growth factor 1) and IGFBP-3 (insulin-like growth factor binding protein 3) and serum BNP level. A downregulation of growth in the setting of heart failure is a relationship that might be expected. The relationship also opens up the possibility of theoretically treating heart failure and optimizing Fontan circulatory hemodynamics to reverse the decline in growth factors with a goal of creating healthier bones and improving longitudinal growth. Further understanding of the temporal changes of these factors in relation to the Fontan operation itself could provide an opportunity to intervene earlier to promote both bone health and long-term linear growth.

Obesity in the Patient With Fontan Circulation

The longitudinal development of obesity is similar to that of the general population but poses particularly hazardous consequences for patients with Fontan cir-

Table 10. Key Points: Somatic Growth

Patients with Fontan circulation tend to have short stature relative to the normal population.
Decreased vitamin D levels, increased levels of parathyroid hormone, low lean muscle mass, and decreased cortical bone mineral density are identified in many patients with Fontan circulation.
Overweight and obesity are present in up to 50% of adult patients, which contributes to increased morbidity.

ulation.^{281,282} At the time of Fontan surgery, ≈10% of patients are overweight or obese, increasing to 20% to 30% by 12 years of age and 38% to 50% in adulthood.^{281–284} Similar to other populations, childhood overweight or obesity markedly increases the risk for obesity in adulthood for the Fontan population.²⁸² Obesity imposes uniquely negative factors for the Fontan circulation that contribute to heart failure: increased pulmonary vascular resistance, increased ventricular mass, diastolic and ultimately systolic ventricular dysfunction, atrial fibrillation, and elevated blood pressure.^{285–287} Obesity contributes to nonalcoholic liver disease and an increased risk of cancer development, including HCC.^{243,288–291} For the general population, recent data suggest that a body mass index of <25 kg/m² is optimal for cardiovascular health, which should also be a target for patients with Fontan circulation.²⁹² The prevention of overweight and obesity may be a critically important and modifiable risk factor for the long-term health of the patient with Fontan circulation.^{163,287,292,293} Key take-away points for growth and development are listed in Table 10.

BRAIN AND NEUROCOGNITIVE FUNCTION

Neurological, neurodevelopmental, and behavioral abnormalities have emerged as important comorbidities in survivors of CHD.^{294–297} In general, risk factors for late psychomotor and neurodevelopmental problems in patients with complex CHD such as a single ventricle include both patient factors (eg, genetic abnormalities, low birth weight, preterm and early-term birth, low socioeconomic status) and medical factors (eg, certain bypass variables such as low hematocrit, perioperative seizures, longer hospital stays, and global morbidity).^{295,298–303}

The potential causes of brain injury in CHD are cumulative and interactive. First, the same genetic abnormalities that cause heart disease can affect brain development.³⁰⁴ In utero, disturbed fetal cerebral hemodynamics can reduce cerebral oxygen delivery and alter brain maturation.^{305–311} Children with a single ventricle generally undergo multiple operations and cardiac catheterizations, with risks of hypoxic-ischemic injury, macroemboli, and microemboli. Those with hypoplas-

tic left heart syndrome are particularly exposed to preoperative and postoperative hemodynamic instability and complications, longer use of anesthetic agents and sedatives, and prolonged hospital length of stay.³¹² Cyanosis and inadequate nutrition may also affect neurodevelopment.^{313,314} The prothrombotic state of individuals with a single ventricle, combined with the potential for right-to-left shunting and the propensity of patients with Fontan circulation for atrial arrhythmias, creates lifelong risk for chronic cerebrovascular microemboli and stroke.^{41,315,316}

Brain MRI studies in fetuses and neonates with complex CHD have shown abnormalities of maturation, volumetric growth, and white matter brain tissue beginning in fetal life.³⁰⁵⁻³¹¹ Given the multitude of risk factors for central nervous system injury, it is not surprising that brain MRI studies in those with Fontan circulation show striking deviations from normal.³¹⁷⁻³²² In a study that included brain MRIs of 144 adolescents with Fontan circulation, abnormalities on routine anatomic MRI were found in 66% compared with 6% of 105 normal control subjects, with a predominance of focal/multifocal abnormalities.³²⁰ Among the 19 patients (13%) with MRI findings of prior stroke, 7 had not previously had a neurological diagnosis; that is, the stroke had been silent. Investigators report that the percentage of patients with single ventricles with brain injury, including nonacute ischemic changes, atrophy, and ventriculomegaly, accumulates throughout staged surgical reconstruction to Fontan.³²³ In a subset of 53 children in this study who underwent brain MRI 3 to 9 months after the Fontan procedure, periventricular leukomalacia was observed in 28%, definite generalized atrophy was seen in 4%, focal tissue loss and atrophy were noted in 19%, definite ventriculomegaly was observed in 13%, and acute or chronic intracranial hemorrhage was seen in 8%. In 128 preteens and adolescents with Fontan circulation compared with 48 healthy control subjects, investigators documented widespread, significant reductions in cortical and subcortical gray matter volumes and reduced cortical thicknesses on volumetric brain MRI.³²¹ The lower volumes and thicknesses spanned the frontal, temporal, parietal, and occipital lobes and were seen throughout the subcortical gray matter. Finally, an analysis of white matter microstructure in 102 adolescents with Fontan circulation compared with 47 control subjects showed widespread white matter injury involving major fiber tracts involved in cognitive function. The extent of white matter microstructural change was directly associated with lower Full Scale IQ and lower cognitive processing speed.³⁷

Numerous studies over the past 2 decades have identified a high prevalence of cognitive, neuropsychological, and behavioral deficits in adolescents with critical CHD, including patients with Fontan circulation.^{317,320,324-329} In general, patients exhibit a some-

what lower IQ, lower academic achievement in reading and math, and issues with visual-spatial skills, working memory (holding information and performing operations on it), and processing speed compared with the normative population. In a cross-sectional study of patients with Fontan circulation 10 to 19 years of age, Full Scale IQ (91.6 ± 16.8), mean Reading Composite score (91.9 ± 17.2), and mean Mathematics Composite score (92.0 ± 22.9) were significantly lower than the expected population mean of 100 ± 15 .³²⁰ Scores on the Full Scale IQ, Reading Composite, and Math Composite were >1 SD below the population mean in 31%, 29%, and 35% of patients and >2 SDs below the expected population mean in 12%, 12%, and 19%, respectively.³²⁰ Similarly, scores on the General Memory Index of the Children's Memory Scale were <1 and 2 SDs below the expected population mean in 34% and 18% of patients; scores on the Wechsler Memory Scale Composite were <1 and 2 SDs lower in 39% and 14% of patients.³²⁰ Many individuals have achievement that is lower than expected in view of their Full Scale IQ scores, consistent with a history of a diagnosis of learning disability in more than one-third of adolescents with Fontan circulation.³²⁰ As in most patients with CHD with complex disease, patients with Fontan circulation demonstrate particularly weak visual-spatial skills that may affect academic outcomes.³⁰⁰

Executive functioning challenges, attention-deficit/hyperactivity disorder, and social cognition problems have become increasingly recognized in those with Fontan circulation.³³⁰ Impairment in executive function is a striking characteristic of many adolescents who have undergone the Fontan procedure.^{320,331} In a study of 463 children and adolescents, 145 of whom had Fontan circulation, one-third of parents and teachers scored such individuals in the at-risk range for executive dysfunction on the Behavior Rating Inventory of Executive Function. In another study of 156 adolescents with Fontan circulation, one-third were diagnosed with attention-deficit/hyperactivity disorder.³³² Executive dysfunction and attention-deficit/hyperactivity disorder are of particular concern because lower childhood self-control is predictive of adult well-being, independently of social class origins and IQ.³³³ Finally, adolescents who have undergone the Fontan procedure are at significant risk for impaired social cognition. Specifically, adolescents with Fontan circulation have worse scores on tests that assess their ability to interpret the emotions of other people, social situations, and relationships, as well as more difficulty in recognizing their own emotions. In addition, they show more autism-like behaviors than a referent population.³²⁰

Risk factors for adverse neurodevelopmental and behavioral outcomes are highly correlated. Those that have emerged as independent risk factors across multiple studies include the presence of genetic disorders,

Table 11. Key Points: Brain and Neurocognitive Function

Brain MRI studies have identified widespread abnormalities in white matter microstructure associated with cognitive performance, as well as gray matter.
Neurodevelopmental disabilities are common.
Neurocognitive impairment impedes academic achievement in many patients, and evaluation in the early school years is needed to identify those who may benefit from targeted interventions

MRI indicates magnetic resonance imaging.

lower birth weight and gestational age, lower socioeconomic status and maternal education, longer total circulatory support time, a greater number of operations and catheterizations, longer hospital length of stay, and a greater number of complications. As the population with Fontan circulation ages, further research is needed to assess the translation of neurodevelopmental and behavioral findings in childhood and adolescence into neurocognitive function in adulthood.²⁹⁷

Recognition and management of the neuropsychological and behavioral impairments that affect many but not all patients with Fontan circulation have important implications for patient education, medical adherence, the transition from pediatric to adult healthcare systems, completion of higher education, and adult employment. Thus, a collaborative approach among patients, their families, the educational system, and both pediatric and adult healthcare teams is key to promoting well-being in the high-risk adult Fontan population. Characterization of abnormalities of brain structure, cognitive and neuropsychological ability, and behavior provides an opportunity not only to better elucidate the causes of disability but also to develop and implement strategies to optimize long-term outcomes. Awareness and recognition of neuropsychological and behavioral impairments in patients with Fontan circulation can facilitate counseling and increase access to diagnostic testing and educational resources. Periodic surveillance screening and evaluation for neurodevelopmental disabilities starting in early life and beyond are recommended.²⁹⁴ Identification of deficits allows appropriate therapies and education and creates opportunities to enhance academic, behavioral, psychosocial, and adaptive functioning, thus allowing each individual to achieve his or her optimal potential. Key take-away points for brain and neurocognitive function are listed in Table 11.

PSYCHOSOCIAL CHALLENGES AND ADVANCED CARE PLANNING

Psychosocial Challenges

Living with a chronic health condition carries potential psychosocial impact, and having undergone a Fontan procedure is certainly no exception. Compared with healthy

peers, individuals with Fontan physiology face potential psychosocial challenges in childhood, adolescence, and adulthood. As a group, many children and adolescents with CHD are at risk of psychosocial maladjustment, particularly according to parental report.³³⁴ A recent study compared the psychiatric and psychosocial status of 156 patients (mean age, 15 years) who had undergone Fontan procedures with that of 111 healthy peers.³³² The patient cohort had a significantly higher rate of lifetime psychiatric diagnosis (65% versus 22%); anxiety and attention-deficit/hyperactivity disorder were most common. Furthermore, as a group, patients had worse outcomes on measures of global psychosocial functioning, anxiety, depressive symptoms, posttraumatic stress, and disruptive behavior. Risk factors of poorer psychiatric/psychosocial outcomes include male sex, lower birth weight, longer duration of deep hypothermic circulatory arrest, and lower intelligence.

In adults, a meta-analysis of international studies using survey assessment of psychological distress revealed no consistent evidence of poorer outcomes among adults with CHD of various subtypes, although methodological heterogeneity was evident.³³⁵ The results of 3 North American studies, however, suggest that one-third of adults with CHD meet diagnostic criteria for a mood or anxiety disorder when clinical interviews are administered.^{336–338} Although depression has received much of the attention in the behavioral cardiology literature, adults with CHD are also at risk of elevated anxiety and posttraumatic stress disorder.^{339–341} Patients' subjective health status has been more strongly associated with psychosocial outcomes than objective assessment,^{337,342–345} an important consideration for physicians faced with the symptomatic adult patient with Fontan circulation. Among adolescents and young adults with Fontan physiology, elevated symptoms of depression have been reported (28% with mild symptoms, 32% with moderate symptoms) and demonstrated to be a negative predictor of quality of life.³⁴⁶ Furthermore, more than half of patients endorsed worry about current health, employment, and living independently.³⁴⁷ Anxiety is common; an Italian study revealed that anxiety symptoms were more elevated than depressive symptoms and that more than half of the patients were considered to have possible anxiety.³⁴⁸ MRI of the brain in adolescents with a single ventricle reveals injury in select areas that control anxiety and depression, suggesting a structural basis for the functional deficits seen.³⁴⁹

Qualitative research offers a rich understanding of post-Fontan life. In-depth interviews with adolescents and young adults with Fontan circulation (17–32 years of age) revealed difficulties and challenges, as well as 3 positive themes: feeling happiness in being themselves (eg, feeling proud, mature, healthy, and special), focusing on possibilities (eg, managing physical restrictions and medical procedures), and being com-

mitted to life (eg, living with uncertainty and making the most out of life).³⁵⁰

Improving the understanding and management of cognitive and psychiatric outcomes in adults with CHD was identified as a research priority in a working group of the National Heart, Lung, and Blood Institute and the Adult Congenital Heart Association.³⁵¹ Patients who have undergone Fontan repairs represent a subgroup of patients with CHD for whom increased research and clinical resources targeting psychosocial outcomes are paramount. This is a group for whom the question is typically when, not if, significant medical sequelae will present, and the complex interplay between physical and psychosocial outcomes warrants attention. Congenital cardiology teams are encouraged to be proactive in their approach to the growing cohort of patients with Fontan circulation by developing efficient ways to identify psychosocial maladjustment, collaborating with mental health professionals, and developing pediatric-based preventive approaches to encourage positive psychosocial adaptation.

Advanced Care Planning

Although the Fontan procedure has certainly extended life spans and mortality has largely shifted from the pediatric to adult setting, a mortality risk remains that is associated with the original Fontan procedure and a Fontan conversion. Research has suggested that many adolescents and adults with CHD, including those with complex disease, overestimate their life expectancy.³⁵² Qualitative research revealed that adolescents and adults with Fontan circulation “made a pledge to themselves that they would stay alive as long as possible”³⁵⁰ yet also expressed uncertainty about the future and were aware of the possibility of shortened life expectancy. Thus, it is critical that patients, families, and healthcare providers are well prepared for the premature mortality facing individuals with Fontan circulation.

Advance directives provide the valuable opportunity for patients to decide whom they want to convey their preferences for medical and palliative care should they become unable to speak for themselves. These directives benefit not only patients nearing the end of their lives but also family members and health providers facing this difficult phase. Guidelines recommend completion of advance directives and addressing end-of-life matters as part of the routine care of adolescents and adults with CHD.^{353,354} Patients should be encouraged to complete advance directives “ideally at a time during which they are not morbidly ill or hospitalized, so that they can express their wishes in a less stressful setting.”³⁵³ Although many deaths among patients with Fontan physiology occur after a period of decline, some deaths occur unexpectedly. Thus, waiting for the end

stage of disease to initiate advanced care planning is discouraged.

North American studies that surveyed adults with CHD in the outpatient setting revealed that <15% recalled discussing advanced care planning with their provider, only 5% to 21% had completed advance directives, and the majority preferred advanced care planning discussions to be initiated when healthy.^{355–358} On a scale from 0 to 10, with 10 being most important, the average rating for discussing advanced care planning with providers was 7, and participants preferred a median age of 18 years (range, 5–60 years) as the most appropriate age to initiate the discussions.³⁵⁸ Variables for timing of discussions include the patients’ expressed wishes and cognitive functioning, familiarity with the physician, and timing in relation to transitioning care to a new provider. Thus, these conversations should not be postponed until end-stage disease progression. Room for improvement in clinical care was similarly demonstrated in a study of adults with CHD, most with advanced disease who died during a hospital admission.³⁵⁹ Very few had documented end-of-life discussions. Attempted resuscitation was less likely among patients with documented end-of-life discussions and did not occur at all among patients referred to palliative care.

In summary, documentation of advanced care planning discussions and the completion of advance directives occur for a minority of adults with CHD who, as a group, value these discussions and wish for them to occur earlier in the disease course. A common provider-reported barrier to end-of-life discussions is being unable to reliably estimate life expectancy.³⁵⁷ However, challenges in prognostication can be shared directly with patients and families, and providers may be reassured to know that it is general information on the life expectancy of patients with their form of CHD that most patients are seeking.^{356,358}

Recommendations for patients with Fontan circulation include normalizing conversations about advanced care planning and end-of-life care, scheduling separate visits to discuss these important matters with patients (and their chosen loved ones) with later-stage disease approaching the end of their lives, using patient-friendly language to discuss health expectations and prognoses, and exploring patient preferences for end-of-life care while recognizing that they might shift over time.³⁶⁰ Soliciting guidance from mental health professionals and providers experienced in how best to approach these conversations is important. When working with adolescents and young adults, it is important to be mindful of neurodevelopmental abilities, capacity for decision-making, and cultural background.^{354,360–362} Providers are encouraged to partner with palliative care providers to manage symptoms and patient and family distress.³⁶⁰ It is also important for healthcare teams to recognize

Table 12. Key Points: Psychological, Mental Health, and Social Challenges

Mood and anxiety disorders are prevalent and contribute to impaired quality of life.
Discussions about lifestyle, prognosis, and advanced care planning should be incorporated into healthcare visits in an age- and development-appropriate manner.

their own emotional reactions that often accompany the death of a younger person in whose care they may have been involved for years or even decades.³⁶⁰ Key take-away points for psychological, mental health, and social challenges are listed in Table 12.

UNIQUE ASPECTS AND CHALLENGES IN THE ADULT

Despite an extraordinary physiology that would not seem compatible with normal adult experiences, many adults with a Fontan palliation lead normal adult lives. However, the natural history of this physiology places the burden of many of the complications described in this statement on adults. The time-dependent nature of many of the cardiac, hepatic, renal, and other sequelae is such that they develop in the years and decades after completion of the Fontan, thus manifesting in adulthood. In addition, the superimposition of noncardiac medical issues occurs more frequently with age, and management of even simple medical problems may be complicated by the hemodynamic deficiencies of the Fontan circulation.

Many of the cardiac complications after the Fontan operation become more common with time and consequently are more likely to affect adult patients. Mortality is higher in patients with Fontan circulation than with most other types of CHD, the sole exception being Eisenmenger syndrome. In a study of mortality comparing patients with the normal expected life span in the United States, a 40-year-old patient with Fontan repair has a risk of death equivalent to that of a 75-year-old.³⁶³ Adults are also more likely to have the surgical histories associated with higher cardiac complication rates such as atriopulmonary or Bjork-type modifications of the Fontan surgery, later age at Fontan completion, and longer periods of time with volume-loading shunts or cyanosis. Emblematic of the progression of complications seen in adults with Fontan palliation is the experience described by the ANZFR, in which survival of those who were alive at 16 years of age to 30 years of age was 90% but fell to 80% at 40 years of age, with only 53% of patients in New York Heart Association class I heart failure at the time of last follow-up and only 41% without a serious adverse event by 40 years of age.³⁶⁴ A report from the Mayo Clinic describes the 40-year outcomes of >1000 patients who had undergone a Fontan operation and gives 10-, 20-, and 30-year survival rates

of 74%, 61%, and 43%.⁶ The association of poor outcomes was reported as a variety of perioperative and operative features that have improved over time, and not surprisingly, mortality has improved in the more recent decades. However, their experience emphasizes the mortality facing adults with Fontan circulation. In another report from the Children's Hospital of Philadelphia, two-thirds of patients who underwent Fontan surgery between 1992 and 2009 required catheter or surgical interventions in the ensuing 20 years, with many occurring in young adults.³⁶⁵ Hospitalizations are more frequent in adults with Fontan circulation than in adults with other CHDs.³⁶⁶

Fontan Conversion and Revision Surgery

Adults are the group of patients who have old-style atriopulmonary Fontan operations and are thus the population for whom surgical conversion remains a treatment option. The primary indications for Fontan conversion include difficult atrial arrhythmias, atrial clots, and hemodynamic derangements (eg, AVV regurgitation) that require surgical intervention. The procedure involves takedown of the atriopulmonary connection, reduction of the right atrium, creation of an extracardiac TCPC, and modifications of atrial arrhythmia surgery. A report of 140 patients who underwent Fontan conversion describes a freedom of atrial arrhythmias of 77% and survival free of death or transplantation at 5, 10, and 15 years of 90%, 84%, and 66%, respectively.¹²⁵ Fontan conversion with arrhythmia surgery is successful in reducing arrhythmias and improving symptoms, but as more children are treated with lateral tunnel or TCPC repairs, the number of patients for whom a Fontan conversion is indicated is decreasing over time.⁶ With the more recent advent of extracardiac conduit-type Fontan operations, some have speculated that a small-diameter conduit (<16 mm), although satisfactory for a child, might increase inferior vena caval pressure and potentially exacerbate FALD when patients grow to adulthood.^{367,368} There are currently few data to refute or support this hypothesis; more elapsed time is needed before we can determine whether a relatively small extracardiac conduit may ultimately require future surgical revision or catheter-based intervention.³⁶⁹

Concomitant Medical Challenges in the Adult Patient

The coexistence of other medical or surgical problems is more typical in adulthood, and management of these problems may be complicated by underlying Fontan physiology. In 1 series, adult patients with Fontan palliations had more periprocedural complications (15%) than patients with CHD and a biventricular repair or patients without CHD.³⁷⁰ In an administrative study of

costs of admissions for noncardiac reasons, adult patients with CHD in general had higher costs, longer stays overall, higher rates of intensive care unit stay, and higher mortality.³⁷¹ There is a paucity of robust data on the impact of Fontan physiology on the outcomes of other medical problems. For example, the risk of cancer is increased in the adult with CHD and is a considerable challenge to manage in the patient with Fontan circulation.²³⁶ More data on the impact of Fontan physiology on the management of common conditions are needed to provide guidance on optimal management strategies. Care in adult CHD centers has been demonstrated to reduce mortality in patients with moderate to complex CHD.³⁷² Evaluation and care by adult CHD specialists is of benefit in optimizing management strategies for the unique and complex aspects of caring for the adult with Fontan circulation. Guidelines for the general management of adults with CHD were updated for 2018.³⁷³

Contraception and Pregnancy

Women with Fontan circulation may desire contraception and may consider the possibility of pregnancy. Counseling on pregnancy can be a challenge because there are few data on the long-term cardiovascular impact of the circulatory changes of pregnancy, particularly volume overload, on Fontan physiology. Nevertheless, because of the strong natural desire to have a family, there is growing experience with women with Fontan circulation experiencing pregnancy. Maternal complications of pregnancy include arrhythmias, heart failure, and thromboembolic complications, which can occur in up to 25% of women. Strikingly high rates of fetal loss are demonstrated in the few series of women with Fontan circulation who achieved pregnancy. In a study of 50 women with 124 pregnancies, the miscarriage rate was nearly 55%.³⁷⁴ Women who are cyanotic are more likely to have miscarriage.³⁷⁵ In a meta-analysis of pregnancies reported in women with Fontan circulation, arrhythmias and heart failure were more common than in the normal populations or in those with simpler forms of CHD; fetal complications were dramatically higher, with up to 50% of pregnancies ending in miscarriage.³⁷⁶

Counseling women with Fontan circulation about pregnancy should take into account the cardiovascular status, hepatic status, thromboembolic risk, potential heritability of the CHD, and potential for a long-term decrease in cardiovascular function as a result of pregnancy. An important, but difficult, conversation concerns the life expectations for women with Fontan physiology, in terms of both morbidity and mortality. In a study of outcomes of preconception counseling of women with a Fontan palliation, most women agreed to participate; however, the majority chose to pursue

pregnancy even after being given information about the higher rates of maternal and fetal complications.³⁷⁷

Women with Fontan circulation have higher rates of primary amenorrhea; thus, menarche may be delayed.³⁷⁸ For some women, assisted reproduction may be considered. The hormonal manipulations needed for various forms of assisted reproduction may be poorly tolerated by a woman with Fontan circulation because of the potential for thrombosis and blood volume shifts. Pregnancy surrogacy may be a desirable alternative for some women. Ethical considerations related to maternal longevity concerns are also present when the use of advanced technology-based assisted reproductive technologies is considered. Assisted reproduction also carries a risk of multiple embryos, which can produce an even greater hemodynamic burden on the pregnant woman with Fontan circulation.

SURVEILLANCE STRATEGIES: PROPOSED SCHEMA OF HOW TO MONITOR THE PATIENT WITH FONTAN CIRCULATION

Given the relatively high prevalence and possible progressive nature of end-organ dysfunction in those with Fontan circulation, in particular during the early formative years of organ growth and development during childhood, adolescence, and early adult life, a compelling argument can be made for performing serial surveillance testing.³⁷⁹

On the basis of expert consensus, the authors of this AHA statement believe the following:

- For patients with Fontan circulation who appear clinically well, it is reasonable to offer surveillance testing that systematically evaluates cardiovascular and end-organ health periodically.
- Individual patients, in particular those who are unwell, will have specific needs that determine the most appropriate testing required, and such testing should be individualized at the liberty of their healthcare provider.
- At this time, there is an insufficient evidence base, as strictly defined by the AHA guidelines for developing and grading recommendations, to support recommendations for specific tests or for the frequency/interval of testing. Nevertheless, we believe that surveillance testing for cardiovascular and end-organ system consequences of the Fontan circulation is reasonable, clinically important, and to be encouraged as part of overall high-quality patient care.
- Surveillance may be provided by individual practitioners or by specialty multidisciplinary Fontan/single-ventricle care clinics. Surveillance should be offered by healthcare providers and centers

Table 13. Cardiovascular System Surveillance Testing

Test	Child	Adolescent	Adult
Outpatient visit, including physical examination	Every 6–12 mo	Every 6–12 mo	Every 6–12 mo
ECG	Every 6–12 mo	Every 6–12 mo	Every 6–12 mo
Echocardiogram	Yearly	Yearly	Yearly
Holter 24-hour monitor	Every 2–3 y	Every 1–2 y	Every 1–2 y
Exercise stress test	Every 2–3 y*	Every 1–3 y	Every 1–2 y
Serum BNP or NT-proBNP	Once in childhood	Every 1–3 y	Every 1–2 y
Cardiac MRI	Once every 3 y	Every 2–3 y	Every 2–3 y
CT angiography	As clinically indicated	As clinically indicated	As clinically indicated
Cardiac catheterization	As clinically indicated	Once every 10 y	Once every 10 y

BNP indicates brain natriuretic peptide; CT, computed tomography; MRI, magnetic resonance imaging; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

*In young children unable to participate in a complete exercise stress test (bike or treadmill) with metabolic assessment, testing may include a 6-minute walk to assess for distance, duration, and oxygen saturation measures of exercise capacity.

familiar with and experienced in the unique aspects of Fontan circulation care and comfortable with interpreting the results.

- The optimal surveillance testing elements and frequency of testing are age related and change as the patient moves through childhood and adolescence and into adulthood, as organ system complications emerge, and as the rate of progression of dysfunction changes.
- It is anticipated that practice patterns will, and should, change over the coming years as further collaborative study ensues and higher-quality evidence emerges to guide selection of the most appropriate surveillance tests to undertake.

Through development of consensus opinion by this AHA writing group, we propose a Fontan Circulation Surveillance Testing Toolkit (Tables 13–16). Cardiovascular system surveillance testing is already common practice. Cardiovascular assessment at set intervals in all age groups throughout life is a reasonable approach. Obtaining a good interval history and performing a careful physical examination cannot be replaced by any test. Findings such as progressive cyanosis, new murmur, elevated jugular venous distension, ascites, leg edema, or unexpected changes in weight during serial surveillance should be noted. Examples of specific cardiovascular tests and suggested surveillance intervals are provided in Table 13. Surveillance of end-organ status in the patient with Fontan circulation is a relatively new concept. Tests within this toolkit are proposed as a means of characterizing organ systems in the individual with a single ventricle and Fontan circulation.

A variety of potential tests exist for characterizing the end-organ systems. As an evidence base for the most disease-specific and valuable tests emerges, and in order to assist healthcare practitioners who wish to test their patients at various levels of depth of surveillance, we stratify the various organ system tests as basic (fundamental and rudimentary level of assessment), in-depth (more detailed level of characterization), and investigational (possible or likely of value; however, greater experience and study may be necessary before widespread use can be suggested).

End-organ system surveillance testing frequency should be tailored to patient age. It is reasonable to consider surveillance testing every 3 to 4 years in childhood (<12 years of age; Table 14), every 1 to 3 years in adolescence (12–18 years of age; Table 15), and every 1 to 2 years in adulthood (>18 years of age; Table 16). Findings of surveillance testing may influence decisions concerning the next interval until testing is repeated.

EXERCISE: A MEANS FOR ASSESSMENT AND AS THERAPY

Subnormal exercise capacity is extremely common in patients with Fontan circulation, with a wide variety of potential contributing factors. Cardiac limitations can include impaired chronotropic responses, inability to raise right-sided heart output on exertion because of the lack of a subpulmonary ventricle, and possible limitations of pulmonary vascular reserve. Resting and exertional hypoxemia may also be relevant (from a systemic to pulmonary venous chamber fenestration or venovenous collaterals). Extracardiac sources of limitation can include restrictive lung issues (eg, after thoracotomy), reduced skeletal muscle mass (sarcopenia), and physical deconditioning. In particular, sarcopenia is a common and underappreciated finding in patients,²⁷² relevant to exercise intolerance.

Exercise as a Test

Cardiopulmonary exercise testing (CPET) can be particularly useful in patients with Fontan circulation to quantify (serially) maximum exercise capacity and to infer the reason(s) for any exercise limitation observed. On CPET, key parameters of interest include $\dot{V}O_2$ max to assess aerobic capacity and the ratio of $\dot{V}E$ to $\dot{V}CO_2$ to assess respiratory efficiency and anaerobic threshold. Impaired CPET parameters are associated with increased risk of hospitalization in patients with Fontan circulation,⁶² and both maximal and submaximal exercise data appear to have prognostic value in this population.³⁸⁰ Deterioration in CPET parameters on serial study identifies a population at increased risk for later cardiovascular events.¹³³ Other specific parameters can provide

Table 14. Proposed Childhood* Organ System Surveillance Testing Toolkit

Organ System	Basic	In-Depth	Investigational
Liver	CMP	PT/INR	Liver imaging via CT or MRI
	Platelet count	Serum FibroSure biomarkers	Liver elastography (ultrasound or MRI)
	Serum GGT	Serum α -fetoprotein	Liver biopsy
		Abdominal (liver) ultrasound	
		Total serum cholesterol	
Kidney	Serum BUN, creatinine	Urinalysis albumin/creatinine ratio	Renal ultrasound with Doppler
	Serum cystatin C		Nuclear scan GFR
Lymph	Serum albumin, total protein	Serum IgG	T2-weighted MRI lymphatic imaging
	Absolute lymphocyte count	Fecal α -1 antitrypsin level	
Endocrine/metabolic	Serum calcium	Parathyroid hormone	Serum insulin-like growth factor
	Vitamin D	Bone densitometry/DXA scan	
	Tanner staging, developmental assessment	Nutritional evaluation and consultation	
Heme	CBC, Hgb, Hct	Serum iron	Coagulation factors
		TIBC	
		Ferritin	
Lungs	...	Chest x-ray	Pulmonary function testing
Neurological/psychological	Neurodevelopmental/cognitive testing†	Psychological evaluation and consultation	Brain MRI scanning

BUN indicates blood urea nitrogen; CBC, complete blood cell count; CMP, comprehensive metabolic panel; CT, computed tomography; DXA, dual-energy x-ray absorptiometry; GFR, glomerular filtration rate; GGT, γ -glutamyl transferase; Hct, hematocrit; Hgb, hemoglobin; IgG, immunoglobulin G; INR, international normalized ratio; MRI, magnetic resonance imaging; PT, prothrombin time; and TIBC, total iron-binding capacity.

*Our group expert consensus found it reasonable to consider surveillance testing every 3 to 4 years in the child (<12 years of age) with Fontan circulation.

†Neurodevelopmental testing is in accordance with recommendations made by Marino et al.²⁹⁴

insights into respiratory reserve, stroke volume, and ventilation-perfusion matching. Detailed knowledge of contributors to exercise limitation in patients with Fontan circulation can suggest potential therapeutic strategies for consideration such as fenestration closure for excessive hypoxemia or atrial pacing for important chronotropic incompetence.

Table 15. Proposed Adolescence* Organ System Surveillance Testing Toolkit

Organ System	Basic	In-Depth	Investigational
Liver	CMP	Serum FibroSure biomarkers	Liver biopsy
		Platelet count	Serum α -fetoprotein
		Serum GGT	Abdominal (liver) ultrasound
		PT/INR	Total serum cholesterol
			Liver imaging via CT or MRI
Kidney		Liver elastography (ultrasound or MRI)	
	Serum BUN, creatinine	Urinalysis albumin/creatinine ratio	Nuclear scan GFR
	Serum cystatin C	Renal ultrasound with Doppler	
Lymph	Serum albumin, total protein	Serum IgG	T2-weighted MRI lymphatic imaging
		Absolute lymphocyte count	Fecal α -1 antitrypsin level
	Endocrine/metabolic	Serum calcium	Parathyroid hormone
Heme	Vitamin D	Bone densitometry/DXA scan	
		Tanner staging, developmental assessment	
		Nutritional evaluation and consultation	
Lungs	CBC, Hgb, Hct	Serum iron	Coagulation factors
		TIBC	
		Ferritin	
Neurological/psychological	...	Chest x-ray	Pulmonary function testing
			Pulmonary function testing
		Neurodevelopmental/cognitive testing†	Psychological evaluation and consultation

BUN indicates blood urea nitrogen; CBC, complete blood cell count; CMP, comprehensive metabolic panel; CT, computed tomography; DXA, dual-energy x-ray absorptiometry; GFR, glomerular filtration rate; GGT, γ -glutamyl transferase; Hct, hematocrit; Hgb, hemoglobin; IgG, immunoglobulin G; INR, international normalized ratio; MRI, magnetic resonance imaging; PT, prothrombin time; and TIBC, total iron-binding capacity.

*Our group expert consensus found it reasonable to consider surveillance testing every 1 to 3 years in the adolescent (12–18 years of age) with Fontan circulation.

†Neurodevelopmental testing is in accordance with recommendations made by Marino et al.²⁹⁴

Table 16. Proposed Adult* Organ System Surveillance Testing Toolkit

Organ System	Basic	In-Depth	Investigational
Liver	CMP	Serum FibroSure biomarkers	Liver biopsy
	Platelet count	Serum α -fetoprotein	
	Serum GGT	Liver imaging via CT or MRI	
	PT/INR	Liver elastography (ultrasound or MRI)	
	Total serum cholesterol		
	Abdominal (liver) ultrasound		
Kidney	Serum BUN, creatinine	Urinalysis albumin/creatinine ratio	Nuclear scan GFR
	Serum cystatin C	Renal ultrasound with Doppler	
Lymph	Serum albumin, total protein	Serum IgG	T2-weighted MRI lymphatic imaging
	Absolute lymphocyte count	Fecal α -1 antitrypsin level	Lymphatic angiography
Endocrine/metabolic	Serum calcium	Parathyroid hormone	Serum insulin-like growth factor
	Vitamin D	Bone densitometry/DXA scan	
	Nutritional evaluation and consultation		
Heme	CBC, Hgb, Hct	Serum iron	Coagulation factors
		TIBC	
		Ferritin	
Lungs	Pulmonary function testing	Chest x-ray	
Neurological/psychological	Psychological evaluation and consultation	Neurodevelopmental/cognitive testing†	Brain MRI scanning

BUN indicates blood urea nitrogen; CBC, complete blood cell count; CMP, comprehensive metabolic panel; CT, computed tomography; DXA, dual-energy x-ray absorptiometry; GFR, glomerular filtration rate; GGT, γ -glutamyl transferase; Hct, hematocrit; Hgb, hemoglobin; IgG, immunoglobulin G; INR, international normalized ratio; MRI, magnetic resonance imaging; PT, prothrombin time; and TIBC, total iron-binding capacity.

*Our group expert consensus found it reasonable to consider surveillance testing every 1 to 2 years in the adult (>18 years of age) with Fontan circulation.

†Neurodevelopmental testing is in accordance with recommendations made by Marino et al.²⁹⁴

Invasive CPET testing has also been applied in patients with Fontan circulation. Although this involves the insertion of pulmonary and radial artery catheters, which can alter resting physiology, such studies have clearly shown (inter alia) rapid and dramatic increases in systemic venous pressures in exercising patients with Fontan circulation, often exceeding 30 mm Hg at rela-

Table 17. Key Points: Exercise

Reduced exercise tolerance is common and related to lack of subpulmonary pump, chronotropic incompetence, cyanosis, lung restriction, reduced skeletal muscle mass, and deconditioning.
Serial cardiopulmonary exercise testing is useful to quantify exercise capacity and to identify changes in clinical status, allowing therapeutic changes.
Exercise training, in particular specific strategies such as leg muscle resistance training, may prove to be very beneficial because it might improve cardiac output and quality of life.

tively modest workloads.²¹⁴ This phenomenon is associated with poor systemic oxygen delivery.

Because maximal exercise capacity is so often limited in those with Fontan circulation, ranges of normal CPET parameters for children and teenagers are now published (at age 12±3 years).³⁸¹

Exercise Training and Rehabilitation

Exercise training may have particular benefits in patients with Fontan circulation for physical and psychological well-being. Given the importance of peripheral venous return, increased muscle mass may augment venous return and thus influence heart preload. Investigators have shown that leg muscle resistance training can significantly augment peripheral muscle mass, venous return, cardiac output, and $\dot{V}O_2$ max in adults with Fontan circulation.³⁸² Similarly, given the importance of the thoracic bellows to drive inspiratory venous return to the heart, investigators have found that inspiratory muscle training (for 6 weeks) improves resting cardiac output and ventilatory efficiency during exercise.³⁸³ In contrast, results from aerobic training programs have been less encouraging.³⁸⁴ Further studies will be informative concerning the optimal type or combination, frequency, and duration of exercise training for patients with Fontan circulation.

Exercise training certainly appears safe for patients with Fontan circulation. A review of 23 articles on exercise training found only 3 adverse events in >200 participants, all of which were transient.³⁸⁵ When measured, quality of life improved with exercise training in the majority of studies. The main physical benefits documented were improved muscle strength and stroke volume. Key take-away points for exercise are listed in Table 17.

MANAGEMENT STRATEGIES: PHARMACOLOGICAL

The aims of pharmacological therapy are to ameliorate the deleterious impact of Fontan physiology and to prevent and treat specific complications that arise. Given the physiological constraints of the Fontan circulation, mechanistic targets include systolic and dia-

stolic ventricular function, ventricular remodeling, and pulmonary and systemic vascular resistance. Additional targets might address specific complications such as PLE, liver fibrosis, or thrombosis. The interrelationship between these targets is not completely understood. In addition, their relationship with events such as death or morbidities or with patient-level outcomes such as functional health status and quality of life is incompletely known. These issues and the heterogeneity and rarity of patients with Fontan circulation have made the assessment of the efficacy of pharmacological therapies particularly challenging. This has led to a poor evidence base, which has contributed to important clinical practice variation in pharmacological management.³⁸⁶ However, the availability of new agents, particularly pulmonary vasodilators and antithrombotics, has created an opportunity and imperative for increased and more efficient study of the Fontan population.

Given the rarity and extended timeline for events to occur and the nonspecific and poorly responsive measures of patient-level outcomes, the feasibility and validity of using objectively measured surrogate outcomes have been sought. The primary aim of the multi-institutional National Institutes of Health Pediatric Heart Network Fontan Cross-Sectional Study was to determine laboratory measures that would be significantly associated with functional health status for pediatric Fontan survivors.³⁸⁷ The study showed that variation in physical functioning summary scores was explained, albeit poorly, by medical conditions and long-term and current medical problems, not by cardiac and management characteristics.³⁸⁸ Likewise, laboratory measures of ventricular characteristics and function and exercise capacity showed poor associations, variously accounting for only $\approx 10\%$ of the variation in physical functioning summary scores.³⁸⁹ Nonetheless, exercise capacity and exercise hemodynamics have become the outcome of interest for recent trials.

Pulmonary Vascular Resistance

The applicability of agents that modulate pulmonary vascular resistance has generated a great deal of interest for the Fontan population.³⁹⁰ Agents include phosphodiesterase-5 enzyme inhibitors (sildenafil, tadalafil), endothelin receptor antagonists (bosentan, ambrisentan), and prostacyclins (iloprost). A recent systematic review of pharmacological therapy for patients with Fontan circulation examined 9 studies with a total of 267 patients, 8 of which studied a pulmonary vasodilator: 4 studies with sildenafil, 3 with bosentan, and 1 with iloprost.³⁹¹ Most of these studies were small and short term, but a trend toward a positive impact on exercise capacity and hemodynamics was noted. The largest study, a randomized placebo-controlled trial of bosentan in 75 patients treated for 14 weeks, showed

an increase in peak oxygen consumption, exercise time, and functional class without serious adverse events.³⁹² The authors concluded that although the results were promising, further study was necessary. After completion of a pharmacokinetic dose-finding study of udenafil (a relative long-acting phosphodiesterase-5 inhibitor) in 36 patients with Fontan circulation,³⁹³ a larger efficacy and safety placebo-controlled trial of treatment for 26 weeks of 400 patients is currently in progress (Fontan Udenafil Exercise Longitudinal Assessment Trial; URL: ClinicalTrials.gov. Unique identifier: NCT02741115), with a primary outcome of change in peak oxygen consumption. A 52-week open-label extension study will further assess safety outcomes (A Extension Study of Udenafil in Adolescents; URL: ClinicalTrials.gov. Unique identifier: NCT03013751). A placebo-controlled trial of 52 weeks of macitentan (an endothelin receptor antagonist) in 134 patients with Fontan circulation is underway (Clinical Study Assessing the Efficacy and Safety of Macitentan in Fontan-Palliated Subjects; URL: ClinicalTrials.gov. Unique identifier: NCT03153137), also with a primary outcome of change in peak oxygen consumption. These studies will inform the evidence base to support a clinical recommendation, weighing benefit, safety, and cost.

Thrombosis

Thrombosis is an important and unpredictable complication, not only after Fontan operation but also associated with each stage of single-ventricle palliation.³⁹⁴ It is an important cause of morbidity, particularly when it leads to pulmonary embolism or stroke, and contributes to mortality. The predominant predisposing factor for thrombosis is stasis of blood flow. Venous stasis is often evident in the cavopulmonary circuit in light of the absence of a pump for systemic venous return and pulmonary blood flow. Congenital or acquired anatomic areas of stasis may be present such as a hypoplastic left ventricle with poor inflow and outflow or the creation of a blind-ended pulmonary artery stump. A number of reports have described altered levels of clotting and fibrinolysis factors at all stages of palliation but below the clinical threshold for abnormality. However, these altered levels have been associated with features specific to Fontan palliation, including lower systemic oxygenation, low cardiac output, and hepatic congestion. Furthermore, some patients may have inherited or intrinsic alterations in thrombophilia factors. Most alterations in clotting factor levels likely reduce the reserve of the clotting system, whereby an inciting stimulus such as cardiopulmonary bypass or an indwelling central line increases the risk of both bleeding and thrombosis. The presence of further disturbance of the coagulation system such as through excessive factor loss through PLE or synthetic impairment resulting

Table 18. Key Points: Thrombosis

Patients are at increased risk for thromboembolic events
Although the most effective means to prevent thromboembolic events are still unclear, some form of thromboprophylaxis, either an antiplatelet agent or anticoagulant, is warranted.

from severe liver fibrosis or cirrhosis increases the risk of thromboembolic complications.

A targeted approach to thromboprophylaxis is not yet feasible, although patients with a history of thrombosis are at increased risk of recurrence. Additional factors such as atriopulmonary Fontan connection type, Kawashima connection type, dilated atrium, presence of thrombogenic foreign material, ventricular dysfunction, arrhythmias, prolonged immobilization, and PLE have been variously reported. Although clinicians remain concerned about the potential for paradoxical emboli in patients with atrial fenestration, this has not been reported as a risk factor for thrombosis or thromboembolic events.

Both antiplatelet and anticoagulation agents have been used. Some thromboprophylaxis has been shown to be better than none, but the superiority of acetylsalicylic acid (ASA) versus warfarin remains unclear, as was noted in a meta-analysis of 20 observational studies.³⁹⁵ An underpowered randomized clinical trial of ASA versus warfarin failed to show a significant difference in the incidence of thrombosis over a 2-year period immediately after the Fontan procedure,³⁹⁶ although a secondary analysis showed that poorly controlled warfarin was associated with a high risk of thrombosis.³⁹⁷ A small trial of ASA versus warfarin showed greater deposition of material, presumed laminar thrombus, within the extracardiac conduit cavopulmonary connection for those on ASA.³⁹⁸ Current guidelines suggest that it is reasonable for all patients with Fontan circulation to receive ASA, with anticoagulation reserved for those with presumed risk factors or previous thrombosis or older patients.³¹⁶ With either agent, an important residual risk of thrombosis remains; hence, there is an ongoing unmet need for better strategies.³⁹⁹ Newer direct oral anticoagulants are currently being studied in pediatric cardiac populations, including patients with Fontan circulation. They are likely to be an attractive alternative to warfarin, although their comparative efficacy and safety have yet to be determined. Key take-away points for thrombosis are listed in Table 18.

MANAGEMENT STRATEGIES: MECHANICAL CIRCULATORY SUPPORT

The importance of mechanical circulatory support (MCS) as a potential therapy for a single functional ventricle is evident by the steady increase in an aging Fontan population and a shortage of donor organs for trans-

plantation. The application of MCS for Fontan circulatory support remains controversial and poorly defined. At present, there is no MCS device specifically intended for use in this population. Existing devices designed for systemic circulatory support in biventricular circulations have been adapted for use in the single-ventricle Fontan circulation. Although success with existing devices has been reported, the experience is highly variable, generally limited to case reports, and outcomes are still relatively poor.^{400–408}

Unfortunately, MCS device performance is commonly mismatched to the unique physiological needs of the Fontan circulation. Existing technology is better suited to ventricular pump failure in the patient with a single ventricle with Fontan circulation than to Fontan failure secondary to a lack of a subpulmonary ventricle and the circulatory deficiencies that follow. Anecdotal evidence indicates that systemic ventricular assist devices appear to be most effective when applied to a Fontan circulatory system in the setting of impaired ventricular systolic function. At late follow-up, however, most patients with Fontan circulation who have not reached end-stage failure have preserved systolic function.⁵⁰ In the setting of preserved systolic function, the role of systemic MCS may be superfluous and may further congest the right-sided circulation. A cavopulmonary assist device would require a highly specialized low-pressure right-sided circulatory technology, which does not yet exist. From a theoretical perspective, an MCS technology targeted to support the lack of a subpulmonary ventricle could be of tremendous benefit, especially if applied early to preempt the progression of failure by providing a biventricular circulation. Early-stage research is underway to address this important need.^{409–411} At present, the use of commercially available MCS therapy is limited to end-stage Fontan circulation failure as a bridge to transplantation. The total artificial heart has been successfully applied to bridge a patient to heart transplantation.⁴¹² Use of MCS as destination therapy in patients with Fontan circulation has been contemplated but not yet reported.

Moving forward, it will become more important to establish criteria to categorize Fontan circulatory inefficiency as predominant left- or right-sided to inform which MCS technology can be best matched to the deficit. Left-sided failure (systolic dysfunction, low cardiac output) may be best served with a systemic ventricular assist device; right-sided failure (preserved systolic function, diastolic dysfunction, sequelae of systemic venous hypertension) may be best served with a cavopulmonary assist device. In some instances, both forms of support may be needed. Evaluative parameters should be developed to categorize the cause of Fontan failure so that a specific device can be selected to best match to the physiological deficit.⁶⁵

Although exceedingly challenging, MCS provides a tremendous opportunity to cure single functional ventricle and to preempt the insidious progression of chronic Fontan circulatory failure. Research and development of these technologies is critical.⁴¹³

MANAGEMENT STRATEGIES: HEART TRANSPLANTATION

Heart transplantation can be successfully performed among patients who have received the Fontan operation, but many controversies remain, particularly concerning questions of transplantation indications, contraindications, and the optimal timing of transplantation. Although a uniform set of criteria that determine transplantation eligibility for the patient with Fontan circulation would be desirable, current knowledge of the actual survival rates associated with most Fontan complications is too rudimentary to allow such consistency. The patient with Fontan circulation without major complications has a significantly better prognosis than heart transplantation would afford. With the onset of major Fontan-associated morbidities, the prognosis becomes more guarded. Renal dysfunction and hepatic dysfunction, which are common in long-term survivors, further modulate outcomes, but the impact of these factors is not fully understood. Thus, listing decisions are made in a center-specific manner, evaluating Fontan circulation–specific morbidities, as well as the status of ventricular systolic and diastolic function and AVV insufficiency, to estimate prognosis and to compare this with the expected prognosis of transplantation.

Heart transplantation is best performed at a center with substantial experience in transplantation in individuals with CHD, including patients with Fontan circulation. Of patients who are listed for transplantation, the most common diagnoses include PLE (40%), ventricular dysfunction (50%), and other diagnoses such as PB and arrhythmias (10%).^{414,415} These categories are not mutually exclusive, and these proportions are rough estimates. It is not unusual for patients with PLE to be listed for transplantation, but it is probably more common for transplantation to be reserved for those patients who no longer respond to medical or interventional options. Patients with Fontan circulation and ventricular systolic dysfunction are generally listed on the basis of the severity of heart failure symptoms, the ejection fraction, and the clinical trajectory. For other forms of morbidity or failure, the decisions about listing remain highly individualized.

The process by which cardiac donors are assigned to potential candidates is determined on a national level in the United States, with priority levels defined by the United Network for Organ Sharing, incorporating input from both clinicians and patients. For children, CHD is

afforded prioritization, with eligibility for the highest level of priority (status 1A) available to patients with CHD who require a single inotropic agent as continuous infusion. This priority is available only for patients with dilated cardiomyopathy who have received MCS or require mechanical ventilation. This prioritization reflects the large number of patients with CHD who receive transplantation as children, recently estimated as 55% of the total infant transplantation population and 40% of those <1 year of age.⁴¹⁶ It should be noted, however, that even this approach largely benefits only the subset of patients with Fontan circulation with reduced ventricular systolic function, who make up approximately half of those who require transplantation. It is of much less value for those with PLE or other forms of Fontan failure with preserved ventricular function.

For adults, patients with CHD make up a very small fraction of the total transplantation population, and the prioritization scheme reflects a lack of focus on this population. The priority criteria for adults are currently in evolution, with new criteria approved but not yet implemented.⁴¹⁷ However, in both the old and new schemes, CHD is not associated with any elevation in priority status, and the factors that lead to priority (eg, placement of MCS, continuous infusion of inotropes in combination with pulmonary artery catheter) are not commonly used in Fontan circulatory failure, leading to ongoing challenges in obtaining donors for these patients even after they are listed for transplantation.

For those patients who receive heart transplants, outcomes in children are known to be excellent and have been shown to be improving in the current era compared with earlier results. The most robust data for this comes from the PHTS (Pediatric Heart Transplant Study), a multicenter database. Initial reports from the PHTS showed 1-year survival after transplantation of 76% for patients with Fontan circulation, significantly lower than the survival of 91% for control subjects without CHD ($P=0.0004$).⁴¹⁸ More recently, outcomes in the PHTS for patients with Fontan circulation have improved, with a 1-year survival rate of 89%, which is not distinguishable from the control population.⁴¹⁵ For adults, the picture is murkier. There are far fewer adult patients with Fontan circulation who undergo transplantation, and the results are not as well documented. The largest single-center experience includes 26 patients over 26 years, with 1-year survival of 65%.⁴¹⁹ Inasmuch as a large portion of the mortality after transplantation in the patient with Fontan circulation is attributable to extracardiac morbidities and these morbidities progress over time, there is concern about whether the outcomes in adults will reach the levels demonstrated in children. With the growing number of patients with Fontan circulation reaching adulthood, this question will take on increasing importance in the next epoch of Fontan care. Given the level of specializa-

tion required to provide transplantation evaluation and care and the relatively small size of the population, patients with Fontan circulation in need of these services should be offered referral to specialized centers.

GAPS IN KNOWLEDGE, GOALS, AND NEXT STEPS

Surgical innovation has led to a pathway of survival for those born with a single ventricle. However, this success has created a population of individuals with increasing morbidity and medical needs. Healthcare resource use and expenditures for patients with a single ventricle are increasing and expected to continue to increase,¹⁰⁷ with a paucity of evidence-based clinical care strategies currently in place to affect outcomes.

To meet the challenge of providing a normal quality and duration of life for patients with Fontan circulation, a number of gaps in knowledge need to be bridged and a series of objectives achieved.

Improved Understanding of the Basic Science and Biology of the Single Ventricle

To develop novel strategies, a better foundation of scientific understanding is necessary. A scientific summit was held at Stanford University in April 2018 in which a number of research objectives were summarized. Insights into the genetics of single-ventricle CHD are required. Models of single-ventricle CHD are necessary to elucidate the mechanisms of arrested ventricular development. Processes such as decreased cell proliferation, increased apoptosis, and mitotic cell cycle arrest and associated metabolic and mitochondrial changes in both the fully formed ventricle and the hypoplastic ventricle should be investigated. Exploring the common developmental pathways of the placental and fetal cardiovascular systems may offer clues to the origins of single-ventricle CHD. Investigation of the relationship between genotype and phenotype to elucidate mechanisms of heart failure and to guide counseling for individual families could be accelerated by the development of large clinical registries, modeling single ventricles with induced pluripotent stem cells, high-throughput screening for mechanisms of single-ventricle failure, and identification of biomarkers to serve as a plasma signature of myocardial events. Strategies using stem cell-based therapies to prevent or treat ventricular failure are being explored. Further work in computer modeling, 3D printing, and tissue engineering would help to drive the design and creation of vessels, heart valves, organs, and auxiliary pumps. A large-animal model of Fontan circulation would be of tremendous benefit in further experimental design of

the circulation and new surgical and mechanical support therapies.

Improved Understanding of Fontan Physiology

To achieve progress in the care of this growing population, we need to deepen our understanding of the basic physiological mechanisms underlying this extraordinary circulation. Understanding the physiological “critical bottleneck” in the circulation (ventricular dysfunction, valvular dysfunction, Fontan cavopulmonary connection, pulmonary vasculature, etc) will allow a targeted therapeutic strategy, which may vary from patient to patient and within individual patients over time. We now understand how dilatation of the atrial chamber in the classic atriopulmonary Fontan is associated with atrial arrhythmias, thromboembolic events, and ultimately ventricular failure.^{420,421} We now also understand that patients with Fontan circulation live with decreased cardiac output and increased systemic vascular resistance, but it is still uncertain whether lowering systemic vascular resistance will be beneficial or deleterious to these patients.⁴²² The decline of the Fontan circulation is often associated with decreased oxygen saturation, increased cardiac volumes, and altered mesenteric blood flow, but how these factors interact is unclear.^{44,423–425} We understand that patients who have adverse characteristics such as decreased ventricular function, distorted or small pulmonary arteries, AVV regurgitation, and arrhythmias will have a worse outcome. However, we do not yet know whether patients who do not have any such adverse features will be affected by rapid deterioration of their Fontan circulation and, if so, in what time frame. It is suspected that all patients are at risk to be impaired because of the gradual increase of their pulmonary vascular resistance and their decreased diastolic ventricular function, but the evidence for when and how these impairments occur is weak.^{58,426,427}

Characterizing the State of the Fontan Circulation

The main parameters helping us to identify the quality of a cavopulmonary circulation are invasive measurements of central pulmonary artery pressures and end-diastolic pressure of the systemic ventricle. Unless grossly abnormal, these parameters have been poorly correlated with adverse outcomes. It is likely that these parameters are unreliable and highly variable even within individual patients because they are measured in only 1 instance when most patients are fasted, in a supine position, and frequently under sedation or general anesthesia. A more real-life, dynamic mode of characterization of the Fontan circulation that better reflects the natural, daily state is necessary.

Understanding the Mechanisms of End-Organ Damage

A large proportion of patients will incur hepatic and renal end-organ damage driven likely in combination by the excessive venous pressure and altered cardiac output characterizing this circulation.⁸ Differences from normal in baseline substrate organ state as a consequence of altered development may increase vulnerability to the rigors of the Fontan circulation and thus place specific organs at risk. The model of a different-from-normal organ structure at birth, with acquired, additive insult along the way, is likely the process in play in neurological injury and its clinical manifestations. Such a model may similarly apply for other organ systems in the single ventricle. The potential for reversibility of these organ system damages is still unknown. A deeper understanding of the pathophysiology of end-organ damage will allow the development of specific treatments that may mitigate or alter the trajectory of decline and further inform the optimal timing to offer heart transplantation.

Lymphatic Circulation

Emerging knowledge indicates that the lymphatic circulation is under significant duress in the Fontan circulation. Increased venous pressure leads to increased production in organs such as the liver, as well as impediment to drainage. New imaging techniques for the first time allow visualization of the severe degree of lymphatic channel abnormalities present.⁴²⁸ The most feared complications after Fontan operation—PLE, PB and, in terminal patients, ascites and edema—are clearly driven by the incapacity of the lymphatic circulation to drain this increased lymphatic flow.^{167,197} Lymphocytes are depleted and specific T-cell populations are perturbed in patients with Fontan circulation.¹⁷⁶ Defining the pathophysiology behind the trajectory from mild lymphopenia, common and progressive after Fontan operation, to the life-threatening conditions of PLE or PB is important. Exploring the relationship between lymphatic congestion and end-organ dysfunction such as liver fibrosis and intestinal absorptive abnormalities that may be the source of nutritional and vitamin deficiencies would be of great value. Whether there are individual variations in the lymphatic circulation—*inherent, acquired, or a combination*—is unknown. Research should be focused on studying the capacity for the lymphatic circulation to sustain these abnormal flows. Mechanical or medical interventions for decompression or reducing production may affect the function of the lymphatic circulation and thus profoundly influence outcomes after Fontan operation.^{429–431}

Individual Variation

There is clearly a subset of patients with Fontan circulation who are doing well from both the physiological and

the psychosocial perspective. Discovering what factors contribute to resilience and sustained success is critically important. Despite the heterogeneity of this population, practitioners still try to establish management strategies that would fit the entire population. There seems to be little doubt that the variation in innate and acquired characteristics of these patients necessitates a more balanced approach to management and treatment. It is reasonable to believe that the characteristics of the circulation such as cyanosis and increased venous pressures, as well as lymphatic circulatory variation and organ system vulnerabilities, are tolerated in various ways by individual patients, but this possibility is still unexplored. Exploring the genetic basis of ostensible phenotypic variability is essential to understanding this individual variability.

Risk Stratification

There is a continuity spectrum of incremental health status between the perfectly well-appearing, well-functioning patient with Fontan circulation and progressive degradation leading to failure and risk of premature death. However, we are lacking appropriate metrics for characterization specific to the state of patients with this unique circulation. Such metrics would provide a capacity to stratify risk and to better gauge prognosis and the best time to initiate therapies. A validated risk stratification scheme could likely be based on a rich host of features such as morphological and functional characteristics, cardiopulmonary fitness indexes, biological parameters, and estimates of end-organ functionality.

Neurodevelopmental Outcomes, Quality of Life, and Socioeconomic Impact

Neurodevelopmental status and psychological function are some of the most important factors that influence outcome and quality of life in patients with Fontan circulation. Today, the determinants of only 30% of the variations in neurodevelopmental outcomes are elucidated.^{295,296} Psychosocial well-being is a major concern voiced by families of a patient with Fontan circulation. Mental health concerns affect not just the patient but also parents and siblings, with potential influence on family socioeconomics and quality of life. Mental health therapies for active problems and preventive measures along the therapeutic trajectory starting early in life may improve outcomes but have not yet been clearly identified. Social integration of those born with a single ventricle is a goal, with education, gainful employment, and creation of a meaningful, productive life. Strategies to achieve these goals must emerge as the population grows further into adulthood. Although major physiological changes may not yet be readily available, we should exert greater efforts at the earliest possible

points of care to promote wellness through strategies of optimizing exercise, nutrition, and mental health—factors that may very well prove to be readily modifiable and could have great impact on improving quality of life.

Achieving these goals and objectives will require collaboration and the development of multicenter networks. Registries can provide a data resource that may facilitate answering many of the above questions and provide further insight into the design of clinical trials evaluating drugs, exercise regimens, or other interventions. Adherence to the proposed surveillance toolkit suggestions may lead to a reduction in clinical practice variability with learning and discovery of optimal clinical practice strategies. Finally, building a culture of research investigation among patients is important. Healthcare providers should convey to those with single-ventricle heart disease that the best path forward to wellness and a long and healthful life is evolving, and thus, their participation in discovery and investigational research endeavors is essential and should be encouraged. This approach can allow the best evolution of optimal treatment strategies moving forward.

TAKE-AWAY MESSAGE FOR THE PATIENT, PARENTS, AND FAMILIES

This statement characterizes the health profile of the patient with Fontan circulation. The detailed listing of many issues and challenges within the cardiovascular system and other organs may, by the wealth of information provided, overwhelm patients and their families. The authors of this AHA statement express concern that through the exhaustive articulation of these many challenges, we risk the possibility of painting a very depressing picture of the life of those born with a single ventricle. We therefore believe it is necessary to take a step back and appropriately frame the current situation for the patient with Fontan circulation.

An Extraordinary Story

The survival of patients undergoing the Fontan procedure has been an extraordinary success. At the outset, it was never suspected that patients with such life-threatening birth defects could live for such extended periods in such relatively good condition. A substantial number of patients are now entering their fifth decade and beyond.^{61,364} We had not predicted the burden that this circulation would have on the physical and psychological health of our patients because at first the focus was on survival. The fear of death remains the highest concern of patients and their families.⁴³² Nevertheless, the extraordinary survival of most born with this condition today is a testimony to the perseverance of

numerous practitioners, patients, and their families and should be considered an amazing achievement of modern cardiovascular medicine.

Characterizing the Condition Is an Essential Initial Step

Today, we are in the early phase of characterizing this circulation and its consequences. One should realize that we are reporting population averages with relatively small numbers in most of our investigational studies and that individual patient measures will be spread along a wide variation spectrum. As an example, it was previously suspected that the Fontan circulation was incompatible with a normal exercise capacity. It is now reported that a substantial proportion of patients have better than normal, normal, or near-normal exercise capacity.⁴³³ The same is likely possible to hold true for liver, kidney, and brain function. Characterization of the condition in every patient is therefore a necessary step to discover care pathways that can allow the individualization of management and improve personal well-being. This is the fundamental principle underlying our consensus on suggested schema for surveillance.

We Have Not Yet Started to Evaluate the Impact of Interventions

Interventional and preventive strategies of care are evolving for the patient with Fontan circulation. For example, we know that better psychological support of families from the early stages of life may improve psychological well-being of patients, their parents, and their siblings.⁴³⁴ Of great promise but not yet fully tested is the impact of cardiac rehabilitation programs, enhanced nutrition, and interventions aimed at improving neurodevelopmental outcomes. Programs targeting patient education and health self-awareness may be of great value. Trials testing various medications are underway with anticipation of identifying optimal drug therapies to enhance and sustain cardiovascular and end-organ wellness.^{392,435} Instead of a reactive approach to complications, an era of proactive health maintenance is emerging as experiences unfold and understandings improve.

A Rich and Fulfilling Life

As healthcare practitioners, we may often lose perspective and not appreciate that the life of our patients is not necessarily limited to their medical condition. Between hospitalizations, complications, and fears, our patients enjoy a rich and satisfying life. Although some studies show patients to have a decreased quality of life, others identify patients with Fontan circulation to have a quality of life similar to that of their peers.^{436–438}

Even among some of the oldest patients, many attain higher levels of education, have jobs, and build their own families with satisfying and fulfilling lives.⁶¹

We are now entering a new phase in the management of patients born with single-ventricle CHD. Provided that patients undergo regular follow-up, adopt a healthy lifestyle, and are encouraged to participate in investigational clinical protocols and research, health-care providers and patients can share an optimistic view for a brighter future.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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*Modest.

†Significant.

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