Clinics Review Articles

HEART FAILURE CLINICS

Heart Failure in Adult Congenital Heart Disease

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Failure of the Fontan Circulation

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KEYWORDS

• Fontan circulation • Chronic low output • Circulatory failure • Pulmonary vascular resistance

KEY POINTS

- The essence of a Fontan circuit is the creation of the Fontan "neoportal system": this allows for oxygenation at near normal levels, but at the cost of a chronic state of systemic venous congestion and decreased cardiac output.
- The heart, while still the engine of the circuit, cannot compensate for this major flow restriction: the ventricle has lost control of the output and of systemic venous congestion; systolic and diastolic ventricular dysfunction are common and may contribute to overall circulatory failure.
- The abnormal hemodynamics inherent in the Fontan circulation affect organs outside the heart and may lead to liver cirrhosis, protein-losing enteropathy, or plastic bronchitis.
- Failure of the Fontan is progressive; over time there is an insidious increase in both pulmonary vascular resistance and ventricular end-diastolic pressure, which may lead to progressive functional impairment.

THE "FONTAN" CONCEPT

A normal mammalian cardiovascular system consists of a double circuit, pulmonary and systemic, connected in series and powered by a double pump. In the absence of congenital heart disease, the right ventricle pumps to the pulmonary circulation and the left ventricle pumps to the systemic circulation (**Fig. 1**A).

Many complex cardiac malformations are characterized by the existence of only one functional ventricle. This single ventricle has to maintain both the systemic and the pulmonary circulations, which at birth are not connected in series but in parallel (see **Fig. 1**B). Such a circuit has 2 major disadvantages: diminished oxygen saturation of the systemic arterial blood and a chronic volume load to the single ventricle. The chronic ventricular volume load will lead to progressive impairment of ventricular function and altered pulmonary vasculature, causing a gradual attrition resulting from congestive heart failure and pulmonary hypertension from the third decade, with few survivors beyond the fourth decade.

In 1971, Francis Fontan[1] from Bordeaux, France, reported a new approach to the operative treatment of these malformations, separating the systemic and pulmonary circulations. In a "Fontan circulation" the systemic venous return is connected to the pulmonary arteries without the interposition of a pumping chamber (see **Fig. 1**C). In this construct, residual postcapillary energy is used to push blood through the lungs in a new portal-like system.[2] Advantages of a Fontan circuit include (near) normalization of the arterial oxygen saturation, and abolishment of the chronic volume load on the single ventricle. However, because venous return through the pulmonary vasculature

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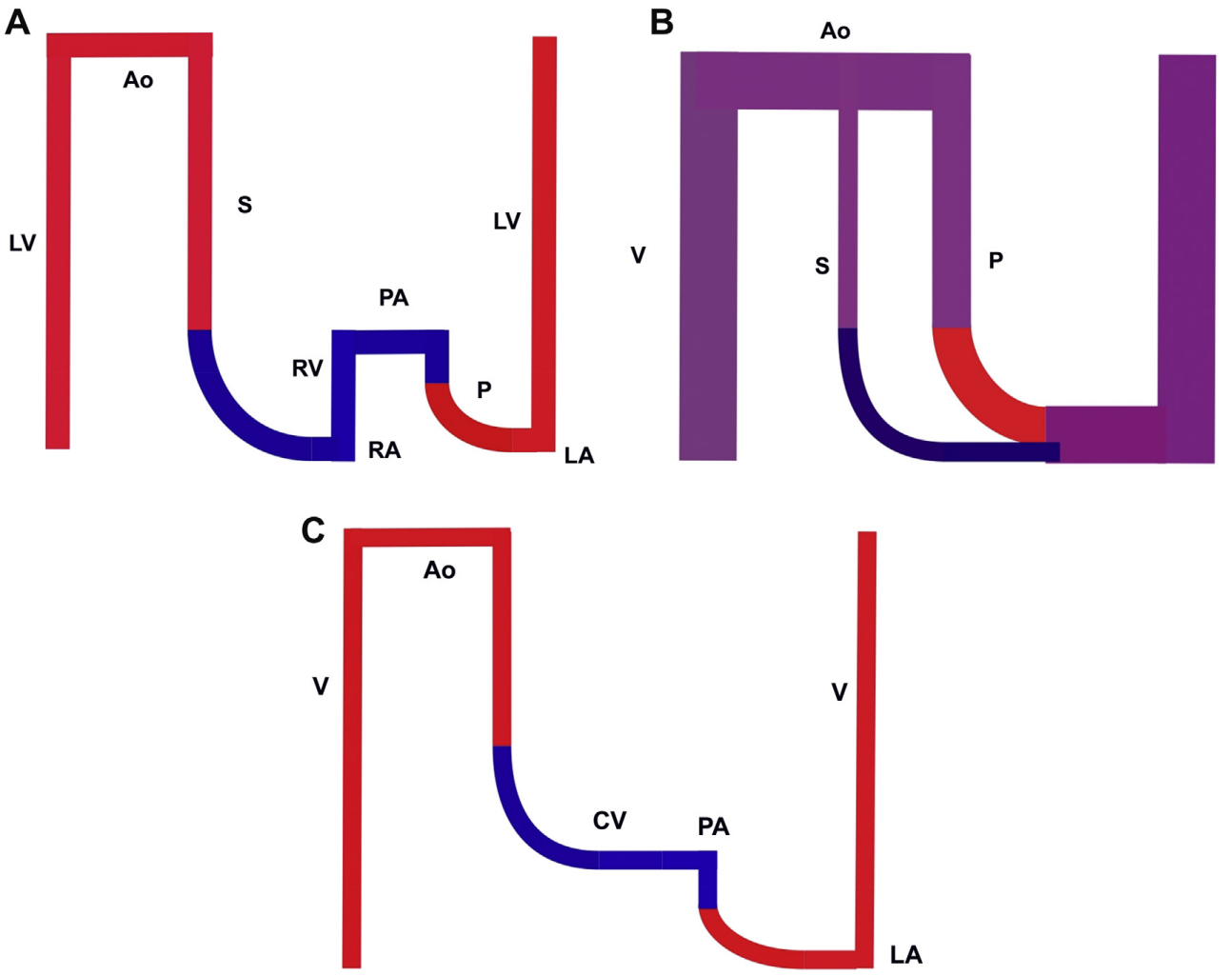

Fig. 1. Normal cardiovascular circulation (*A*), shunted palliation (*B*), and Fontan circulation (*C*). (*A*) Normal circulation. The pulmonary circulation (P) is connected in series with the systemic circulation (S). The right ventricle maintains the right atrial pressure lower than the left atrial pressure, and provides enough energy for the blood to pass through the pulmonary resistance. (*B*) Shunted palliation. The systemic (S) and pulmonary (P) circuits are connected in parallel, with a considerable volume overload to the single ventricle. There is complete admixture of systemic and pulmonary venous blood, causing arterial oxygen desaturation. (*C*) Fontan circuit. The systemic veins (V) are connected to the pulmonary artery, without a subpulmonary ventricle or systemic atrium. The lungs are thereby converted into a neoportal system, which limits flow to the ventricle. In the absence of a fenestration, there is no admixture of systemic and pulmonary venous blood, but the systemic venous pressures are markedly elevated. A fenestration allows the systemic venous blood to bypass the Fontan portal system and limits the damming effect, thereby increasing output and decreasing congestion, but also arterial saturation. Ao, aorta; CV, caval veins; F, fenestration; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle; V, single ventricle. Line thickness reflects output, color reflects oxygen saturation.

is hindered by the pulmonary impedance, this circulation creates a state of chronic hypertension and congestion in the systemic veins, and results in decreased cardiac output, both at rest and during exercise (Fig. 2).[3,4] It is these 2 inherent features of the Fontan circulation, elevated systemic venous pressure and chronically low cardiac output, which are the root cause of most of the physiologic impairments, collectively termed Fontan failure.

CARDIAC OUTPUT IN THE FONTAN CIRCULATION

By creating a total cavopulmonary connection, a new portal system is made. A portal system occurs when one capillary bed pools blood into another capillary bed through veins without passing through the heart; for example, the hepatic portal system and the hypophyseal portal system. The Fontan neoportal system dams off and pools the systemic venous blood. As a result, transit of

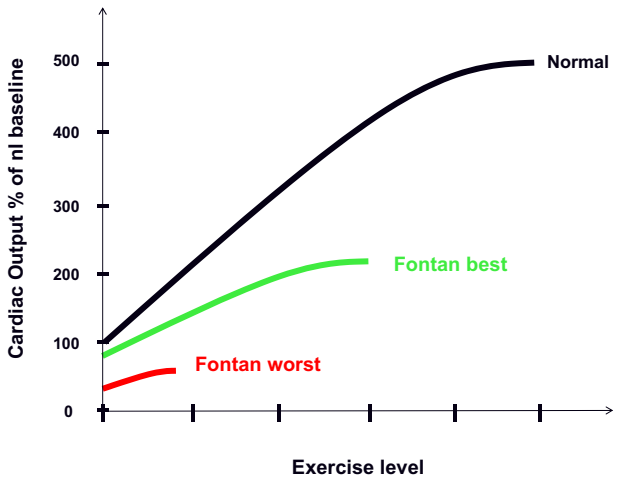

Fig. 2. Exercise and output: normal versus Fontan circulation. A normal subject with a biventricular circuit can increase his output by a factor of 5 (*black line*). In Fontan patients, output is significantly impaired both at rest and during exercise; at best (*green line*), the output is mildly decreased at rest, with moderate capacity to increase flow during moderate exercise. At worst (*red line*), the output is severely reduced at rest and barely augments during minimal exercise.

blood through this neoportal system depends on the pressure gradient from the systemic postcapillary vessels to the pulmonary postcapillary vessels (see Fig. 1C). As there is no pump to add energy to the system, small changes in the static resistances and dynamic impedances of the structures within this portal system have a profound impact on the blood flow.

Fontan failure is different from pure systolic or diastolic heart failure in that although the heart itself may function well, the inherent limitations of the Fontan neoportal system determine the degree of circulatory compromise. It is this neoportal system that is the limiting factor of flow, and the underlying cause of venous congestion and diminished cardiac output. The heart, while still the engine of the circuit, cannot compensate for this major flow restriction: the suction required to compensate for the damming effect of the Fontan portal system cannot be generated. The heart therefore no longer controls cardiac output, nor can it alter the degree of systemic venous congestion. In cases where the systemic ventricle functions poorly, the heart can make an already compromised circulation worse. Fig. 3 illustrates the relationship between output, ventricular contractility, and pulmonary vascular resistance (PVR).

The components that make up the Fontan neoportal system are critically important in the overall function of the Fontan circuit. These components include the venoarterial Fontan connection itself (atriopulmonary in older patients), pulmonary arteries, pulmonary capillary network (including precapillary sphincters), pulmonary veins, and the venoatrial connection. Impairment at any level of this portal system will have profound consequences on the output of the Fontan circuit, much more so than a comparable dysfunction in a 2-ventricle circulation. These impairments

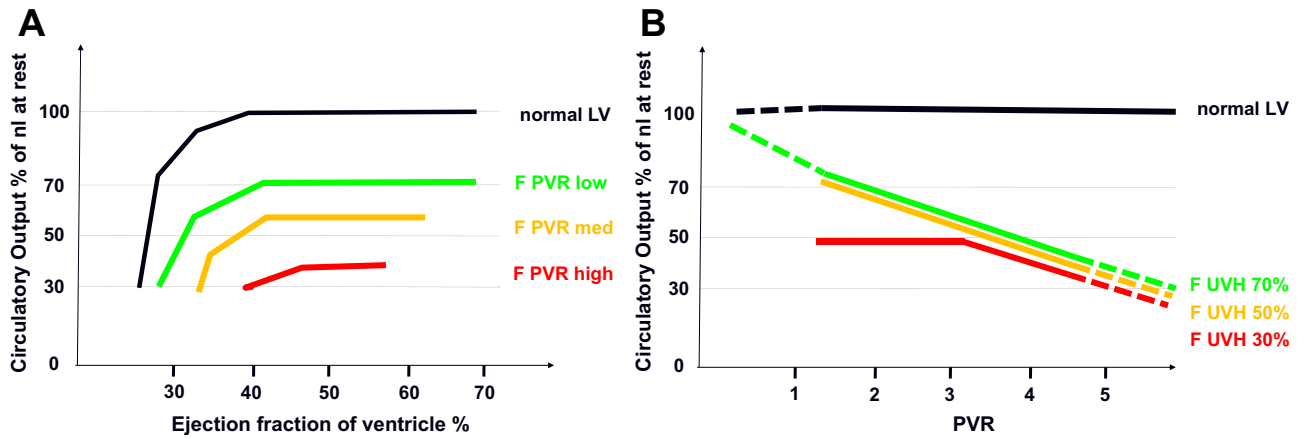

Fig. 3. (*A, B*) Relationship of output at rest, ventricular function, and pulmonary vascular resistance (PVR). (*A*) Modulation by PVR. In a normal subject (*black line*), output at rest is minimally influenced by ventricular function, except when severely depressed. In Fontan patients (*colored lines*), PVR is the primary modulator of cardiac output. As in a 2-ventricle system, systolic performance will only affect output at rest when cardiac function is severely depressed. If ventricular function is not severely depressed, squeezing harder will not result in more output. (*B*) Modulation by ventricular function. In a normal subject (*black line*), cardiac output is not influenced by a mild increase of PVR up to 5 Woods Units. In all Fontan patients (*colored lines*), an increase in PVR is invariably associated with a decrease in cardiac output. If PVR is low, a reasonable output is achieved in patients with normal or moderately depressed ventricular function (*green and yellow lines*). However, severely depressed ventricular function invariably results in low output (*red line*). F, Fontan; LV, left ventricle; PVR, pulmonary vascular resistance; UVH, univentricular heart.

include, but are not limited to, stenosis, hypoplasia, distortion, vasoconstriction, pulmonary vascular disease, loss or exclusion of large or microvessels, turbulence and flow collision, flow mismatch, and obstruction by external compression.

The restriction to cardiac output imposed by the neoportal system can be partially reversed by bypassing the pulmonary vasculature. A Fontan fenestration allows flow to bypass the Fontan neoportal system, resulting in an increase in cardiac output and a decrease in venous congestion. However, while a fenestration can increase overall output, it does so at the expense of diminished arterial oxygen saturation. Nevertheless, in the setting of a fenestration, the increase in cardiac output can result in an increase in peripheral oxygen delivery even if the saturation is mildly diminished. **Fig. 4** shows the relationship between output, congestion, and arterial saturation in a good and bad (failing) Fontan circuit, and the effect of partial undoing by a fenestration. In a good Fontan circuit, the low-resistance portal system will cause a mild decrease of output with modest increase in systemic venous pressures, making a fenestration unnecessary. In a bad Fontan circuit, inclusion of a high vascular resistance portal system will decrease output and create venous congestion to unacceptable levels; a fenestration will attenuate these changes, but in bad candidates with increased PVR an acceptable compromise may not be possible.

FUNCTIONAL IMPAIRMENT AFTER THE FONTAN OPERATION

The restriction to cardiac output and the inability to power blood through the pulmonary vasculature results in a circulation whereby the ability to perform exercise is reduced. Under resting conditions, cardiac output in a patient with a Fontan circulation is approximately 70% to 80% of what would be normal for age or body surface area. During exercise, the limitations of the Fontan circuit are substantially magnified such that the small differences in cardiac output at rest become much larger differences in cardiac output during activity (see **Fig. 2**). At peak exercise, a well-trained athlete with a normal heart can increase blood flow through the lungs by up to 5-fold. This increased flow is accomplished through a substantial increase in right ventricular systolic pressure (up to 70 mm Hg![5]) as well as flow acceleration coupled with a decrease in PVR. In a patient with Fontan physiology, there is no physiologic mechanism to allow for a similar increase in cardiac output: the maximal mean venous pressure rarely reaches 30 mm Hg, there is no blood acceleration, and the reactivity of PVR is attenuated or absent.[6] In combination, these limitations result in a diminished ability to augment cardiac output in response to increased metabolic demand, and therefore limit the ability of a patient with a Fontan to perform exercise.

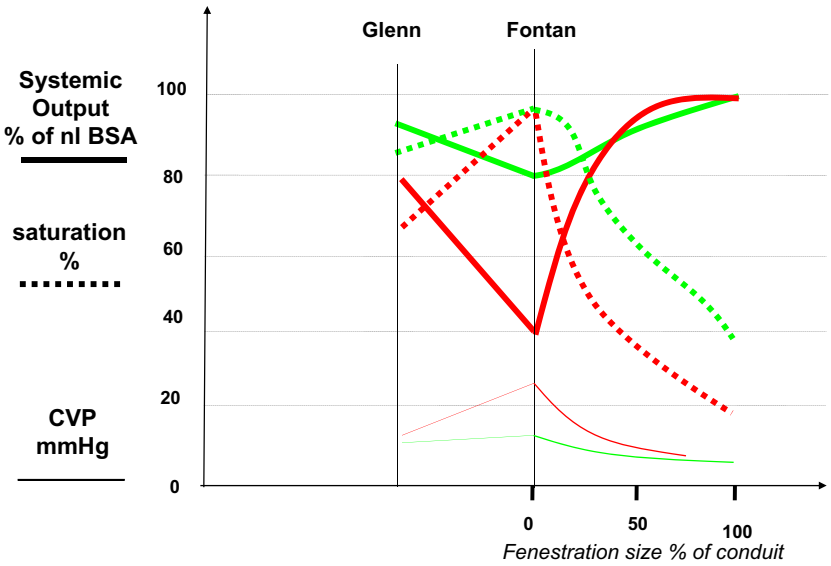

Fig. 4. Effect of various degrees of pulmonary bypass in a Fontan circuit on systemic output, saturation, and systemic venous congestion. A "good Fontan" with low neoportal resistance (*green lines*) has an output (*thick solid lines*) of about 80% of normal for body surface area (BSA), with a high saturation (*dotted lines*) and a mildly elevated central venous pressure (CVP) (*thin lines*). The "bad Fontan" with a high portal resistance has an output with a similar saturation, but with a very low to unacceptable output despite a high CVP. Partial bypassing of the Fontan portal system by a fenestration invariably increases systemic output and decreases systemic congestion, but in the "bad Fontan" this occurs at an unacceptable degree of cyanosis.

Through childhood and until puberty, the mean maximal exercise capacity for patients with a Fontan circulation is in the range of 65% predicted for gender and age.[7] The situation worsens as patients pass through puberty and their body composition changes while the efficiency of the Fontan circuit diminishes. Whereas good Fontan patients may remain stable for many years, poor Fontan patients suffer an accelerated increase of PVR and increasing filling pressures of the ventricle as a result of chronic preload deprivation with disuse hypofunction. Longitudinal studies of late adolescents and young adults demonstrate this point well; as patients progress to late adolescence and early adulthood, exercise capacity tends to continue to decline by about 2.6% predicted per year.[8]

The impact of the functional impairment of the Fontan patient may only limit activities at first, but at an advanced stage is predictive of the need for hospitalization and, possibly, death and/or the need for transplant. In many forms of congenital heart disease, an exercise capacity of 45% to 50% predicted appears to be the cutoff for the development of symptoms of heart failure.[9] In the Fontan physiology, assuming a starting point of 65% predicted for age at the onset of puberty and a decline of 2.6% per year thereafter, the cutoff of 45% predicted can be expected to be reached at the end of the second decade of life. Not surprisingly, this is fairly close to what is actually reported. Diller and colleagues[10] followed 321 patients with various Fontan connections for a median of 21 months. The mean age of patients at the onset of the study was 21 years, with a maximal predicted oxygen consumption of 52%. Not surprisingly, during the follow-up period 41% of patients required hospitalization for heart failure and 9% of patients either died or underwent heart transplantation.

Although the exercise data and the rate of functional decline suggest significant impairment by the end of the second decade, there are several reasons why adults with a Fontan circuit in the current era do not reflect where the current cohort of patients will be in several decades. Many of the original candidates for a Fontan operation, the current adult cohort, were suboptimal for this type of surgery from a hemodynamic standpoint, with many significant residual lesions and sequelae related to the original cardiac malformation and palliative procedures. A shunt procedure performed during the period from the 1960s to the 1980s was evaluated based on the goal of the long-term relief of cyanosis: “the pinker the better.” Often a second aortopulmonary shunt was created to augment pulmonary blood flow after the first shunt was deemed inadequate. The idea that these shunts could induce pulmonary vascular disease, ventricular overgrowth, hypertrophy and dysfunction, or pulmonary artery distortion was not—as it is now—a principal preoccupation of the surgeon. At present, the success of a shunt is evaluated by obtaining acceptable relief of cyanosis without significant volume overload to the ventricle, and by the induction of adequate pulmonary growth without causing changes to PVR. In addition, in the modern palliation the systemic to pulmonary shunt is designed to last 4 to 6 months, enough time to allow vascular resistance to drop such that a partial cavopulmonary connection can safely be created. **Fig. 5** illustrates the different loading conditions of the single ventricle at the various stages of palliation, highlighting the differences in management before the 1990s (typically 2 aortopulmonary shunts before full Fontan) and after (typically 1 shunt, then partial and later complete Fontan).

THE HEART AND PULMONARY VASCULATURE IN THE FONTAN CIRCULATION

The Heart

In the Fontan construct, the heart is exposed to several stressors that can result in altered structure and impaired function. Chronic preload deprivation and increased systemic vascular resistance create a milieu that favors development of both systolic and diastolic dysfunction. Although the heart is not the primary determinant of cardiac output after the Fontan, alterations in cardiac function can result in functional impairments beyond what might be expected from the Fontan construct itself, and so cannot be overlooked.

Over the long term, systolic dysfunction of the single ventricle results from both decreased preload and the chronic impact of pumping against increased resistance. The effects of chronic deprivation are significantly aggravated by the ventricle being overgrown by the time it reaches the Fontan state.[4] This combination leads to a situation whereby the optimal point for contractility on the Frank-Starling preload-contractility curve cannot be achieved and the heart appears both underfilled and hypertrophied; an “overgrown pump.”[11] In addition to the factors related to the limitations of the Fontan physiology, the single ventricle may also exhibit systolic dysfunction as a result of the malformation itself (right vs left ventricle, fiber disarray), or as a result of overgrowth and damage by the volume or pressure overload state that was present early in the palliative course.

Diastolic function after the Fontan is also typically abnormal, and the impairment is progressive. The unloading of the ventricle at the time of the

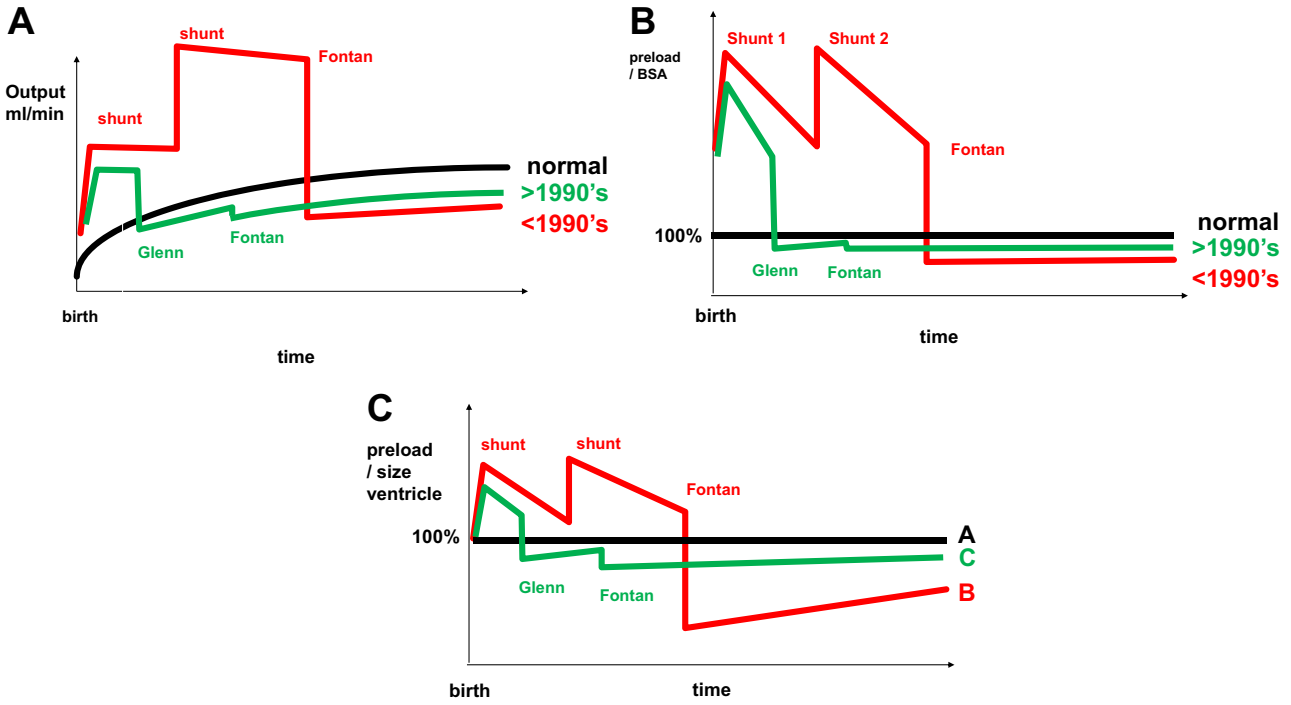

Fig. 5. (*A–C*) Cardiac output versus time in the normal left ventricle and the univentricular heart (UVH) managed before and after the 1990s. Each graph tells the same story but expressed with a different reference frame: in absolute value (*A*), related to BSA (*B*), and related to ventricular size (*C*). (*A*) Cardiac output expressed as absolute value: The black line shows output of a normal ventricle, which increases proportional to growth. At birth the volume load to the UVH is about 250% to 300% of that of a normal left ventricle. Before the 1990s, a neonatal and infant large shunt is created with significant increase in output (*red line*); the shunts are abolished at the time of the Fontan operation, and the Fontan portal dam reduces preload even further. After the 1990s, a small neonatal shunt is created for a short time, and the ventricle is progressively unloaded at both the Glenn and the Fontan operation (*green line*). (*B*) Cardiac output related to BSA. Black line: output of normal remains at 100% for body surface area (BSA). This representation assumes only dilation and stretch without any overgrowth of the ventricle. The patient with a UVH is born with a large ventricle (volume load of 250% of normal for BSA). Before the 1990s (*red line*), the preload to the ventricle is augmented shortly after birth by a shunt procedure to ±350% of normal for BSA. The patient slowly outgrows his shunt, thereby gradually reducing the volume overload. A second shunt is created, augmenting the volume overload again. As this patient again outgrows his shunt, a Fontan circuit is made, reducing the volume load to less than 80%. After the 1990s (*green line*), a small neonatal shunt is created for a short time; the patient slowly outgrows his shunt, and the ventricle is progressively unloaded at both the Glenn and Fontan operation (*green line*). (*C*) Cardiac output related to ventricular size. This representation assumes adapted overgrowth of the ventricle at every stage in the function of chronic preload, A: output of normal remains at 100% for ventricular size. The patient with a UVH is born with an appropriate ventricle for volume load (100% of normal for ventricular size). Before the 1990s (*B*, *red line*), the preload to the ventricle is augmented shortly after birth by a shunt procedure to ±150%. The patient slowly outgrows his shunt and adapts his ventricle, thereby gradually reducing the volume overload to ±100% for its size. A second shunt is created, augmenting the volume overload again to 150%. As this patient again outgrows his shunt, a Fontan circuit is made, reducing the volume load to 25% of its "due" preload. After the 1990s (*C*, *green line*), a small neonatal shunt is created for a short time; the patient slowly outgrows his shunt, and the ventricle is progressively unloaded at both the Glenn and Fontan operation in much milder steps, avoiding acute unloading and severe deprivation.

Fontan procedure results in less recoil, impaired compliance, and decreased suction in the acute phase.[12] Owing to persistent preload deprivation, the pressure-volume curve may show "reversed creep," with an upward shift and increasing filling pressures (Fig. 6). The ventricle may now enter a vicious cycle whereby the chronic low preload results in remodeling, reduced compliance with increasing diastolic pressures, poor ventricular filling, and, eventually, progressively declining cardiac output. This phenomenon of progressive "disuse hypofunction" occurs at a chronic preload of less than 70% of the preload expected for ventricular size.[13]

The response of the heart to the stressors associated with the Fontan operation appears to be heterogeneous. In some patients the heart can appear fairly normal for many years, and function

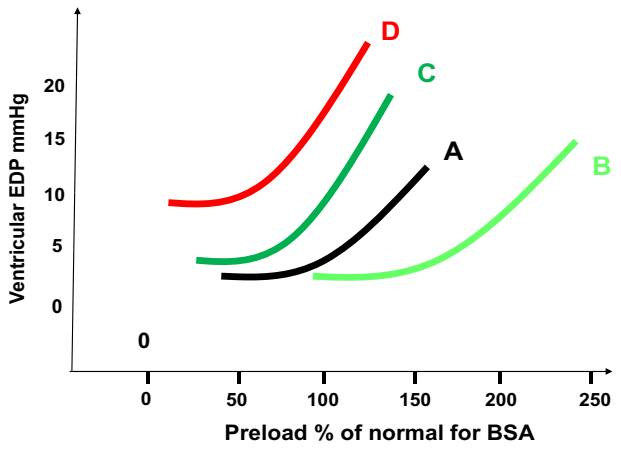

Fig. 6. Ventricular end-diastolic pressure (EDP) in various phases of ventricle. A, normal ventricle; B, shunted ventricle with chronic volume overload leading to enhanced compliance; C, Fontan ventricle after acute phase, with mild preload deprivation of the overgrown ventricle; D, Fontan ventricle with low output as a result of severe chronic preload deprivation, leading to elevated filling pressures.

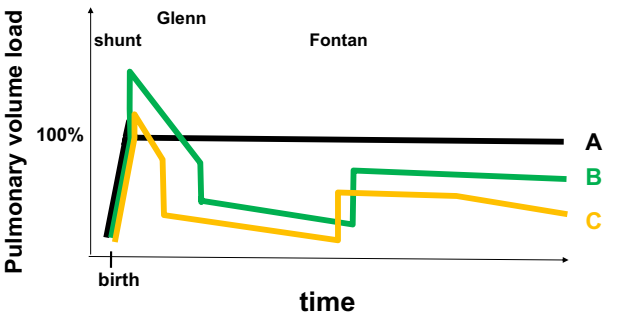

Fig. 7. Pulmonary volume load (and outcome) of Fontan since the 1990s. In the normal circulation, pulmonary blood flow increases at birth and remains at 100% of normal for BSA (*A*, *black line*). In a univentricular heart, a phase of significant pulmonary overflow exists immediately after birth until a shunt or band is placed to limit blood flow. With adequate pulmonary growth (*B*, *green line*), pulmonary blood flow is reduced to about 50% of normal for BSA after the superior cavopulmonary connection (stage 2 palliation). Pulmonary flow is then increased by completion of the total cavopulmonary connection (the Fontan operation). If flow to the lungs is too low after the initial palliation, this may result in inadequate growth (*C*, *orange line*). The cyanosis from low pulmonary blood flow may lead to early referral for superior cavopulmonary connection, which may further reduce flow and growth. When the Fontan circuit is created, the Fontan portal system will have a high impedance, resulting in a poor Fontan circulation irrespective of the ventricular function, with low cardiac output and a progressive functional impairment.

may be relatively well preserved, whereas in other patients the ventricle appears thickly trabeculated and "overgrown" starting at, or even before, the time of Fontan surgery. The variability may be related in part to native anatomy or myocardial disarray from conformation changes resulting from the palliative surgeries preceding the Fontan, but there may also be a genetic heterogeneity in the response of an individual to the stressors associated with single-ventricle physiology. Polymorphisms in the renin-angiotensin-aldosterone system have been shown to have measurable impact on ventricular hypertrophy and on the response of the myocardium to treatment with angiotensin-converting enzyme inhibitors.[14] It may be that these and other unmeasured genetic variants are in part responsible for the variable response of the heart to the Fontan circulation. However, even for those in whom the genetic preprogramming is favorable, the basic physiology of the Fontan will invariably lead to some element of progressive systolic and diastolic dysfunction.

The Pulmonary Vasculature

Abnormal growth and development of the pulmonary vasculature are a hallmark of single-ventricle congenital heart disease. Decreased flow to the pulmonary arterial tree may begin during fetal life, depending on the specific lesion, and will certainly exist by necessity after the first stage of palliation during partial or complete cavopulmonary connection (Fig. 7). As a result, hypoplasia of the pulmonary vascular bed is common. Stenosis resulting from abnormal connections, ductal constriction, or surgical scarring can further compromise the normal pulmonary architecture. The loss of pulsatile flow after cavopulmonary connection complicates the matter further by affecting the usual vasoreactivity of the pulmonary bed. Ideally the lung vessels should be slightly oversized with low resistance. However, more frequently the abnormal development may result in relative hypoplasia of the large vessels coupled with endothelial dysfunction. The chronic low-flow conditions will induce an overall state of pulmonary (and systemic) vasoconstriction, bringing the whole circuit into a negative spiral. Failing Fontans typically have a high PVR, although this is often reversible after transplantation (higher output of pulsatile flow).[15] The low-flow hemodynamic condition of the Fontan may also cause microthrombi, which further increase PVR.

SECONDARY COMPLICATIONS OF THE FONTAN CIRCULATION

Liver Fibrosis/Cirrhosis

The liver is in a particularly precarious state following the Fontan operation, as it is wedged between the capillary bed of the organs of the abdominal viscera and the capillary bed of the

lungs. This placement results in substantially diminished perfusion of the liver from decreased portal flow, in addition the burden imposed by the chronic elevation in the pressure in the central veins of the liver.[16]

In recent years, the impact of abnormal flow patterns on the liver has become more evident. A large and growing number of imaging and histologic studies have demonstrated significant fibrosis and even frank cirrhosis in patients with the Fontan circulation.[17,18] In some cases this has led to the need for heart/liver transplant as end-stage therapy following Fontan failure, whereas in other cases changes to the liver parenchyma have resulted in malignant transformation of the hepatocytes and the development of hepatocellular carcinoma.[19]

The timing of the onset of the pathologic changes in the liver is variable. Reviews of autopsies performed in patients with Fontan failure demonstrate fibrotic changes even in fairly young patients.[20] However, there does also seem to be an element of time associated with liver changes, such that those who have lived with Fontan physiology for a longer duration seem to have more substantial disease.[21] This aspect suggests that changes in liver architecture may occur early in those with a complicated early course, while the Fontan physiology itself may result in slowly progressive changes on top of the burden imposed by the early years of multiple surgeries, congestion, and chronic hypoxemia.

Protein-Losing Enteropathy

In a circulation characterized by low cardiac output and high venous pressure, the gastrointestinal tract is at a particularly high risk for poor perfusion as the autoregulatory systems attempt to maintain perfusion to other vital organs. Poor perfusion and dilated lymphatic vessels, perhaps in combination with inflammation and a genetic predisposition, are thought to be responsible for the development of protein-losing enteropathy (PLE).[22] In support of this notion, investigators have described an increase in vascular resistance in children with Fontan physiology, even in those without PLE. In children with PLE this elevation in vascular resistance has been more pronounced, and results in a substantial decrease in both systolic and diastolic blood flow.

Although PLE can occur at any time after the Fontan, there appear to be 2 particular peaks in the onset of disease. The first peak occurs in the early years after the Fontan operation, and can occur in patients who seem otherwise reasonably well. In this group, treatment with oral controlled-release budesonide appears to result in some improvement in symptoms, with a normalization in protein levels after an induction period of several months.[23] The second peak in the onset of PLE is in late adolescence or early adulthood, and may occur more frequently in patients with more severely impaired hemodynamics. This group does not seem to be as responsive to steroids, suggesting that inflammation may not play as much of a role in the pathogenesis.[24] In this group, chronic dilation of the lymphatic system, as a result of the underlying hemodynamic abnormalities, likely plays a more pronounced role.

It is not yet clear why some patients develop PLE while others with similar hemodynamics are spared. However, the difficulty in predicting which patients will develop PLE points to the possibility of a prominent genetic predisposition. Recently, a diminished expression of glycosaminoglycan in the enterocytes of children with PLE has been suggested (Rychik J, unpublished data, 2013). This protein is essential for maintaining the integrity of the gut epithelium, and the underexpression may be a significant contributor to the pathophysiology of the disease. An altered expression of glycosaminoglycan would suggest either that those who develop PLE have a baseline deficiency in this protein, or that the inflammation and hemodynamic abnormalities of the Fontan operation result in altered expression.

While much remains to be understood about the development and pathophysiology of PLE in the Fontan population, it is clear that the development of this illness results in chronic debilitation and early death. Although new approaches to medical therapies have improved outcomes over the last 2 decades, there is still no definitive cure. Early cardiac transplantation has been used in some cases and does seem to be effective at eliminating the stimulus for the disease, but transplantation in this population is a high-risk endeavor with its own constellation of morbidities and a limited life span of graft.[25]

Plastic Bronchitis

In rare cases, the accumulation of proteinaceous material in the airways of patients with Fontan physiology may result in the formation of “casts” associated with plastic bronchitis. These casts can lead to acute obstruction of the airway, resulting in acute respiratory distress or airway compromise. The underlying pathophysiology of plastic bronchitis remains poorly understood, although abnormal connections between the lymphatics in the mediastinum and the airways are thought to contribute. Inhaled tissue plasminogen

activator has been described as a medical treatment option to control the formation of plastic casts, likely by dissolving or breaking up the protein formations.[26] A case report describing the resolution of plastic bronchitis following thoracic duct ligation suggests that limiting lymphatic flow may also result in symptomatic improvement.[27] However, in severe intractable cases of plastic bronchitis, fenestration and cardiac transplantation have also been reported to result in resolution of symptoms.[28–30]

TREATMENT OF CIRCULATORY FAILURE IN FONTAN CIRCULATION

In "classical cardiology" with primary myocardial disease such as ischemic heart disease or cardiomyopathy, ventricular function is most frequently the limiting factor of cardiac output; typically ventricular preload is abundant. Most cardiac algorithms and treatment strategies have focused on augmenting systolic performance. However, in some conditions the systemic ventricle is not the limiting factor but rather the preload of that ventricle: obstructed inflow after Mustard repair, primary pulmonary hypertension, constrictive pericarditis, supravalvular and valvular mitral stenosis, and the Fontan circuit.

The circulatory problem in a Fontan circuit is primarily created by the damming effect of the Fontan neoportal system and the subsequent limit on cardiac preload. As such, strategies aimed at maximizing the efficiency of this portal system may be more effective than "traditional" heart-failure therapies. Such modulation may consist of increasing the pressure before the dam (systemic venous pressure), lowering the height (resistance of Fontan neoportal system) of the dam, enhancing the runoff after the dam (ventricular suction), or bypassing the dam (fenestration).

Elevated Systemic Venous Pressure (Increasing Pressure Before the Dam)

An acute increase of systemic venous pressure, as is achieved during exercise (up to 30 mm Hg), can temporarily increase output.[31] However, such an elevation cannot be maintained for a long time. A chronic elevation of venous pressures higher than 18 to 20 mm Hg, as in patients with a high-resistance Fontan portal circuit, will result in unacceptable side effects such as vascular congestion, edema, ascites, and lymphatic failure. Diuretics can partially control these complications of congestion, but may further increase the problems of low output. General aerobic fitness may play a role in the transient ability to increase central venous pressure, but even then the venous pressure cannot approximate the change in driving pressure that can be achieved by a subpulmonary ventricle.

Impedance and Pulmonary Vascular Resistance (Lowering the Height of the Dam)

In the current era, the surgical technique used to create a total cavopulmonary connection is usually satisfactory, with minimal focal stenoses, reduced turbulence, and flow of the inferior caval vein (with the "hepatic factor") to both lungs.[32,33] Previous connections, including valved pathways and atrial-ventricular-pulmonary connections, are now considered outdated or even obsolete. For those who received older-style Fontan operations, conversion to cavopulmonary connection should be considered when the patient becomes symptomatic, or even prophylactically, to limit any energy loss in the Fontan portal system[34,35] and to avoid recurrent atrial arrhythmias. Nevertheless, in the setting of elevated Fontan pressure or reduced physical capacity, care should be taken to ensure that focal areas of stenosis, hypoplasia, distortion, or abundant collateral flow are addressed when possible.

The total cross-sectional area of the pulmonary vascular bed is an important factor for Fontan efficiency, but one that is hard to modulate in the absence of a subpulmonary ventricle following Fontan. The first palliative procedure is probably the most important and crucial intervention in the development of the pulmonary vasculature in a patient with single-ventricle physiology (see **Fig. 7**). It is during these early days that pulmonary arterial growth is most likely. However, the goal of providing sufficient pulmonary blood flow must be balanced with the concern of creating increased vascular resistance.

In the last few years, the pulmonary vasculature itself has emerged as a therapeutic target to improve output. In the Fontan circuit, PVR is generally mildly elevated at baseline but, in the absence of pulsatile flow, it does not decrease normally with increased cardiac output. Advances in the treatment options for primary pulmonary hypertension suggest that the pulmonary resistance might also be considered as a potential target of medication intervention in the Fontan circulation. Several agents have been reported (oxygen at altitude, sildenafil, bosentan, inhaled iloprost), although the short-term improvements as a result of these agents have been modest.[36–39] Longer-term studies with pulmonary vasodilators are needed to understand whether these agents can affect the long-term outcomes of patients after Fontan, and alter what is characteristically a

slow, downward slope of exercise capacity and cardiovascular functionality.

Ventricular Suction (Enhancing Runoff After the Dam)

The contraction of the ventricle itself has a role in helping blood flow through the pulmonary vascular bed. As the atrioventricular annulus contracts toward the apex of the heart, a vacuum is created to "pull" blood into the pulmonary atrium. The total contribution of this "suction" is hard to quantify, but is clearly lost in the settings of atrioventricular dyssynchrony or significantly elevated atrial pressure. In the Fontan circulation, the systemic ventricle functions in a preload-deprived state. In this state, ventricular contractility is limited (as dictated by the Frank-Starling curve), further limiting the contribution of ventricular suction.

Fenestration (Bypassing the Dam)

One sure way to improve cardiac output in the Fontan is to create a bypass around the congested pulmonary circuit in the form of a small fenestration. This concept was originally reported as a means to help with the physiologic adjustment in the perioperative state following the Fontan surgery itself.[40] After the institution of the fenestration, the incidence of prolonged pleural effusions and long hospital stays decreased significantly. In addition, a limited bypass of the Fontan portal system also results in chronic improvement of congestion and circulatory output in the Fontan circuit. The downside to a fenestration is decreased arterial oxygen saturation. Nevertheless, the improved output may result in better overall oxygen delivery, and will also help to alleviate the congestion felt in upstream organs, particularly the liver.

Whereas a fenestration at the time of Fontan is well tolerated and may be viable for years or decades after surgery, the creation of a fenestration in later years in a patient who has not had one is not as well tolerated. These patients are referred for fenestration creation because of the failure of their Fontan circuit, often characterized by elevated PVR and a high transpulmonary gradient. In this setting, achieving the proper balance in the creation of a fenestration is difficult, and may not be possible. A small fenestration will not allow the degree of decompression necessary to alleviate symptoms, and a larger fenestration might alleviate congestion and augment cardiac output, but in so doing will result in an unacceptable level of cyanosis (see **Fig. 4**). Nevertheless, fenestration creation may have a role in a failing Fontan as a bridge to heart transplantation.

Heart Rate, Contractility, and Afterload

In a ventricle with preload reserve, an increase of heart rate within the normal physiologic range will result in increased output. In a Fontan circuit with no ventricular preload reserve, an increase in heart rate will result in a proportional decrease of stroke volume, and subsequently no change in output.[41] In excessive bradycardia, pacing with a heart rate in physiologic range will increase output and decrease congestion.[42] However, excessive tachycardia may actually result in a decrease in cardiac output related to the inability to augment diastolic filling.

Because systolic performance is not generally the primary issue in the Fontan circulation, the role of inotropic agents is often limited. These agents can make the Fontan ventricle squeeze harder, but will not result in clinically significant more output. Such a response is typical for a preload-deprived ventricle. There may be a role for inotropes in the Fontan patient with significant ventricular dysfunction that is not due to chronic underloading, but in general the role of these agents is somewhat limited.

The afterload faced by the systemic ventricle may have a role in the structural characteristics of the ventricle, and thus some thought should be given to the use of an afterload-reducing agent. Any patient who is in a chronic state of low cardiac output will invariably generate an increased systemic vascular resistance to maintain blood pressure. In a failing but normally connected biventricular circulation with a hypocontractile ventricle and preload reserve, a decrease of afterload results in an increase in output, which will counter the tendency for hypotension, thus resulting in a good clinical response. However, in a Fontan patient a substantial decrease of afterload without preload reserve will not result in an increase in output, but may be detrimental by causing hypotension. Whether there is a role for low-dose afterload reduction in attempting to modulate ventricular diastolic function remains as yet unknown. In the only randomized trial of enalapril after Fontan, no beneficial effect was seen.[43] However, the time course in this trial was 10 weeks; it may be that the benefit of afterload-reducing agents lies in the chronic impact on diastolic function rather than the short-term impact on systemic resistance.

MECHANICAL SUPPORT AND HEART TRANSPLANTATION

Mechanical support for the failing single ventricle is still in its infancy. The usual ventricular assist

devices are designed to aid a failing systemic ventricle. In the failing Fontan circulation, the problem is typically not systolic performance, but rather failure of the physiology itself related to the neoportal system and chronic preload deprivation. In this setting the interposition of a subpulmonary assist device is required, and this has been reported in one instance as a bridge to transplantation.[44] In a second case, a total artificial heart was used to bridge a patient with a failing Fontan circulation to transplantation.[45] The surgery to place a subpulmonary assist device or a total artificial heart is extensive, and requires the takedown of the Fontan construct itself.

In many cases of Fontan failure, heart transplantation is likely to be the final outcome. Heart transplantation in the Fontan cohort is constitutes a higher risk than in those without congenital heart disease, and may be even higher in those with Fontan failure but preserved ventricular function.[46]

SUMMARY

The Fontan construct has allowed for the survival of countless children born with congenital heart disease. However, this palliation creates a form of man-made heart failure characterized by a neoportal system that leads to chronic preload deprivation, resulting in low cardiac output and systemic venous congestion. Careful attention to pulmonary blood flow and pulmonary arterial growth in the initial stages of Fontan palliation are crucial, as are the technical details of the geometry of the Fontan connections. Avoiding overload of the systemic ventricle is important, while excessive protection from volume overload may result in pulmonary artery hypoplasia. Nevertheless, even in a "perfect" Fontan, it can be difficult to predict how durable this man-made form of heart failure will be over the longer term.

Overall treatment options for circulatory failure of a Fontan circuit are disappointing; avoidance of problems is most important, because once the Fontan circuit is created it "runs on auto-pilot," and allows little modulation. However, trials are under way to evaluate the potential benefits of modulators of PVR and to determine whether aerobic training may help to forestall the insidious onset of circulatory failure. At the same time, new support devices are coming to the market that may help to bridge those patients with a failing Fontan to cardiac transplantation.

REFERENCES

1. Fontan F, Baudet E. Surgical repair of tricuspid atresia. Thorax 1971;26:240–8.
2. Gewillig M. The Fontan circulation. Heart 2005;91:839–46.
3. Gewillig M, Brown SC, Eyskens B, et al. The Fontan circulation: who controls cardiac output? Interact Cardiovasc Thorac Surg 2010;10:428–33.
4. Gewillig M, Kalis N. Pathophysiological aspects after cavopulmonary anastomosis. Thorac Cardiovasc Surg 2000;48:336–41.
5. La Gerche A, Gewillig M. What limits cardiac performance during exercise in normal subjects and in healthy Fontan patients? Int J Pediatr 2010;2010. pii:791291.
6. Van de Bruaene A, La Gerche A, Claessen G, et al. Sildanafil improves exercise hemodynamics in Fontan patients [abstract]. Cardiol Young 2013;23:S54.
7. Paridon SM, Mitchell PD, Colan SD, et al. A cross-sectional study of exercise performance during the first 2 decades of life after the Fontan operation. J Am Coll Cardiol 2008;52:99–107.
8. Giardini A, Hager A, Pace Napoleone C, et al. Natural history of exercise capacity after the Fontan operation: a longitudinal study. Ann Thorac Surg 2008;85:818–21.
9. Diller GP, Dimopoulos K, Okonko D, et al. Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. Circulation 2005;112:828–35.
10. Diller GP, Giardini A, Dimopoulos K, et al. Predictors of morbidity and mortality in contemporary Fontan patients: results from a multicenter study including cardiopulmonary exercise testing in 321 patients. Eur Heart J 2010;31:3073–83.
11. Gewillig MH, Lundstrom UR, Deanfield JE, et al. Impact of Fontan operation on left ventricular size and contractility in tricuspid atresia. Circulation 1990;81:118–27.
12. Gewillig M, Daenen W, Aubert A, et al. Abolishment of chronic volume overload. Implications for diastolic function of the systemic ventricle immediately after Fontan repair. Circulation 1992;86:II93–9.
13. Silverstein DM, Hansen DP, Ojiambo HP, et al. Left ventricular function in severe pure mitral stenosis as seen at the Kenyatta National Hospital. Am Heart J 1980;99:727–33.
14. Mital S, Chung WK, Colan SD, et al. Renin-angiotensin-aldosterone genotype influences ventricular remodeling in infants with single ventricle. Circulation 2011;123:2353–62.
15. Mitchell MB, Campbell DN, Ivy D, et al. Evidence of pulmonary vascular disease after heart transplantation for Fontan circulation failure. J Thorac Cardiovasc Surg 2004;128:693–702.
16. Rychik J, Veldtman G, Rand E, et al. The precarious state of the liver after a Fontan operation: summary of a multidisciplinary symposium. Pediatr Cardiol 2012;33:1001–12.

17. Bulut OP, Romero R, Mahle WT, et al. Magnetic resonance imaging identifies unsuspected liver abnormalities in patients after the Fontan procedure. J Pediatr 2013;163:201–6.
18. Wu FM, Ukomadu C, Odze RD, et al. Liver disease in the patient with Fontan circulation. Congenit Heart Dis 2011;6:190–201.
19. Asrani S, Warnes C, Kamath P. Hepatocellular carcinoma after the Fontan procedure. N Engl J Med 2013;368:1756–7.
20. Schwartz MC, Sullivan LM, Glatz AC, et al. Portal and sinusoidal fibrosis are common on liver biopsy after Fontan surgery. Pediatr Cardiol 2013;34:135–42.
21. Friedrich-Rust M, Koch C, Rentzsch A, et al. Noninvasive assessment of liver fibrosis in patients with Fontan circulation using transient elastography and biochemical fibrosis markers. J Thorac Cardiovasc Surg 2008;135:560–7.
22. Rychik J. Protein-losing enteropathy after Fontan operation. Congenit Heart Dis 2007;2:288–300.
23. Thacker D, Patel A, Dodds K, et al. Use of oral budesonide in the management of protein-losing enteropathy after the Fontan operation. Ann Thorac Surg 2010;89:837–42.
24. John AS, Driscoll DJ, Warnes CA, et al. The use of oral budesonide in adolescents and adults with protein-losing enteropathy after the Fontan operation. Ann Thorac Surg 2011;92:1451–6.
25. Griffiths ER, Kaza AK, Wyler von Ballmoos MC, et al. Evaluating failing Fontans for heart transplantation: predictors of death. Ann Thorac Surg 2009;88:558–63 [discussion: 563–4].
26. Heath L, Ling S, Racz J, et al. Prospective, longitudinal study of plastic bronchitis cast pathology and responsiveness to tissue plasminogen activator. Pediatr Cardiol 2011;32:1182–9.
27. Shah SS, Drinkwater DC, Christian KG. Plastic bronchitis: is thoracic duct ligation a real surgical option? Ann Thorac Surg 2006;81:2281–3.
28. Chaudhari M, Stumper O. Plastic bronchitis after Fontan operation: treatment with stent fenestration of the Fontan circuit. Heart 2004;90:801.
29. ElMallah MK, Prabhakaran S, Chesrown SE. Plastic bronchitis: resolution after heart transplantation. Pediatr Pulmonol 2011;46:824–5.
30. Wilson J, Russell J, Williams W, et al. Fenestration of the Fontan circuit as treatment for plastic bronchitis. Pediatr Cardiol 2005;26:717–9.
31. Shachar GB, Fuhrman BP, Wang Y, et al. Rest and exercise hemodynamics after the Fontan procedure. Circulation 1982;65:1043–8.
32. de Leval MR, Kilner P, Gewillig M, et al. Total cavopulmonary connection: a logical alternative to atriopulmonary connection for complex Fontan operations. Experimental studies and early clinical experience. J Thorac Cardiovasc Surg 1988;96:682–95.
33. Van Haesdonck JM, Mertens L, Sizaire R, et al. Comparison by computerized numeric modeling of energy losses in different Fontan connections. Circulation 1995;92:II322–6.
34. Conte S, Gewillig M, Eyskens B, et al. Management of late complications after classic Fontan procedure by conversion to total cavopulmonary connection. Cardiovasc Surg 1999;7:651–5.
35. Mavroudis C, Deal BJ, Backer CL, et al. The favorable impact of arrhythmia surgery on total cavopulmonary artery Fontan conversion. Seminars in thoracic and cardiovascular surgery. Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu 1999;2:143–56.
36. Darst JR, Vezmar M, McCrindle BW, et al. Living at an altitude adversely affects exercise capacity in Fontan patients. Cardiol Young 2010;20:593–601.
37. Goldberg DJ, French B, McBride MG, et al. Impact of oral sildenafil on exercise performance in children and young adults after the Fontan operation: a randomized, double-blind, placebo-controlled, crossover trial. Circulation 2011;123:1185–93.
38. Ovaert C, Thijs D, Dewolf D, et al. The effect of bosentan in patients with a failing Fontan circulation. Cardiol Young 2009;19:331–9.
39. Rhodes J, Ubeda-Tikkanen A, Clair M, et al. Effect of inhaled iloprost on the exercise function of Fontan patients: a demonstration of concept. Int J Cardiol 2013;168(3):2435–40.
40. Bridges ND, Lock JE, Castaneda AR. Baffle fenestration with subsequent transcatheter closure. Modification of the Fontan operation for patients at increased risk. Circulation 1990;82:1681–9.
41. Barber G, Di Sessa T, Child JS, et al. Hemodynamic responses to isolated increments in heart rate by atrial pacing after a Fontan procedure. Am Heart J 1988;115:837–41.
42. Cohen MI, Rhodes LA, Wernovsky G, et al. Atrial pacing: an alternative treatment for protein-losing enteropathy after the Fontan operation. J Thorac Cardiovasc Surg 2001;121:582–3.
43. Kouatli AA, Garcia JA, Zellers TM, et al. Enalapril does not enhance exercise capacity in patients after Fontan procedure. Circulation 1997;96:1507–12.
44. Pretre R, Haussler A, Bettex D, et al. Right-sided univentricular cardiac assistance in a failing Fontan circulation. Ann Thorac Surg 2008;86:1018–20.
45. Rossano J, Goldberg D, Fuller S, et al. Successful use of the total artificial heart in the failing Fontan circulation. Ann Thorac Surg, in press.
46. Seddio F, Gorislavets N, Iacovoni A, et al. Is heart transplantation for complex congenital heart disease a good option? A 25-year single centre experience. Eur J Cardiothorac Surg 2013;43:605–11 [discussion: 611].