Transplantation of the failing Fontan

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Abstract: Half a century has passed since the original Fontan palliation. In the interim, surgical and medical advancements have allowed more single ventricle patients to reach Fontan and long-term survival for Fontan patients to improve significantly. However, the risk for Fontan failure and need for heart transplantation remains. In this article we discuss mechanisms of Fontan failure, risk factors and special considerations for Fontan patients in both medical and surgical management around heart transplantation and provide an updated review of survival for Fontan patients after heart transplantation.

Keywords: Heart defects; congenital; heart transplantation; risk factors

Introduction

For children with complex congenital heart disease and single ventricle physiology, staged palliation ending in the Fontan procedure is the standard of care. Initially described in 1971 by Francis Fontan with a goal of eliminating cyanosis in a young woman with tricuspid atresia, the Fontan palliation is a total cavopulmonary connection of the inferior and superior vena cavae to the pulmonary arteries, with no subpulmonary ventricle (1). The procedure has greatly improved the short term morbidity and mortality for children with single ventricle heart disease, however Dr. Fontan himself said the procedure imposes a "*gradually declining functional capacity and premature late death… the Fontan operation is, therefore, palliative but not curative*" (2). In the nearly five decades since Dr. Fontan's original report of the Fontan palliation, the procedure has undergone several surgical advances in technique with subsequent improvement in patient outcomes (3,4). While most initial reports of Fontan survival were single center reports, several recent studies based on multi-center data have shown significant improvement in previous survival estimates. A 2018 meta-analysis of Fontan patients estimated 20-year Fontan survival at 75–85% (5). Studies looking only at Fontans completed in the modern era are even more optimistic. The Pediatric Heart Network's 2017 report of their Fontan cohort estimated 12-year survival at 90% (6). Indeed, multiple retrospective single center studies have shown that when Fontan patients are divided into eras, accounting for changes in clinical and surgical practice, that survival improves in the later years (7,8). With this in mind, the number of patients both reaching Fontan as well as living with Fontan is likely to increase in the upcoming decades (9). Although the improvement in recent Fontan survival is certainly impressive, the fact remains that even the most optimistic reports have 10% or more of Fontan patients either dying or requiring heart transplant by early adulthood.

As the population of patients living with Fontan physiology continues to grow, the population is itself also changing. Hypoplastic left heart syndrome is now the most common diagnosis of patients undergoing Fontan completion as the result of surgical advancements as well as increased knowledge in the field of intensive care about perioperative management for the first two stages of palliation (10). Furthermore, registry data has found that

patients with hypoplastic left heart syndrome are more likely to develop Fontan failure (11,12), thus possibly increasing need for heart failure management and cardiac transplantation as this population survives longer into adulthood. The purpose of this article is to review the unique indications and challenges of evaluation and peri-operative management of heart transplantation of the growing Fontan population.

Fontan circulation and categories of failure

The indications for heart transplantation in Fontan patients are inherently linked to the consequences of Fontan physiology. The Fontan circulation places the pulmonary circulation in series with the systemic circulation with no subpulmonary ventricle and relies on passive flow through the pulmonary bed resulting in obligatory systemic venous hypertension. Because of the lack of a subpulmonary pumping chamber, the Fontan circulation results in less preload than the two-ventricle circulation and remodeling of the pulmonary venous vasculature (13). Thus, Fontan physiology results in chronic vascular changes both in the systemic venous and pulmonary venous circulations. Each of these physiologic changes may lead to symptomatic intolerance of Fontan physiology, often collectively termed Fontan failure despite the appearance and progression of Fontan failure being heterogenous. To help guide both prognostication and treatment, modalities of Fontan failure are often grouped into phenotypical and mechanistic subtypes (14). For all these phenotypes, failure may progress despite aggressive medical management, and heart transplantation may become the only option for improved quality of life and long-term survival. Of these phenotypes, ventricular failure (50%) and protein losing enteropathy (PLE) (40%) are the top two most common reasons for transplant referral (15,16).

To provide a framework for referral for advanced heart failure consultation, the Advanced Cardiac Therapies Improving Outcomes Network (ACTION), a national collaborative of pediatric heart failure clinicians, researchers, parents, and patients has recently released a reference entitled "*Considerations for Advanced Heart Failure Consultation in Fontan Patients*", included in *Figure 1* (17). The ACTION collaborative is hopeful that timely referral for advanced heart failure consultation and collaborative care of Fontan patients with heart failure will continue to enhance patient outcomes but the effect of changing referral patterns remains to be seen.

Ventricular dysfunction

Failure of the Fontan circulation can be the result of systolic or diastolic ventricular dysfunction, perhaps more analogous to heart failure in the patient with two-ventricle circulation (14). Chronic effects of single ventricle physiology result in changes to the geometry and function of the ventricle itself, manifesting in abnormal relaxation or contraction of the myocardium or distortion of the systemic atrioventricular valve (18). Despite being a common indication for referral for heart transplantation, there is overall a paucity of published data about ventricular failure in the Fontan population. The Pediatric Heart Network identified that right ventricular morphology was associated with poorer ventricular function (12). It has also been suggested that systolic ventricular failure may impact outcomes in the pediatric Fontan population more than in adults, as systolic ventricular dysfunction is not a predictor of death or heart transplantation listing in the adult Fontan population (19). The impact of diastolic heart failure in the Fontan population is also likely underappreciated, with several studies showing that increased atrial pressures after Fontan are predictive of non-survival (7,20). Better described than either systolic or diastolic dysfunction is the association of atrioventricular valve insufficiency and poor Fontan outcomes. A recent international study found that atrioventricular valve failure was significantly associated with failure of the Fontan circulation (21).

Fontan circuit failure

Fontan failure can also be unique to the Fontan (or pulmonary) circuit itself. Fontan pathway failure clinically manifests as chronic right heart failure with hepatomegaly, ascites, and edema, as well as cyanosis from right-to-left shunts within the pulmonary pathway (14). It has been shown in multiple studies that cyanosis in Fontan patients is associated with death (6), adverse events around procedures (22), and that increased oxygen saturation decreases the risk of a major event (19).

Lymphatic failure

Also related to the Fontan circulation is abnormalities of the lymphatic system. PLE, or leakage of lymph from the intestinal lumen, is an independent risk factor for mortality in the Fontan population (23). The intestinal lymphatics in Fontan patients are likely inherently abnormal, as immune abnormalities in Fontan patients are similar to

Figure 1 Considerations for Advanced Heart Failure Consultation in Fontan Patients, from the Advanced Cardiac Therapies Improving Outcomes Network. Reproduced with permission from Schumacher and Kindel (17).

those found in non-Fontan patients with PLE caused by intestinal or hepatic lymphangiectasia (24). Likewise, plastic bronchitis or leakage of lymph from the bronchial tree is also associated with increased mortality (25). Advances in MRI based lymphatic imaging has identified abnormal pulmonary lymphatic perfusion in Fontan patients with plastic bronchitis (26). Lymphatic failure in Fontan patients

is exceptionally challenging from a management perspective not only because of the limited treatment options, but also because many of these patients have seemingly normal hemodynamics (27,28). There appears to be a subset of individuals who develop lymphatic abnormalities that manifest in a variety of ways only partly affected by hemodynamics (29). There is some suspicion that lymphatic

failure results not only from abnormalities of the lymphatic tree but also from vascular changes of non-vital organs such as the mesentery, resulting in relative local changes in systemic venous resistance and leakage of lymph (30).

Extra-cardiac organ failure

Even in hemodynamically well compensated Fontan patients, cardiac output is impaired with less ability to increase output during high demand (31), resulting in chronic subacute cardiac insufficiency that may eventually lead to end organ damage particularly affecting the liver and the kidneys. Fontan associated liver disease (FALD) is a known entity secondary to chronic liver congestion in patients after Fontan completion. Pathology studies have shown that most if not all patients after Fontan will have changes on a histological level, with more advanced disease progressing to cirrhosis or even hepatocellular carcinoma (32). The degree of fibrotic change appears to only be associated with the length of time spent as a Fontan patient and not with hemodynamic or other patient or systemic factors, suggesting that the disease is both progressive and directly results from Fontan circulation alone (33). Screening and monitoring for progression of FALD can be very challenging, as even patients with advanced disease tend to be asymptomatic with near normal biochemical and functional hepatic tests (34). While less discussed than FALD, kidney disease in Fontan patients is also an important consideration. Kidney disease is probably under-recognized in patients after Fontan, with several studies showing reduced glomerular filtration rate (GFR) (35), increased risk of glomerular and tubular injury (36), and chronic kidney disease (CKD) stage 2 or greater in 10–25% of patients (37).

Fontan heart transplant outcomes

Early studies of outcome from heart transplant in Fontan patients showed decreased post heart transplant survival in pediatric Fontan patients when compared to other patients undergoing heart transplantation (38-40). Recent studies are more optimistic and suggest that survival for pediatric Fontan patients after heart transplantation is similar to non-Fontan congenital heart disease patients (16,41,42). Pediatric Fontan patients with preserved ventricular function previously were reported to have worse survival compared to patients with impaired ventricular function (43), however even pediatric Fontan patients with

preserved ventricular function have had improvement in survival in more recent years (42). Likewise, survival after pediatric heart transplantation as a whole has also improved. (44). *Table 1* lists reports from multiple single center and multicenter studies regarding Fontan survival after heart transplantation. Improved survival after heart transplantation for Fontan patients as well as pediatric patients in general is likely multifactorial, secondary to advances in surgical technique, pre- and post-operative care, and immunosuppression as well as possible temporal changes in patient selection. Careful consideration during the pre-listing evaluation and surgical planning may continue to improve post-transplantation outcomes in this population.

Risk factors, patient optimization, and post-transplant outcomes

Lymphatic failure

Although a common indication for heart transplantation and frequently discussed as a risk factor for post-transplant outcomes, the diagnosis of PLE alone does not increase wait list or post-transplant mortality (50,51). In addition, although It has been suggested that patients with PLE are relatively immunocompromised (24), a recent study from the Pediatric Heart Transplant study found no difference in rejection or post-transplant infection rates between PLE and non-PLE Fontan patients. In a separate multicenter study, there was no change in wait-list or post-transplant mortality with aggressive treatment of PLE (51). Mortality was also not associated with degree of growth impairment or duration of disease in patients with PLE. However, there was an association between using non-standard immunosuppression in patients with PLE and post-transplant mortality, specifically nonuse of mycophenolate mofetil. Further studies are needed to determine what if any alterations in immunosuppression should be used in this patient population. Of note, multiple studies have noted resolution of PLE after transplantation (38,41,45,52-54). The most recent multi-center report of plastic bronchitis and post-transplantation outcomes showed that plastic bronchitis is a far less common indication for transplantation, and that patients with plastic bronchitis have worse early mortality than controls but no difference in long term outcomes. Similarly to PLE, plastic bronchitis appears to resolve post transplantation (55).

Table 1 Review of studies of survival after heart transplantation for pediatric Fontan failure

First author, year	Era	Multi-center	Cases	Survival (%)	Time from transplant
Michielon, 2003 (40)	1998–2002	No	6 Fontans	33	30 days
Gamba, 2004 (45)	1990–2002	No	14 Fontans	86	1 year
				77	5 years
				62	10 years
Jayakumar, 2004 (38)	1984–2001	No	35 (24 Fontans, 11 Glenns)	71.5	1 year
				67.5	5 years
				62	10 years
Griffiths, 2009 (43)	1994–2008	No	20 Fontans	85	2 years
Lamour, 2009 (39)	1990–2002	Yes	107 Fontans	71	1 year
				60	5 years
Davies, 2012 (46)	1984–2007	No	43 Fontans	75	30 days
				62.4	1 year
				58.7	5 years
				47.5	10 years
Backer, 2013 (47)	1990–2012	No	22 Fontans	77	1 year
				66	5 years
				45	10 years
Michielon, 2015 (48)	1991–2011	Yes	61 Fontans	81.9	1 year
				73	5 years
				56.8	10 years
Kanter, 2016 (41)	1988–2015	No	33 Fontans	84.8	1 year
				70.8	5 years
Miller, 2016 (42)	1995–2008, 2009–2014	No	47 Fontans	90 [2009–2014]	1 year
Berg, 2017 (49)	1991–2014	No	36 Fontans	75	1 year
				58	3 years
Simpson, 2017 (16)	1993–2006, 2007–2014	Yes	402 Fontans	89 [2007–2014]	1 year

Sensitization

Fontan patients are often human leukocyte antigen sensitized. Multiple prior surgeries result in significant blood product exposure. Homograft material is also often used in vascular reconstruction during the staged palliation and associated with long-term sensitization in half of patients (56). For these reasons, Fontan patients may be more likely to be sensitized prior to transplant, which is known to be associated with decreased 1-year post transplant survival (57,58). A study from the Pediatric Heart Transplant Study in 2006 found that 16.5% of Fontan patients and 12.8% of non-Fontan patients with congenital heart disease had a pre-transplantation panel reactive antibodies (PRA) >20%, compared with only 2.3% of patients without congenital heart disease (52). However, these relatively higher PRAs may not in actuality affect post-transplant outcomes. A recent study described a third

of Fontan patients with a PRA greater than 10%, but with no significant differences in outcome (16). More studies are needed to determine if sensitization affects outcomes in this population, and in turn if desensitization would improve outcomes. A small study of highly sensitized patients with congenital heart disease awaiting transplantation found a significant decrease in PRA with intravenous immunoglobulin and rituximab treatment (59). Using decellularized graft material in the initial stages of palliation may also decrease sensitization at time of transplant listing (60).

Age

Timing of listing for Fontan patients must be carefully considered. There are no established criteria for patients with Fontan failure and timing of transplant listing (43,61). Not only current clinical status, but also wait list time and age at listing need to be considered. A recent study showed that patients had a significantly longer wait time when listed after their 18th birthday than those listed before their 18th birthday. While this study did not show any significant difference in waitlist mortality between the two groups, timing of listing for Fontan patients who are medically fragile should be carefully considered (62). The effect of age at listing on outcomes is unclear, with one study showing an increased risk of death in an early age group (39), and another multi-center study of only adult patients showed that Fontan patients who were listed at a younger age had improved mortality over time (63).

Functional status

A recent study has shown that worse functional status prior to transplant is associated with worse short and long term outcomes (64). Therefore, for Fontan patients prior to transplant exercise and mobility should be emphasized and improved upon if safe and possible. Fontan patients have at baseline a decreased VO_2 from predicted and show a decline of VO_2 over time (65). It is also well documented that a substantial decline in VO_2 over time is a predictor of mortality or need for heart transplantation in Fontan patients (66,67). This may not only potentially improve post-transplant outcomes but also may improve heart failure symptoms in general in this population. There is a growing body of literature that exercise, especially focusing on lower body resistance training, can improve VO_2 and clinical status in Fontan patients. Resistance muscle training has been shown to improve cardiac filling, stroke volume,

and exercise capacity in adult Fontan patients (68). Referral to cardiac rehabilitation or physical therapy as appropriate should be considered for all Fontan patients being considered for heart transplantation.

Nutrition

Multiple studies have suggested that nutrition and growth are risk factors for perioperative heart transplant outcomes in the congenital heart disease population. Poor nutrition has been shown to increase wait list mortality in patients with congenital heart disease (69). Likewise, poor growth is a risk factor for worse outcomes in congenital heart disease patients following heart transplant (70). There is likely an opportunity to further improve outcomes by optimizing nutrition in Fontan patients prior to transplant. This may have increased importance in patients with chronic protein losses, like Fontan patients with PLE.

Non-cardiac end organ failure

End organ failure in Fontan patients is prevalent and is a risk factor for need for heart transplantation (71,72). Of particular interest is FALD and its role in timing of heart transplant listing. Despite its initial subclinical nature, FALD can complicate Fontan failure and may be significant enough to be a contraindication to heart-only transplantation (34). Progressive Fontan failure symptoms with progressive liver dysfunction may be a trigger earlier consideration for heart transplantation prior to further deterioration of the liver, however these patients may not meet more urgent listing criteria and thus may have a longer wait list time. Those with more advanced disease may require heart-liver transplantation, although the exact indications for heart-liver transplant in this population is not yet well understood (73). A single-center study showed no difference in 1-year post transplant survival for Fontan patients with or without cirrhosis (74), and thus even more advanced disease may not be a complete contraindication to heart-only transplantation. Furthermore although several case series from single centers report good outcomes heart-liver transplantations in single ventricle patients with end state liver disease (75,76), more information is needed to determine which patients truly require both organs.

Likewise, kidney function should be carefully considered in the transplant evaluation. Pre-operative renal failure is known to be a predictor of worse outcomes in all patients post heart transplant (77), and similarly pre-transplant

renal failure is a strong predictor of early mortality in Fontan patients after heart transplantation (46). Similar to liver failure, advanced kidney disease may be a relative contraindication for heart only transplantation, and heart-kidney transplantation may be a consideration for some patients. Monitoring of kidney function in patients with Fontan failure is key to identifying patients prior to development of advanced kidney failure.

Mechanical ventilation

Ventilator support has been consistently associated with increased mortality after heart transplantation both for patients with and without Fontan palliation (15,52,61,78). Mechanical ventilation in Fontan patients, like other patients with complex congenital heart disease, may be related to abnormalities of pulmonary vasculature or lung parenchyma, lung or diaphragm injury, or airway abnormalities (79). It could also be secondary to cardiac insufficiency and Fontan failure and be an indication of worse clinical status (15). Attempts should be made to optimize cardiac status and remove the patient from invasive mechanical ventilation; this both reduces the independent risk and also allows for improved rehabilitation and other optimization. Evaluation and listing for transplantation prior to need for mechanical ventilation will likely continue to improve post-transplant outcomes (52).

Ventricular assist devices (VADs)

The VAD experience in the single ventricle population is growing. While most of the published literature is case reports, it would appear that some Fontan patients may benefit from use of VADs prior to transplantation. These patients are primarily those with systolic dysfunction, diastolic dysfunction, or both as their mechanism of failure (80,81). There may also be a role for biventricular support devices in patients with very high central venous pressures to improve end-organ function, transplant candidacy, and post-transplant outcomes (82,83). Because of the prevalence of aorto-pulmonary collaterals in Fontan patients, it is generally accepted that continuous flow assist devices are preferable to account for the changes in inflow in the presence of these vessels (80). A recent review of case reports of VADs in Fontan patients had fourteen out of nineteen successful cases of VAD therapy (bridged to transplant, bridged to recovery, or still supported) (80). Another single center series of all single ventricle patients

with assist devices reported only four Fontan patients with only one surviving to transplant (84). Finally, the Berlin Heart registry lists three out of five patients with Fontan who survived to transplant (85). While the risks of VAD must be considered prior to using mechanical support in this patient population, some Fontan patients may benefit from VAD bridge to transplant to mitigate severity of illness and improve upon some of the above risk factors including avoidance of mechanical ventilation, end-organ damage and optimization of functional status and nutrition. Collaboration across centers, like through the ACTION group as previously mentioned, will allow increased knowledge about assist devices in this patient population.

Catheter based intervention of aorto-pulmonary collaterals

Evaluating for and intervening on collateral vessels is also important in the pre-transplant optimization process. Collateral vessels are common in Fontan patients and increase the risk of bleeding as well as potentially affect post-operative hemodynamics. Patients with single ventricle physiology are known to develop aorto-pulmonary collateral vessels which can lead to recirculation and increased volume load on the systemic ventricle or the new graft (86). Aggressive pre-heart transplant embolization of aortopulmonary collateral vessels increases systemic flow pre-transplant (87) and may decrease bleeding post-transplant. Additionally, the presence of aortopulmonary collaterals post-transplant may lead to prolonged inotropic need and inadequate cardiac output despite good graft function (42,88).

Surgical risk

Transplantation of the Fontan patient presents surgical challenges unique to this patient population (46,89). Fontan patients have several surgical risk factors for worse mortality after heart transplantation including multiple previous sternotomies and longer ischemic times due to the need for Fontan takedown and pulmonary artery reconstruction at the time of their transplant (39,44). Using donor ischemic time and bypass time as surrogates for operative complexity, a single center study showed that Fontan patients have more complex transplant operations than controls (41). Multiple studies have shown that when compared to other patients with congenital heart disease, Fontan patients are more likely to require pulmonary artery reconstruction and have longer cardiopulmonary bypass times at time

of heart transplantation (38,46,47,90). Pulmonary artery reconstruction has previously been identified as a risk factor for worse outcomes after heart transplantation, although this finding included all congenital heart disease and was not specific to Fontan (91). All of these surgical risk factors also contribute to risk of post-operative hemorrhage, which has been identified as a cause of early mortality for Fontan patients post-transplantation especially in the early era (38,92). Surgical planning prior to transplantation may minimize some surgical risks. Multiple single center reports have included pre-operative cross sectional imaging to better definite intrathoracic relationships and anatomy to decrease intraoperative hemorrhage as well as minimize cardiac bypass time and decrease warm ischemic time during reconstruction (42).

Post-operative risk: intensive care management

Post-operatively although transplanted Fontan patients no longer have Fontan physiology, vascular changes from longstanding Fontan circulation may impact post-operative care. There is data that some failing Fontan patients have decreased systemic vascular resistance with preserved cardiac index (93). Likewise, markers of decreased endothelial function correlate with decreasing exercise capacity in Fontan patients (94) and thus many Fontan patients at time of transplant will have abnormalities of their systemic vascular function. These patients are likely at increased risk for abnormal vascular tone post-operatively after heart transplantation and use of close hemodynamic monitoring, inotropic support, and extra-corporal membrane oxygenation should be used as necessary. Vasoplegia syndrome, or persistent low systemic vascular resistance despite multiple intravenous pressors at high dose, is associated with high morbidity and mortality after heart transplantation in adults (95,96). Beyond factors unique to Fontan patients that cause vascular dysfunction previously noted, Fontan patients also have multiple operative and medical risk factors for vasoplegia syndrome including potentially long cardiopulmonary bypass time due to the need for reconstruction at the time of transplant and aspirin use (95). Attention to vasoplegia management post heart transplantation has been identified as a potential reason for improved outcomes in the modern era (42). In addition to traditional vasoactive infusions used to manage post-operative vasoplegia, there may be a role for extra-corporeal membrane oxygenation (ECMO) support. The authors' own institution has had good anecdotal success

with transient ECMO support in refractory vasoplegia following cardiac transplantation; in the last 6 years, 3 out of 4 Fontan patients requiring post-transplant ECMO have had >1-year survival.

Abnormalities of the pulmonary vasculature may also affect post-operative care. Autopsy studies have shown that Fontan patients have adverse pulmonary vascular remodeling, with the degree of changes correlating with time since Fontan completion (97). Additional studies have shown that patients farther from their Fontan completion have evidence of elevated transpulmonary gradients post heart transplantation (98). While Fontan patients may not meet diagnostic criteria for pulmonary hypertension, aggressive use of pulmonary vasodilators post-transplant should be considered.

Finally, given the many surgical risks for post-operative hemorrhage including repeat sternotomies, relative coagulopathy, and vascular reconstruction, bleeding should be carefully monitored for and blood products should be given and coagulopathy corrected appropriately.

Conclusions

The population of patients living with Fontan physiology is increasing with more patients reaching Fontan completion and patients with Fontan living longer. Ultimately, many of these patients will develop Fontan failure and require heart transplantation. Survival for Fontan patients after heart transplantation is improving in the modern era, likely due to increased knowledge about risk factors affecting pre and post-operative management. Fontan patients have unique challenges in the medical management peri-heart transplantation including high prevalence of liver and kidney disease, sensitization, relative immunosuppression and increased risk of infection, vasoplegia and increased pulmonary vascular resistance. Surgical challenges include complex pulmonary artery reconstructions, long cardiac bypass times, and increased risk of hemorrhage. The need exists for increasing collaboration via multicenter efforts as well as national and international Fontan registry data to increase knowledge of risk factors for Fontan failure, for morbidity and mortality around heart transplantation, and to overall improve outcomes for this growing community of unique patients.

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Footnote

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