Single-Ventricle Physiology

Lydia Taranto, MD,[1] and Tabitha Moe, MD[2,3]

1. HonorHealth Hospitals, Scottsdale, AZ; 2. Arizona Cardiology Group, Phoenix, AZ; 3. Phoenix Children's Hospital, Phoenix, AZ

Abstract

Single-ventricle physiology occurs in patients with hypoplastic ventricular heart defects, either on the right or left, who have undergone stepwise palliation surgeries ending with the Fontan procedure. After Fontan completion, these patients are dependent on passive venous return to the pulmonary circulation. The implications of passive flow are potentially devastating to the patient. We discuss some of the basic changes to the patient's experience after a Fontan procedure, as well as the common complications. We also touch on some of the emerging management strategies for the common complications.

Keywords

Fontan, single-ventricle physiology, Fontan physiology, Fontan heart failure, Fontan-associated liver disease, protein losing enteropathy, plastic bronchitis

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Correspondence: Tabitha Moe, Arizona Cardiology Group, 340 E Palm Lane #A175, Phoenix, AZ 85004. E: tmoe@azcard.com

As we approach 50 years since the original publication describing the Fontan procedure for palliation of single-ventricle congenital heart disease, we review the basics of Fontan circulation, and the current literature concerning long-term complications. Surgical interventions have allowed children with former lethal defects to survive into adulthood and we recognize that this has led to a new cohort. Their physiology is divergent from people with two ventricles and their clinical complications highlight the directions for further research to give them a higher quality of life. In this article, we discuss some of the basic physiological changes in single-ventricle physiology regarding the Fontan operation, and introduce the common physiological complications.

Dynamics of the Fontan Procedure

The Fontan procedure is the final stage in the stepped palliation of single-ventricle disease.[1,2] It was initially described by Fontan and Baudet in 1971 as a corrective intervention for tricuspid atresia, and while it is now seen as palliative, it has been applied to most forms of single-ventricle defects.[3–5] The Fontan is a method of diverting the systemic venous return away from the right side of the heart directly into the pulmonary artery, through a series of stepwise operations, until all the systemic venous blood flows passively and without ventricular thrust into the pulmonary circulation.[3,6–8]

The principle behind this concept was the discovery that the pulmonary vascular bed had a much lower pressure than systemic venous pressure. The pressure gradient between the two vascular beds was enough to allow blood to flow forward without ventricular thrust.[8] Conversely, this implies that pulmonary vascular resistance, diaphragmatic excursion, and thoracic cage mobility all contribute to a complicated process determining cardiac output.[8,9]

This operation places the pulmonary and the systemic vasculature in series, with the systemic ventricle effectively functioning as the only pump. In this sense, the Fontan procedure is a palliation, rather than a physiological cure, which would both imply and require a pulmonary circulation pump. This change has profound implications for preload, afterload, cardiac output, and stroke volume.[7,8]

This system is inherently one of decreased preload and increased afterload. People who have had the procedure are dependent on passive venous return due to the pressure gradient between systemic venous vasculature and pulmonary vasculature, with the skeletal muscle pump and ventilation mechanics supporting secondarily.[6–8]

Additionally, as the systemic circulation and the pulmonary circulation are placed in series, systemic venous pressures are increased and exceed the upper normal pressure limit by two to three times. Thus, these patients face significantly increased afterload. Having both a decreased preload and an increased afterload, with only a single ventricular pump, creates a challenge for cardiac output and leaves these patients with little hemodynamic reserve.[8]

After the Fontan procedure, patients are almost entirely dependent on heart rate and atrioventricular conduction to increase their cardiac

output, and thus they have very little hemodynamic tolerance for decreases in venous return. They are largely dependent on skeletal muscle pump and ventilation mechanics during exercise to increase their venous return and stroke volume.[7,8] It has been demonstrated that in adults with Fontan circulation, nearly 30% of their venous flow through the pulmonary artery is dependent on respiration, whereas in patients with two ventricles this number is closer to 15%.[8,10]

Due to the increase in their venous vasculature resistance, people with Fontan circulation also have a diminished venous capacitance.[8,11] In people with two ventricles, approximately 70% of total blood volume is stored in the venous vasculature.[8,12] Fontan patients do not have this reserve immediately available to them and this makes them susceptible to decreases in intravascular volume, or to agents that may decrease their vascular tone, either of which can decrease their pulmonary return and cardiac output.[8]

Pulsatile flow is partially responsible for recruiting pulmonary capillaries, which reduces pulmonary vasculature resistance and increases compliance. Without this pulsatile flow, studies have shown reduced vascular recruitment and impaired lung growth, both of which serve to increase overall pulmonary vascular resistance and decreased compliance.[8,13,14] This increase in pulmonary resistance causes a decreased preload and cardiac output. Exogenously administered vasodilators, such as oral sildenafil and baseman have shown some benefit in certain situations, such as cardiovascular exercise, a physiological situation that single-ventricle patients have little tolerance for.[8,13–15]

Survival Outcomes after a Fontan Procedure

Survival outcomes have varied, with reduced survival in patients who underwent the original Fontan procedure (atriopulmonary connection), and improved survival rates in those who underwent revised Fontan procedures (total cavopulmonary connections). Survival is significantly affected by the long-term complications of the operation, as detailed below. In the largest cohort analyses, survival has been shown to be 90% at 30 years and 80% at 40 years, with significantly worse survival for people who had atriopulmonary connection.[16] The analysis found that most patients (65%) had systemic left ventricular morphology. The survival rates of hypoplastic left heart syndrome had significantly worse outcomes, with survival ranging from 72% to 85% at 10 years.[7]

Heart Failure after a Fontan Procedure

Heart failure in people who have had the Fontan procedure is fundamentally different from heart failure in patients with two ventricles.[7,17] While heart failure in people with two ventricles helps provide a framework to understand heart failure in the single ventricle, it is essential that we understand where and how the two types of patient diverge.

There are four types of heart failure described in people who have had the Fontan procedure and in each case the circulation is no longer able to meet the metabolic demands of the body.[7]

Type 1 heart failure in Fontan patients is also called Fontan failure with reduced ejection fraction. It is the most common type seen in children and it presents with consistent signs and symptoms of heart failure with reduced EF, such as pulmonary edema, hepatic congestion, and ascites.[7,17] This closely resembles systolic heart failure in patients with two ventricles.[17]

Type 2 heart failure in Fontan patients, known as Fontan failure with preserved ejection fraction, presents with a preserved ejection fraction, with signs and symptoms of pulmonary venous congestion and hepatic congestion, with elevated venous pressures.[7,17] This type of heart failure in some way mirrors HFpEF in patients with two ventricles.

Type 3 heart failure in Fontan patients, also known as Fontan failure with normal pressures, presents with right-sided congestion, such as hepatosplenomegaly, ascites, and portal venous outflow obstruction, but with normal ejection fraction and hemodynamics.[7,17] Multisystem organ failure in the setting of good hemodynamics is frequently seen, making it challenging to treat.[17]

Type 4 heart failure in Fontan patients, known as Fontan failure with abnormal lymphatics, will present with normal hemodynamics, but signs and symptoms of lymphatic failure, such as plastic bronchitis and protein-losing enteropathy.[7,17] Patients will often have normal Fontan hemodynamics.[17]

Risk of Arrhythmia after Fontan Procedure

Patients with single-ventricle Fontan physiology have multiple risk factors for developing tachyarrhythmias, particularly AF.[7,18] With classic Fontan, the surgical interventions lead to fibrosis near the sinus node and atria and are subject to dilation even to the point of atrial gigantism, both of which can predispose to AF.[7] Sick sinus syndrome, atypical atrial flutter, and incisional interatrial reentrant atrial tachycardia are also seen. People with Fontan circulation have a reduced tolerance to AF and are more prone to hemodynamic instability at elevated heart rates. They are also far less responsive to single-agent anti-arrhythmic drug therapy. Amiodarone continues to be considered the most effective anti-arrhythmic drug in this patient population.

Catheter ablations can be attempted but are fraught with increased risk due to difficult access. Surgical ablations are considered the gold standard. Therefore, anytime a Fontan patient is scheduled for open heart surgery, surgical ablation should be discussed. Although there is currently no consensus on which anticoagulants to use, clinicians typically agree on the use of anticoagulation for atrial arrhythmia in people who have had a Fontan procedure. Recent studies suggest that aspirin alone is not inferior to vitamin K antagonist, and novel oral anticoagulants have not yet been formally evaluated.[7,18,19]

The Impact of the Fontan Procedure on the Hepatic System

All patients who undergo Fontan operations have some degree of Fontan-associated liver disease (FALD), regardless of their clinical status.[6,7] The FALD spectrum ranges from mild fibrosis to fulminant liver failure. As the liver is placed immediately before the heart in the venous return pathway, having systemically elevated central venous pressures impedes venous flow and leads to chronic venous congestion, to which the liver is particularly susceptible. It is this congestion that is believed to lead to the hepatic fibrosis that all Fontan patients experience.[6] Research has demonstrated that it is the chronicity of this

central venous pressure, rather than the severity of it, that increases the risk of hepatic fibrosis. It has been noted that irreversible hepatic dysfunction may occur as early as the teenage years.[7] Unfortunately, the mechanisms leading to this pathology also change the nature of it, both distinguishing it from classic liver fibrosis, and making it more challenging to detect and manage.

While symptoms are often subclinical, manifestations, such as mild hepatomegaly and ascites, are commonly seen. Mild elevation of liver transaminases and mild thrombocytopenia are common, although synthetic function is usually preserved.[6,7] Significant increases in liver enzymes are generally not seen due to the low-grade chronic inflammation with only mild hepatocyte damage.[8] Changes in varices are often not seen due to the long-standing elevated systemic venous pressures; varices are a manifestation of a high-pressure hepatic system decompressing in a lower pressure venous system.[6] People who have had the Fontan procedure have no lower pressure venous systems, and thus the etiology of hepatic fibrosis prevents the complication of varices. Primary portal hypertension is rarely found.[7]

Given that synthetic function is generally preserved and that transaminases may only be mildly elevated, even in the setting of advanced cirrhosis, the traditional model for end-stage liver disease (MELD) score holds limited clinical value in staging and prognosis for these patients. The MELD-XI, a MELD score excluding the international normalized ratio is more appropriate. Cardiac MRI, which is frequently used to monitor these patients, captures a portion of the liver and has been used to trend hepatic dimensions, inferior vena cava size, and spleen size. However, cardiac MRI is limited in patients with epicardial pacemaker leads and intra-abdominal generators as the device limits the interpretation of the imaging.

Abdominal ultrasound with elastography can assess hepatic texture and stiffness, but is limited by its difficulty in distinguishing fibrosis from edema.[7] FibroSure is a biomarker test that has been used to screen patients in these patients with some success as a non-invasive measure of disease progression.[20] More efficacious surveillance options and treatments remain a top research priority in this population.[7,17]

The most devastating complication of FALD remains hepatocellular carcinoma (HCC), and it has been previously recognized as a long-term complication of the Fontan procedure.[7,21] In a recent retrospective study, it was found that 1.3% of 2,470 cases (n=33) had biopsy-proven HCC, with the average age at time of diagnosis being 30 years, and the average length of time from Fontan operation to HCC diagnosis being 22 years.[21] Of the 33 patients identified, 18 (55%) died within 26 months. However, in contrast to other patients with HCC, only 50% of the single-ventricle patients diagnosed with HCC previously carried a diagnosis of hepatic cirrhosis, in contrast to 80% of patients with two ventricles developing HCC.[21,22] This suggested either an underdiagnosis of hepatic cirrhosis in patients with Fontan circulation, or an increased risk of HCC in non-cirrhotic livers in these patients. Unfortunately, advanced tumor burden at time of diagnosis gives many patients only the option of palliative care. Given the risk of HCC and increased incidence of it, 6-month managing surveillance and alpha fetoprotein serum monitoring is recommended in patients with known FALD.[7,21]

The Impact of the Fontan Procedure on the Gastrointestinal System

Protein losing enteropathy (PLE) is a well-known complication of Fontan physiology, in which the mucosal integrity of the gastrointestinal lining is compromised and highly proteinaceous material, including immune globulins and clotting factors, is spilled into the lumen.[6,7] Its manifestations are seen when the rate of loss exceeds the body's ability to produce the same proteins. It occurs in about 5–15% of Fontan patients, on average 3–8 years after Fontan surgery, most commonly seen in children. Symptoms typically manifest as diarrhea; however, even without diarrhea the manifestations can be seen. Symptoms such as ascites, weight loss or gain, fatigue, peripheral edema, pleural or pericardial effusions, muscle tetany, and thromboembolism can all be seen and taken as evidence of PLE.[6,23]

The mechanisms leading to PLE are thought to be a function of chronic hypoperfusion of the gastrointestinal tract due to the chronically low cardiac output of the Fontan physiology, in conjunction with the effects of elevated central venous pressure on the lymphatic system. Over time, chronic hypoperfusion of the gastrointestinal tract leaves the mucosa chronically inflamed and subject to integrity compromise.[7,24]

Diagnosis can be accomplished by testing for alpha 1 antitrypsin (A1AT) in the stool. A1AT is normally excreted in small amounts in the stool and an elevated level found in a 24-hour stool collection can indicate intestinal protein leak. Decreased serum protein levels, including decreased levels of serum A1AT, can reinforce the diagnosis.[7]

PLE is currently treated in a variety of ways with varying degrees of success. Approaches include scheduled albumin infusions, use of enteral budesonide, use of heparin, loop diuretics, spironolactone, sildenafil, and digoxin.[25] There is considerable variation regarding treatment, and only budesonide has demonstrated benefits in a study assessing survival to time of heart transplant.[25] Rapid atrial pacing has been employed in the setting of PLE to help support cardiac output.[26] Embolization of tortuous lymphatic vessels contributing to PLE is also currently being studied.[6,7]

The Impact of the Fontan Procedure on the Pulmonary System

Pulmonary vascular changes are not uncommon. Passive flow through the pulmonary vascular bed is a principle and mechanism of the Fontan single-ventricle state. Any impedance to this can result in worsening venous congestion, elevated central venous pressures, reduced ventricular preload, decreased cardiac output, and worsen all subsequent secondary pathologies. Often children born with single-ventricle physiology have abnormal pulmonary flow patterns; after operative intervention, the body appears to have a compensatory mechanism for passive aorto-pulmonary flow and develops significant aorto-pulmonary collateralization. These collaterals can further impede the flow through the pulmonary vascular bed, contribute to worsening central venous pressure systemic symptoms, and add an additional complicating factor of ventricular overload to the single functioning ventricle.[6–8]

Testing pulmonary function in patients with single-ventricle disease reveals a restrictive pattern, likely due to the multiple operative

interventions and post-surgical changes to the thoracic wall. Reduced forced vital capacity and functional capacity during exercise testing are seen, consistent with restrictive lung disease.[7] Therapeutic approaches with flutter valves, respiratory exercises, and vocal training are strategies currently being evaluated.[27]

Plastic bronchitis is a rare but serious complication in which bronchial mucofibrinous casts develop, resulting in airway obstruction. It can be difficult for patients to expectorate these casts, and if large casts develop, it can result in an urgent, life-threatening event including asphyxiation.[28] This pathology is thought to be secondary to the similar pathology derangements that cause PLE; severe lymphatic distortions leading to protein leak into low-pressure systems, such as the gastrointestinal lumen and the bronchioles.[7,23,29]

The Impact of the Fontan Procedure on the Lymphatic System

While the changes involved in the lymphatic system are not well understood, they have been partially characterized and implicated in the serious conditions of plastic bronchitis and PLE.[30] The lymphatic system drains into the innominate vein, which is under high pressure after the Fontan procedure, due to increased systemic central venous pressure.[6,31] This leads to increased lymphatic fluid production and decreased lymphatic drainage, causing lymphatic insufficiency. Lymphangiography in these patients has revealed dilated, tortuous lymphatic channels throughout the body.[31] When these channels are overwhelmed, they open and spill their contents into areas of low pressure, such as the bronchial tree or the gastrointestinal lumen, contributing to the serious complications of plastic bronchitis and protein-losing enteropathy. New treatments, such as glue embolization of these channels, are being developed to help mitigate this process.[6,7,32]

The Risk of Thrombosis

Single-ventricle patients have a multiplicity of risk factors that promote thrombosis, and it has been shown that thromboembolic events may affect up to 33% of patients, contributing to nearly 25% of mortalities, including death from pulmonary embolism and cerebrovascular accidents.[7,33,34] The underlying risk factors include the very crux of the Fontan, the passive, non-pulsatile venous flow through the pulmonary bed. Also included are chronic venous congestion, low cardiac output, dilated atrium, cardiac arrhythmia, and PLE. This list is not exhaustive, but it illustrates the increased risk that this patient group has for thrombotic complications. To this end, research has supported the long-term use of anticoagulation agents in these patients, regardless of prior history of thrombotic events. Current data suggest that the use of aspirin is non-inferior to vitamin K antagonists and has less risk of bleeding complications. The use of novel oral anticoagulants is promising; however, studies concerning their benefit in Fontan patients have yet to completed.[7,33–36]

Renal system

Patients who have had a Fontan procedure are at higher risk of renal injury, and often have a lower estimated glomular filtration rate (eGFR) than counterparts with two ventricles. The underlying mechanism for this is thought to be secondary to decreased cardiac output and chronically elevated central venous pressures. Of note, these patients deviate here from their double-ventricle counterparts, because using serum creatinine overestimates their eGFR. The use of cystatin C or urinary biomarkers gives a more accurate indication of their eGFR.[7,37]

Surveillance Guidelines

People with single-ventricle disease are the most complex congenital heart patients and it is critical that these patients maintain continuity of care with congenital heart disease providers. The Adult Congenital Heart Disease (ACHD) certification exam now establishes physicians' competence to care for these complex patients. Routine follow-up every 6–12 months with associated testing is recommended; at these visits it is recommended to obtain repeat ECG, transthoracic ECHO, pulse oximetry, Holter monitor study, and at extended intervals to obtain cardiac CT and exercise testing.[38]

Future Directions

Research is ongoing on the timing and appropriateness of both single-organ and dual-organ transplants for people with a single ventricle, and the future of stem cell research, as well as single-ventricle assist devices, is on the horizon. The Rodefeld Fontan pump is one device that may potentially assist a failing Fontan as a portable right ventricular implantable device.[39] Registries, as well as biobanks, are allowing cumulative data to assist with informed decision-making and treatment planning.[40] The Adult Congenital Heart Association is now building a registry for adult congenital heart disease – the Quality Enhancement Research Initiative ACHD Registry. Ongoing efforts to keep patients in care are going to be crucial to strategies in the long-term preventive approach to managing risks and complications for this patient group. ■

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