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THE ADULT FONTAN PATIENT: UPDATE FOR 2011

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Background

Congenital heart disease is the most common birth defect, with an estimated incidence of moderate to severe disease of 4-6 per 1,000 live births.[1] Due to the dramatic advances in cardiac surgery and general pediatric cardiology care, approximately 85% of neonates with congenital heart disease (CHD) survive to adulthood.[2] The most recent information, published in 2004, estimated 787,800 to 1.3 million adults with CHD living in the United States.[3, 4] This is expected to increase by 5% per year. It is estimated that within the next decade, 1 in every 150 young adults will have some form of CHD.[2, 3, 5]

Due to the changing therapeutic options, a higher percentage of the adult CHD population will consist of more complicated cardiac disease during the coming years.[2] It is estimated that 1-2% of children with CHD have single-ventricle physiology.[6, 7] Thus, as survival in this complex portion of the CHD population improves, the number of adult patients with previous Fontan palliation will dramatically increase.

The goal of this article is to provide a brief background of the Fontan procedure and then discuss the late-term outcomes and complications in this unique patient type. The majority of the article will focus on information needed to adequately care for the adult Fontan patient.

Fontan Procedure

First described by Fontan in 1971, the original Fontan procedure reported the successful treatment of a patient with tricuspid atresia. In contemporary terms, the "Fontan pathway" has now evolved to describe any cavopulmonary connection that enables all systemic venous blood to bypass the heart and flow directly into the pulmonary arteries. While a complete Fontan can be done in a single procedure, most current patients have previously undergone a bidirectional Glenn anastomosis — in which the superior vena cava (SVC) is connected to the branch pulmonary arteries, usually the right pulmonary artery (PA) or the left PA if a left SVC is present.[8, 9]

The Fontan procedure is the preferred surgical option in patients who have a functional single ventricle or who have single-ventricle physiology due to their congenital heart defect. While most patients who eventually undergo Fontan palliation can be described by a specific congenital heart defect (for example, tricuspid atresia, hypoplastic left heart syndrome, double outlet right ventricle, or double inlet left ventricle), many types of CHD may require Fontan-type palliation if the ventricles cannot be separated into a functional left and right heart.[8] Although the Fontan operation may be done during the adolescent and adult periods, it is typically performed between ages 2 and 4 years of life.[10]

The Fontan Operation

The First Fontan Operation

Dr. Frances Fontan, who first performed the procedure on a patient with tricuspid atresia, published his initial atriopulmonary connection operation in 1971. This procedure consisted of a surgical anastomosis of the superior vena cava to the right pulmonary artery and the right atrium to the left pulmonary artery.[11] Soon thereafter, Dr. Guillermo Kreutzer described a right atrial to main pulmonary artery anastomosis.[12]

Modifications of the Fontan Operation

Soon after the original Fontan and Kreutzer procedures were described, surgeons began to experiment with modifications of the procedure. Some of the more common modifications include the true atriopulmonary (AP) Fontan, which comprised the majority of operations in the first two decades of the procedure, and the lateral tunnel (LT) Fontan, which became the prominent form performed starting in the late 1980s. In the AP Fontan, the right atrial appendage is anastomosed to the pulmonary artery. The LT procedure consists of creating a baffle in the sidewall of the right atrium to direct blood from the inferior vena cava (IVC) into the pulmonary circulation.[13-15]

The Current Fontan Operation

Since the 1990s, the most common type of Fontan procedure performed has been the extracardiac conduit (ECC) Fontan. This entails using a conduit to anastomose the IVC to the pulmonary circulation.[16] In children, both the LT and ECC Fontans are usually performed between ages 2 to 4 years, after a Glenn anastomosis, to complete the total cavopulmonary connection, which is generally performed between ages 3 to 6 months.[10]

Outcomes of the Fontan Palliation

Functional Status

Adults with Fontan palliation may have many different types of congenital heart defects, each with different surgical and natural histories and outcomes. Most Fontan patients are asymptomatic with a good functional status during their adolescent and early adult years.[17-19] Depending on the underlying anatomy (specifically the presence of a morphologic right versus left single ventricle), the Fontan patient will frequently begin to experience more complications and a decline in functional status during the third to fourth decade of life.[19] However, most of these data are based on

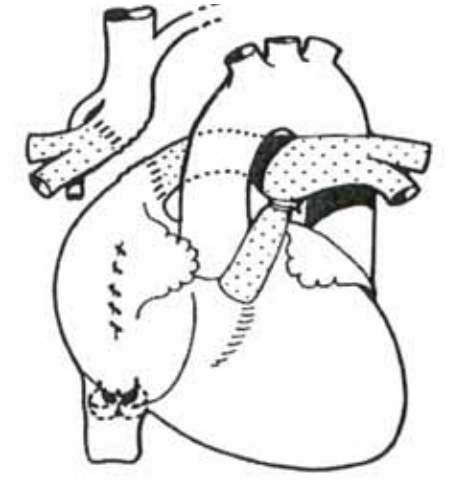

Figure 1. The original Fontan procedure. The right atrium is connected to the left pulmonary artery, and the superior vena cava is connected to the right pulmonary artery connection. The discontinuous left and right branch pulmonary arteries have been separated surgically. Note the surgically implanted valve at the inferior vena-right atrial junction.

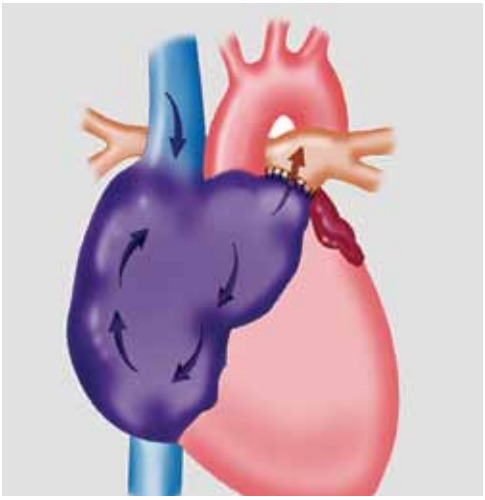

Figure 2. Atriopulmonary Fontan connection. Note the right atrium/right atrial appendage is connected directly to the main pulmonary artery.

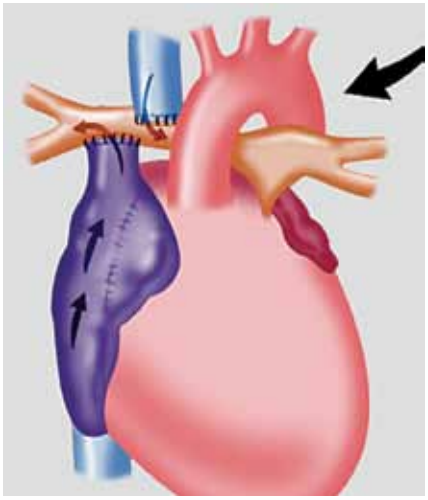

Figure 3. Lateral tunnel Fontan connection. Note the inferior vena cava is baffled through the lateral wall of the right atrium.

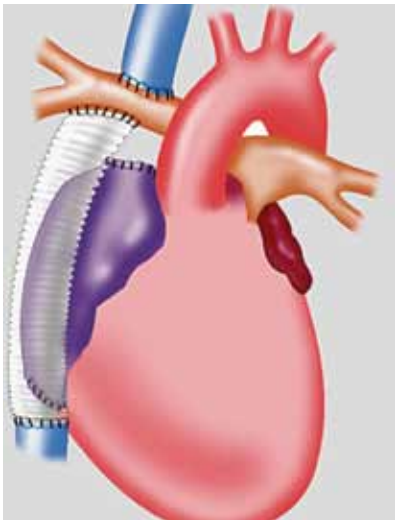

Figure 4. Extracardiac conduit Fontan connection. Note the inferior vena cava is connected to a tube graft that anastomosed to the right pulmonary artery. Also note the superior vena cava to right pulmonary artery connection.

patients with systemic left ventricles, and the success with the Norwood procedure (for hypoplastic left heart syndrome) has created more Fontan-palliated patients with systemic right ventricles. Many of these patients have begun to experience Fontan failure at an earlier age. In fact, the survival of hypoplastic left heart syndrome patients undergoing Norwood at five years of age is approximately 55%.

Studies have shown that Fontan patients report a good quality of life with normal exercise endurance at 5, 10, and 15-year follow-up, though some experts question self-reported exercise ability in the congenital heart patient.[20] Some centers have reported reduced exercise ability, with myocardial oxygen consumption (MVO2) in these patients between 61–65% predicted for age. The exact etiology of this decrease is unclear, and so is the question of whether or not an increased sedentary lifestyle in this patient population contributes to these findings.[21-23]

Morbidity/Mortality

Early — Although operative and early mortality was a significant concern early in the development of the Fontan operation, it has become less so in the modern era. Most surgeons now perform the LT or ECC type of Fontan connection instead of the AP type, and current operative mortality for a primary Fontan operation in children is only 3.5% and approaches less than 2% in most large centers.[24, 25]

Late — Difficulty exists in characterizing late outcomes of the Fontan procedure due to the heterogeneity of the underlying congenital heart disease and the type of operation performed. Most recent studies have noted a Kaplan-Meier overall survival of 91%, 87.3%, 84%, and 70% at 10, 15, 20 and 25 years, respectively. The freedom from death, Fontan failure, and heart transplant are 89% and 83% at 15 and 20 years, respectively.[18, 19, 26]

Complications and Treatment in the Fontan Patient

Arrhythmias

Arrhythmias, predominantly atrial, make up the most common late complication in the Fontan patient. Most studies suggest an incidence as high as 50% of atrial arrhythmias at 20 years post Fontan surgery. These typically are intra-atrial reentry tachycardia (IART), although atrial flutter, atrial fibrillation, and AV nodal tachycardias have also been described. Over time, IART typically degrades into atrial fibrillation.[27-30]

In contrast to patients with normal cardiac anatomy, Fontan patients cannot tolerate prolonged periods of atrial tachycardia and will begin to exhibit depressed ventricular function even within 24 hours of the arrhythmia.[27] Thus, treatment should be directed at terminating the tachycardia. Though this can sometimes be achieved pharmacologically, direct current cardioversion is often required.[27] Transesophageal echo to evaluate for thrombus is recommended prior to cardioversion in all of these patients, especially since patients often cannot recall when their acute episode of tachycardia began, and inefficient flow in the Fontan circuit lends itself to thrombus.[27]

Despite successful cardioversion, many patients will have multiple recurrences. An electrophysiology study (EPS) is frequently indicated to characterize and attempt to treat the tachycardia through radiofrequency ablation. Electrophysiologists with experience in complex congenital heart disease should perform these studies due to the special challenges that they present. This includes venous anomalies (both congenital and acquired), surgically modified cardiac anatomy, intracardiac shunts, and difficulty in cardiac chamber access.[31] There has been varying success with ablation in these patients, with reported initial success rates of 33% to 100%.[27, 28] Even with initial success, reports suggest that these tachycardias will recur. Repeat EPS in this population often has

decreased success rates, and many studies advocate either Fontan revision (discussed later) or surgical ablation.[27]

Cardiac

The major late-term cardiac complications in the Fontan patient include ventricular systolic and diastolic dysfunction and valvular disorders, most commonly atrioventricular (AV) valve regurgitation. Systolic dysfunction is most common in Fontan patients with other causative factors (i.e., arrhythmias, valvular dysfunction, coronary sinus hypertension), although patients with right ventricular morphology exhibit ventricular dysfunction in the third to fourth decade of life.[23, 29] Multiple studies indicate that Fontan patients universally exhibit some degree of diastolic dysfunction.[23, 32]

Valvular dysfunction can occur in many different forms given the heterogeneity of the Fontan population. AV valve regurgitation is most commonly experienced and portends a worse prognosis in this population subset.[23] This is especially true in patients palliated with a Norwood procedure, where significant tricuspid valve insufficiency is the risk factor in all studies that is most strongly associated with poor outcome.

Vascular

Normal Fontan physiology requires that the pulmonary arterial pressure is lower than the systemic venous pressure, thus ensuring passive venous return to the lungs without assistance from a pulmonary ventricle. Problems arise when the pulmonary vascular resistance (PVR) increases such that the systemic venous pressure rises. This elevated venous pressure is postulated to play a large role in multiple Fontan complications, e.g., thromboemboli, hepatic dysfunction, protein-losing enteropathy (PLE), but it has also been shown to play a primary role in systemic venous dysfunction.[33] A recent multicenter study displayed that almost all Fontan patients exhibit some degree of venous stasis and endothelial dysfunction.[34-36]

Coagulation

Fontan patients are significantly predisposed to experiencing thromboembolic events since the population displays the 3 risk factors previously described by Virchow. Bypassing the right heart creates significant stasis in the venous and pulmonary arterial system.[37] Endothelial dysfunction, especially in the venous system, has also been illustrated.[35, 36] Finally, studies have shown that Fontan physiology is a procoagulant state with decreased levels of Protein C as well as other coagulation factors secondary to liver congestion.[38, 39]

Therefore, it is not surprising that 3–8% of Fontan patients experience some form of thromboembolic complication, including thrombosis of the Fontan pathway, pulmonary embolism, intracardiac thrombus, or a cerebrovascular embolic event (specifically occurring in 1–2% of Fontan patients).[8, 19, 40, 41] Of note, pulmonary emboli (PE) are often difficult to diagnose via computed tomography (CT) scan due to the imbalance and delay of contrast filling the pulmonary arteries, often creating the false-positive impression of a filling defect and the misdiagnosis of PE. This is challenging for radiologists, who must understand the venous and pulmonary arterial anatomy to correctly interpret these CT scans.[42] Nonetheless, one study reports that Fontan patients can have "silent" asymptomatic PE when detected by ventilation-perfusion scan and confirmed by CT scan.[42a] Many feel that these "silent" emboli can increase PVR and further cause inefficient Fontan baffle flow.

Protein-Losing Enteropathy

A relatively infrequent and poorly understood late complication of the Fontan procedure is protein-losing enteropathy (PLE), which has an incidence of 1–15%.[43, 44] Elevated venous pressures, liver dysfunction, or gastrointestinal microvillus disease have been suggested as causes, but the etiology of this disorder is still not well understood.[43] A variety of treatment modalities — including budesonide, subcutaneous heparin, oral corticosteroids, atrial pacing, sildenafil, octreotide, diuretics, or fenestration (creation of a connection from the Fontan circuit to the systemic atrium) — have displayed at least initial positive results.[44-50] Despite these initially successful treatments, recurrence often occurs and the mortality rate can approach 50%.[51, 52]

Liver

Due to the hemodynamics of Fontan physiology, nearly all patients exhibit an elevation in venous pressure.[33] Although underrecognized, recent reports have shown that the majority of adult Fontans have underlying liver dysfunction.[53-55] Most patients display abnormal serum liver markers, and in a small number of studies in which liver biopsies were obtained, the majority show an element of hepatic fibrosis and parenchymal atrophy with cirrhosis.[56] We are part of a multicenter trial that is currently underway to evaluate the etiology and incident of liver disease in Fontans.

Neurologic Development

Most adult Fontan patients have typically experienced multiple cardiac operations, usually with significant exposure to cardiopulmonary bypass. Recent studies have suggested stunted somatic and developmental growth in a population of children exposed to multiple periods of cardiopulmonary bypass.[57] It is unknown if the early population of Fontan patients who underwent surgical procedures typically at an older age display these findings since this population has not been well studied. However, more neurodevelopmental outcome studies on Fontan patients are needed.

Plastic Bronchitis

A very rare but critical complication in Fontan patients involves the formation of bronchial casts that can occlude airways. Believed to be etiologically related to PLE, this involves secretion of proteinaceous material through the bronchial mucosa, where it eventually hardens to form occlusive casts.[58, 59] As with PLE, treatment for plastic bronchitis remains challenging and often unsatisfactory.

Fontan Failure

Late "Fontan failure" continues to be the rule and not the exception. Failure starts to become more prominent during the second and third decades following the Fontan operation, specifically the AP Fontan and its variations.[8, 18] There is no universal definition of Fontan failure, but it generally describes the combination of tachyarrhythmias, right atrial dilation — with or without thrombus, reduced systemic cardiac output due to poor prograde pulmonary flow, and lower extremity edema.

Medical Therapy

The initial treatment for a Fontan failure is medical optimization. Individual medical regimens should target the previously described Fontan complications with an emphasis on controlling the tachyarrhythmia. While medical therapy might delay progression of failure, it has not been shown to prevent the eventual need for surgical intervention.[60]

Fontan Conversion

Since the 1990s, Fontan conversion, also known as the Fontan revision procedure, has become a preferred surgical option in the treatment of the failing Fontan at several adult congenital heart disease centers.[61] Since most surgeons who performed the Fontan operation into the 1990s created the AP Fontan connection, there are likely hundreds of these AP type of "failing Fontans" worldwide. The Fontan conversion operation consists of five parts: (1) right atrial debulking, (2) conversion to ECC, (3) surgical cryoablation to treat the right-sided atrial tachyarrhythmia (this can also include a left-

sided MAZE operation if there is a history of atrial fibrillation), (4) epicardial dual-chamber pacemaker placement,[62] and (5) surgical correction of any anatomical resistance to flow (e.g., branch pulmonary artery repair or AV valve repair).

Initially, the Fontan conversion consisted of changing the traditional AP Fontan to the LT Fontan. However, most surgical centers now choose to convert AP Fontans into the ECC type. Although this re-operation was first described in the mid-1990s, intermediate follow-up at several centers have a low operative mortality, with improvement in exercise tolerance and NYHA classification. Studies have shown a significant recurrence in atrial arrhythmia of up to 20%, but early and intermediate results display a morbidity benefit through at least 29 months.[63-65]

Assist Devices

There are defined indications for ventricular assist devices (VADs) in the failing Fontan patient. While multiple case reports have discussed the use of left ventricular assist devices as a bridge to cardiac transplant, there are currently no well-established guidelines for this approach in the univentricular patient.[66, 67] Even though some successes have been reported, the results of LVAD therapy in failing Fontan patients have not been consistent. Fontan failure may be due to ventricular diastolic dysfunction resulting from a chronically underfilled systemic ventricle. Thus, conventional VADs will not produce significant benefit if left-sided filling pressures are low.[68] In 2008, Pretre reported a right-sided univentricular assist device that was used for 13 months as a bridge to heart transplantation.[69] A promising new multidirectional impeller pump has been reported by Rodefeld and colleagues in 2010.[70] Some believe that total artificial heart support with devices like the SynCardia™ may be the best option.

Cardiac Transplantation

Cardiac transplantation can be also considered for the failing Fontan patient. Transplantation for a complex congenital heart defect involves a significantly greater surgical risk as compared to non CHD patients due to their complex anatomy and often multiple previous cardiac procedures and blood transfusions.[71] Although the data are limited, the CHD transplant survivor often exhibits an improved survival compared to non CHD transplant patients, likely due to their younger age and improved noncardiac health.[72, 73] However, patient selection and type of CHD (e.g., bicuspid aortic valve) can confound this apparent benefit. That is, in many studies, CHF patients with simple defects like bicuspid aortic valve or small atrial septal defect were often included in the "CHD group," which may falsely increase the survival rate, whereas more complex CHD patients generally have a lower survival rate than their non CHD counterparts. A smaller number of studies have illustrated an increased mortality in the Fontan population undergoing cardiac transplant.[74-77]

Routine Health Care of the Fontan Patient

In 2008, the American Heart Association and the American College of Cardiology published the first guidelines for the management of adults with congenital heart disease.[5] These guidelines state that all adult Fontan patients should be managed by a cardiologist with an expertise in adult congenital heart disease, preferably at a recognized ACHD center. This should include an annual visit involving patient history, physical examination, electrocardiogram, chest X-ray, and periodic echocardiography.

Atrial arrhythmias should be aggressively treated and can require a hospital admission to initiate antiarrhythmic therapy. Some studies recommend prophylactic use of aspirin for its antiplatelet effect in Fontan patients. Anticoagulation with warfarin is recommended for all patients with atrial arrhythmias, thrombus, atrial level shunting (e.g., Fontan fenestration), or previous embolic event. ACE inhibitors should be used in patients with ventricular dysfunction.

Cardiac catheterization should be utilized to evaluate Fontan patients with unexplained desaturation, PLE, or elevated pulmonary artery or systemic venous pressures. If a catheterization is required, it should be performed in a center with ACHD expertise. When catheterization is unable to address these issues, surgical re-operation is recommended for all Class I indications: unintended residual atrial septal defect with right-to-left shunting, hemodynamically significant aortopulmonary (AP) collaterals that cannot be addressed via catheterization, ventricular-to-pulmonary connections, moderate-to-severe AV valve regurgitation, significant (>30 mmHg peak gradient) subaortic stenosis, Fontan circuit obstruction, pulmonary AVMs, pulmonary venous obstruction, rhythm abnormalities requiring an epicardial pacemaker, and creation or closure of a Fontan fenestration.

Summary

More patients with univentricular hearts are undergoing the Fontan procedure since the 25-year survival for this operation exceeds 70%. However, these patients continue to provide challenges in medical and surgical management as they progress through adulthood, and arrhythmias are especially frequent. "Fontan failure" is a significant long-term risk for patients and can lead to multi-organ system dysfunction with limited mechanical circulatory support and cardiac transplantation options. ACC/AHA guidelines for the care of the adult Fontan patient have now been established.

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