Transplantation in Fontan failure: The final stage

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Feature Editor Note—*The Fontan procedure is just over 50 years old, and we now fully realize that it is not a definitive solution to patients living with single-ventricle physiology. In fact, failure of the Fontan circulation is now one of the most common indications for cardiac transplantation. At Ann & Robert H. Lurie Children's Hospital of Chicago, we have now performed more than 350 heart transplants, of which 64 were for patients with a failed Fontan circulation. This included only 14 patients with failed Fontan circulation from 1990 to 2009 (first 20 years), but 50 of these patients were from 2010 to 2020 (past 10 years).*

Drs Jaggers and Rajab have appropriately labeled transplantation as the fourth or final stage of palliation for patients living with single-ventricle physiology. This realization forces us to carefully characterize the indications for transplantation. In this patient population, however, this is often a difficult decision that is unique for each patient. Waiting too long creates a situation in which the transplant risk is very high (ie, patient with ascites, protein-losing enteropathy, malnutrition). Conversely, it is hard to list a patient for transplant who is seemingly doing well but slowly declining. The decision tree becomes even more difficult when one considers the use of temporary ventricular assist devices as a possible bridge to transplantation, or even as destination therapy.

The guidelines offered here I believe will be useful to clinicians trying to decide when to list for transplant one of these very complex individuals, each of whom will always have a slightly different medical and surgical history. This will definitely be an ever-evolving paradigm, and I believe this current contribution from true experts in this field will be helpful to all clinicians caring for patients facing the fourth stage of single-ventricle palliation.

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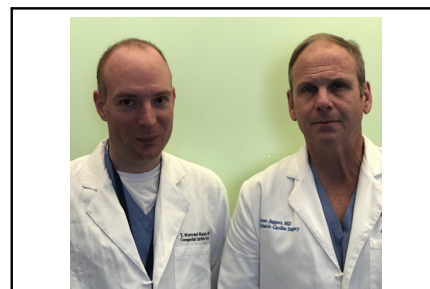Taufiek Konrad Rajab, MD, and James Jaggers, MD

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https://doi.org/10.1016/j.xjon.2020.05.002

THE FONTAN CIRCULATION

Arguably one of the greatest achievements in congenital heart surgery has been the development of a unifying treatment pathway for single-ventricle defects based on the Fontan principle.[1] This treatment pathway converts the unstable parallel circulations into a stable Fontan circulation. The Fontan circulation involves a total cavopulmonary connection that places the systemic circulation in series with the pulmonary circulation without an interposed subpulmonary ventricular pump. Pulmonary blood flow is driven by residual postcapillary kinetic energy in the systemic venous system. Ultimately, pulmonary blood flow is determined by the systemic venous pressure (pulmonary artery pressure), the pulmonary vascular resistance or mechanical obstruction (impedance), and the downstream pulmonary venous pressure.[2] This results in nonpulsatile, low-energy pulmonary blood flow at an elevated pressure. Despite its shortcomings, the strategy results in near-normalization of the oxygen saturation, a balanced systemic and pulmonary blood flow, and resolution of volume load on the systemic ventricle and has allowed the survival of thousands of

patients with single-ventricle heart defects all over the world. Survival rates after the Fontan operation have improved considerably (91% and 82% at 10 and 20 years respectively)[3,4] since the first such procedure was carried out half a century ago.

FONTAN FAILURE

The absence of a subpulmonary ventricle results in a greater central venous pressure, with the residual postcapillary kinetic energy in the systemic venous system driving transpulmonary blood flow. This results in decreased and less-efficient transpulmonary blood flow compared with a biventricular circulation, especially in response to increased demands with exercise. Therefore, systemic cardiac output is dependent on preload, which is dependent on impedance across the pulmonary vascular bed. Together, chronic systemic venous hypertension and chronic low cardiac output are responsible for end-organ dysfunction and even permanent damage. In the words of Francis Fontan, "the Fontan operation is palliative but not curative."[5] Therefore, it is very likely that nearly all patients with Fontan physiology will develop severe adverse effects of the physiology (failed Fontan) and may require eventual transplantation.

MODES OF FONTAN FAILURE

Based on the pathologic mechanisms described previously and characteristic patterns of clinical symptoms, the mode of Fontan failure can be divided on a spectrum into 2 major categories. On one end of the spectrum, Fontan failure results from impaired ventricular function (IVF). Etiologies for IVF include valvular insufficiency, residual aortic obstruction, arrhythmia, coronary insufficiency, or aortopulmonary collateral burden. The clinical picture is often characterized by failure to thrive, limited exercise tolerance, and arrhythmias.

The other mode of failure is impairment of the Fontan circulation but preserved ventricular function (PVF). Etiologies for impairment of the Fontan circulation include anatomic obstructions, thromboembolism, elevated pulmonary vascular resistance, pulmonary venous obstruction, or pulmonary arteriovenous malformations (AVMs). Here, the clinical picture is often characterized by pathologic fluid shifts, endoluminal protein loss (protein-losing enteropathy and plastic bronchitis), and cyanosis. Regardless of the dominant pathophysiology, Fontan physiology may result in liver dysfunction and cirrhosis, esophageal varices, renal dysfunction, nutritional derangement, and thromboembolic events. Some patients with failing Fontan physiology may respond to medical therapy, whereas in some patients with severe end organ dysfunction, the use of mechanical circulatory support can reverse dysfunction and improve the condition of the patient to hopefully allow transplantation, which is the only durable option.

TIMING OF TRANSPLANTATION IN FONTAN FAILURE

Fontan failure has become one of the most common indications for heart transplantation in patients with congenital heart disease.[6] For this reason, heart transplantation has been called the final stage, or stage 4 palliation for single-ventricle heart defects. The timing for referral for heart transplantation is dependent on many factors.[7] Because of the limited durability and long-term risks associated with transplantation, referral should be reserved for those patients in whom remediable causes for failure have been addressed and before patients develop significant end-organ dysfunction. The decision for transplant listing may also depend on anticipated wait time, which can be substantially varied in different regions of the country.

The outcomes for patients with IVF were initially superior to patients with PVF. More recently, it has been shown that outcomes of transplantation for IVF and transplantation for PVF with impaired Fontan physiology may be equivalent due to earlier listing, improved pretransplant care, and critical care post-transplant.[8]

The heterogenous presentation of patients in Fontan failure can make it difficult to decide when the referral for transplant evaluation. The Advanced Cardiac Therapies Improving Outcomes Network (ACTION), a collaborative consisting of clinicians, researchers, parents, and patients, recently published guidance to help with this decision (Table 1).[9] While this list is relatively nonspecific, it does provide some guidance.

PRETRANSPLANT EVALUATION AND PREPARATION IN FONTAN FAILURE

At the time of an advanced heart failure consultation, cardiac anatomy, pulmonary vascular resistance, and general health of the patient need to be considered to determine suitability for transplantation.[9] Evaluation of the cardiac anatomy involves cardiac catheterization, computed tomography, or magnetic resonance imaging. In particular, the systemic venous connections, branch pulmonary arteries, and the aortic arch needs to be evaluated carefully. However, there are no absolute contraindications for transplantation based on the morphology of the single-ventricle defect, nor the anatomic surgical anatomy following palliation.

In contrast, elevated pulmonary vascular resistance can be an absolute contraindication for isolated heart transplantation. Irreversible pulmonary vascular resistance greater than 6 Wood units and transpulmonary gradient greater than 12 mm Hg are considered relative contraindication, whereas irreversible pulmonary vascular resistance greater than 9 Wood units and a transpulmonary gradient greater

TABLE 1. Indications for referral for transplantation: Advanced Cardiac Therapy Improving Outcomes Network (ACTION)[9]

Systemic ventricular dysfunction
1. Severe systolic dysfunction defined as ejection fraction <35% for single LV or <30% for single RV
2. Moderate systolic dysfunction when accompanied by at least moderate atrioventricular valve regurgitation
3. Failure to thrive or linear growth failure
4. Decreasing exercise tolerance
5. Recurrent arrhythmias despite therapy, implantation of a pacemaker, or aborted sudden death

Fontan pathway dysfunction
1. Symptomatic fluid overload resistant to diuretic therapy
2. Chronic pleural effusions or ascites resistant to therapy
3. Symptomatic disturbance of hemodynamics resistant to therapy, including elevated Fontan pressure, or cyanosis

Lymphatic dysfunction
1. Protein-losing enteropathy requiring multiple hospital admissions in a 12-month period or protein-losing enteropathy requiring repeated albumin infusions
2. Plastic bronchitis requiring chronic therapy

Extracardiac dysfunction
1. Liver disease with impaired synthetic function or undergoing evaluation for liver transplantation
2. Chronic kidney disease stage 3 or greater
3. Persistent hemoptysis that is unrelated to infection

LV, Left ventricle; *RV*, right ventricle.

than 15 mm Hg are absolute contraindications for isolated heart transplantation.[10] One cannot assume that pulmonary vascular resistance is low enough to tolerate heart transplantation merely because a patient is living with a Fontan circulation.[11] Unfortunately, estimating pulmonary vascular resistance in patients with Fontan failure can be difficult due to low cardiac output and systemic-to-pulmonary collaterals with possible unequal blood flow in the left and right lungs.[12] Like other groups, we have adopted a policy of transcatheter coil occlusion of the large aortopulmonary collaterals before transplantation. These collaterals have the deleterious effect of increasing the volume load on the systemic ventricle and worsening pulmonary congestion, thereby complicating pretransplant management. If left unaddressed, a large collateral burden can result in decreased systemic blood flow and impaired tissue oxygen delivery in cardiopulmonary bypass, massive pulmonary venous return flow on bypass, increased peritransplant bleeding, and can increase risk of primary graft dysfunction after transplant due to the excess volume load. The presence of pulmonary AVM may also result in artificially low measured PVR. This may complicate post-transplantation care with unexpected high PVR.[11] It is important to note that pulmonary AVMs, despite complicating the pretransplant assessment, will usually regress after successful transplantation.[13]

All organ systems need to be thoroughly evaluated and optimized before transplant. This includes an evaluation of nutritional status, coagulation, hepatic and renal function, and vascular access. Particular attention should be focused on Fontan-associated liver disease (FALD), since transplantation in this context is fraught with risk and uncertainty.[14] Although a detailed discussion of FALD is not possible in this limited review, it is important to note that nearly all patients with Fontan circulation will develop pathologic changes of fibrosis in the liver. The most common finding on pathology is portal fibrosis, but progression to clinical end-stage cirrhosis and even hepatocellular carcinoma can occur. Clinical evaluation for FALD involves multimodal investigations, including laboratory data, axial imaging, liver ultrasound with elastography, and possibly liver biopsy. In patients with FALD and cirrhosis with relatively preserved synthetic liver function and minimal or no varices, we will offer cardiac transplant only. However, patients with severe cirrhosis with ascites, low synthetic function or severe varices, or hepatocellular carcinoma, combined heart liver transplant may be indicated.[15] Even though FALD is ubiquitous, the occasion for combined heart liver transplant is relatively uncommon and with improved recognition, surveillance, and management, FALD will hopefully become less of an issue.

Patients with a failed Fontan have had multiple sternotomies, increasing the risk with sternal re-entry. A careful assessment of the femoral and cervical arteries and veins can help plan peripheral cannulation if necessary. Finally, patients with a Fontan frequently demonstrate immune sensitization with elevated panel-reactive antibodies. Careful pretransplant screening has eliminated some of the uncertainty of this, but in highly sensitized patients, we perform plasmaphoresis on cardiopulmonary bypass before crossclamp removal during transplant. All patients in our program receive induction therapy and early discontinuation of steroids.

VENTRICULAR ASSIST DEVICE (VAD) AS A BRIDGE TO TRANSPLANTATION IN FONTAN FAILURE

Heart transplantation is the preferred treatment for most patients with end-stage Fontan failure, but some patients

may benefit from mechanical circulatory support. In patients with acute decompensation or early failure of Fontan physiology, salvage with extracorporeal membrane oxygenation (ECMO) may be necessary. Outcomes for ECMO as bridge to transplantation in single-ventricle patients are generally poor. In a retrospective analysis of the Extracorporeal Life Support Organization Registry, the survival to hospital discharge in patients with single-ventricle heart defects requiring ECMO was only 33%.[16] VADs may be useful as a bridge to transplant in patients with reversible end-organ dysfunction such as renal insufficiency, secondary pulmonary hypertension, or liver dysfunction. Considering VAD implant for the 2 modes of failure, IVF and PVF, it is unlikely they would have similar outcomes with the same support. Patients with IVF would be expected to benefit quickly from a VAD implanted to support the systemic ventricle, but those with a predominately impaired Fontan circulation physiology VAD may be less effective.

The first patient with Fontan failure who was treated with a VAD for bridge to transplantation was reported in 2005.[17] Since then, VADs have played a progressively more important role in the management of patients with Fontan failure who are possible transplant candidates but have prohibitive risk or end-organ injury that is reversible. Outcomes in patients with single-ventricle defects treated with VAD are worse than patients with biventricular congenital heart disease. For example, an analysis of the Berlin Heart EXCOR Investigational Device Exemption study database identified 26 patients with single-ventricle defects who were treated between 2007 and 2011. Among these, 11 (42%) were bridged to transplantation or recovery, which contrasted with 185 of 255 (73%) of patients with a biventricular circulation. Of note, 5 of the 26 patients with a univentricular circulation were treated after Fontan completion, of whom 3 survived to transplantation.[18] However this poor survival may be the result of the device, as improved outcomes are reported with the use of implantable centrifugal pump devices.

VAD support is more likely to be helpful in patients with impaired ventricular function. If the patient is symptomatic due to other causes, such as failure of the Fontan circuit with elevated pulmonary vascular resistance, a VAD will not be as effective.[19] In this case, a total artificial heart may offer a solution. This approach improves both cardiac output and systemic venous pressure by providing systemic and pulmonary support. However, implantation of a total artificial heart is technically more difficult, limited to larger patients, and has significant risk of bleeding and periprocedural complications.[20,21]

We think it is optimal to list patients for transplant before the development of end-organ injury. However, this can be unpredictable, and patients may experience long wait times with continued risk of decompensation. Therefore, we do recommend mechanical support for patients with decompensation or failure of medical management who are otherwise candidates for transplant.

OUTCOMES AFTER TRANSPLANTATION FOR FONTAN FAILURE

Historically, transplant survival for failed single-ventricle palliation was lower than in patients transplanted for cardiomyopathy. However, outcomes of cardiac transplantation in patients with congenital heart disease have improved to the point where they are nearly equivalent to non-congenital heart disease heart transplantation.

The selection of the donor organ is very important. Because of the risk of increased pulmonary vascular resistance and relative systemic vasoplegia, we increase the lower limit of acceptable weight ratio from 0.8 to 1.0. A larger organ is helpful to bolster right ventricular function but also fill the space in the mediastinum better. We also routinely use vasopressin following transplant to treat vasoplegia.

In a study involving 107 patients with Fontan circulation and 381 patients with other forms of congenital heart disease identified via the combined Heart Transplant Study and Cardiac Transplant Registry Database who were transplanted between 1990 and 2002, the predicted post-transplant survival in Fontan patients was lower (77% and 70% at 1 and 5 years) than patients without Fontan (88% and 81% at 1 and 5 years). This difference was predominantly due to an increase in relative risk for mortality of 8.6 ($P = .003$) during the first 3 to 6 months. Several factors may contribute to this increased early risk (Table 2).

After this early period, the survival curves were not significantly different.[6] In these early studies, it was evident that there was a worse outcome for patients transplanted early after the Fontan palliation versus those with late failure. Further long-term outcomes are available from a retrospective review of 61 patients who underwent orthotopic heart transplant for Fontan failure at 11 European Congenital Heart Surgery Association centers between 1991 and 2011. The mean time interval between Fontan completion and orthotopic heart transplant was 10.7 ± 6.6 years. The overall Kaplan–Meier survival estimate in this series was 82% at 1 year, 73% at 5 years, and 56.8% at 10 years.[22] Similarly, in a series of 22 patients with a failing circulation Fontan who were transplanted from 1990 to 2012, 1-, 5-, and 10-year survival was 77%, 66%, and 45%, respectively.[23]

However, a recent reanalysis of data from the Pediatric Heart Transplant Study database for Fontan patients who were transplanted in the current era (2007-2014) showed that outcomes had improved significantly, especially during the critical early phase. In this study, patients transplanted for Fontan failure had a 1-year survival of 89%, which was similar to the 1-year survival of a patient without Fontan with congenital heart disease of 92%.[24] Patients with preserved ventricular function benefit from this survival

TABLE 2. Factors contributing to increased risk for transplant in failed Fontan

1. Multiple previous sternotomy
2. Severe Mediastinal adhesions
3. Increased risks of bleeding
4. Risk of phrenic nerve injury
5. Need for pulmonary artery and systemic venous reconstruction
6. Pulmonary hypertension
7. Lack of vascular access
8. Presence of systemic to pulmonary collaterals, increased bleeding, and need for altered perfusion strategies
9. End-organ dysfunction
    a. Renal insufficiency
    b. Liver insufficiency and coagulopathy
    c. Malnutrition hypoalbuminemia and altered immune function

advantage in the current era. A review of patients with a previous Fontan operation who underwent heart transplantation showed that patients with preserved ventricular function had increased 1-year survival from 38% in the earlier era to 83% in the current era. There was no increase in benefit for patients with IVF.[8]

SUMMARY

Treatment of patients with single-ventricle defects according to the Fontan principle has arguably been one of the greatest achievements in congenital heart surgery. However, despite successful palliation, these patients can develop Fontan failure with end-organ dysfunction. Heart transplantation should be recommended after all possible remediable causes of Fontan failure have been addressed. There is no clear agreement about when a patient with Fontan failure should be referred for transplantation, but all would agree that it is best to transplant before severe end-organ injury. Mechanical circulatory support with VAD can reverse end-organ dysfunction and improve chances for a successful transplant. Transplantation following Fontan palliation is more technically challenging, but survival in the short and long term is nearly as good as transplant for cardiomyopathy. Perhaps in patients in whom the Fontan circulation results in complications and dysfunction, we should not consider it a failure, rather a not-unexpected outcome and that transplantation is the final stage of the single-ventricle treatment pathway.

Conflict of Interest Statement
The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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