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Review

Heart transplantation in adults for Fontan failure

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1. Introduction

Since the original description of atriopulmonary connection for palliation of univentricular circulations in 1971 by Fontan and Baudet [1], thousands of patients have undergone variations of Fontan palliation for single ventricle physiology. While Fontan surgery offers effective palliation, by 20 years after Fontan palliation approximately 30% of patients have experienced death or need for transplant [2–4]. Management of Fontan failure can be challenging due to varying etiologies, often involving multiple organ systems. Current therapies remain empiric, and the ultimate treatment for refractory Fontan failure is heart transplant, and in rare cases a combined heart–liver transplant. Current knowledge gaps create challenges for clinicians in regard to timing of referral for transplant evaluation, timing of listing, wait-list status and need for heart or combined heart–liver transplant. In addition, cardiac surgeons face significant challenges in surgical planning, and intra- and post-operative management. This article will review the current literature on transplantation in adult patients who have undergone Fontan palliation and discuss the current gaps in knowledge.

2. Natural History of Single Ventricle Patients After Fontan Palliation

Variations of the Fontan procedure have been performed for more than 40 years [5], all with the goal of creating reliable sources of pulmonary and systemic blood flow in patients with a univentricular heart. In the modern era, most single ventricle patients have had two or more surgeries during early childhood to separate the systemic and pulmonary circulations. During the current era of single ventricle palliation, most patients undergo the Fontan procedure in the early childhood years [5]. Over time, the Fontan procedure evolved from the atriopulmonary Fontan to variations of total cavopulmonary connection Fontan. Older adults operated in an earlier surgical era may have had a systemic arterial to pulmonary artery (PA) shunt as a palliative procedure. Prior systemic to pulmonary artery (PA) shunts have implications late after Fontan including myocardial dysfunction and pulmonary vascular remodeling [6,7].

3. Fontan Failure

Fontan failure has been described variably in the literature with a wide range of definitions used in published works, ranging from hard outcomes such as freedom from death/transplant to more commonly encountered Fontan-related morbidities. Late survival free from transplant has been described by d'Uedkem et al. in Australia and New Zealand [2]. In a cohort of over 1000 pediatric and adult single ventricle patients, 76% were alive 25-years after atriopulmonary Fontan procedure, 90% at 20-years after lateral tunnel and 97% at 13-years after extracardiac Fontan [2]. These late outcomes are similar to those described in prior smaller single center studies on freedom from death or transplantation [3,4]. Although the survival curves of the Australian and New Zealand study showed reasonable late survival; significant late morbidity was common. Fontan failure — late morbidity and mortality in this context — was defined as death, transplantation, Fontan takedown or conversion, New York Heart Association (NYHA) Functional Class III/VI symptoms or plastic bronchitis/protein losing enteropathy [2]. With this broad definition of Fontan failure, 17% of patients experienced Fontan failure at 15 years, and 44% by 25 years post-Fontan palliation [2]. Although these studies have started to define late outcomes and long-term predictors of Fontan failure, short-term predictors of survival in these late survivors are unknown.

In the adult population — by definition pediatric survivors — circulatory failure of multi-organ causes may be more important than ventricular failure alone [8]. In a study of adult survivors presenting to an adult congenital clinic, Elder et al. described freedom from death or transplant at 30 years from Fontan operation of 59.8%, and ventricular morphology was not associated with late outcomes, in contrast with the pediatric studies [9]. Similarly, Ohuchi et al. demonstrated significant differences in factors associated with Fontan failure in adult and pediatric cohorts, suggesting that

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the causes of Fontan failure may differ between those who succumb earlier in life to complications, and those in adult survivor cohorts, who may develop late multi-system complications in adulthood [10]. Potential contributors to Fontan failure include systolic and diastolic failure of the single ventricle, pulmonary vascular remodeling, portal venous outflow obstruction with subsequent secondary hemodynamic changes related to splanchnic congestion, and ultimately impaired renal perfusion. These potential contributors to circulatory failure are well described in a review article by Mori et al. [11].

4. When Should the Adult With Fontan Failure be Referred for Heart Transplant Evaluation?

Timing of heart transplant evaluation and listing, in the most simplistic terms, is based on when survival with transplant is anticipated to be better than survival without transplant. The predictors of short-term mortality in Fontan palliated patients are poorly understood, poorly defined, and un-validated. Accurate prediction of poor outcomes over a 12 to 24 month timeline is essential in deciding when to refer and list patients for heart transplantation. A variety of risk scores have been developed for biventricular heart failure that take in account a variety of clinical features. Sartipy et al. created a 3-year mortality risk predictor, Meta-Analysis Global Group in Chronic Heart Failure MAGGIC for heart failure patients. MAGGIC score accounts for age, gender, common comorbidities (diabetes, chronic obstructive pulmonary disease, tobacco abuse, chronic kidney disease), functional status, medications, blood pressure and ejection fraction [12]. Although this model has been validated in large population studies for two ventricular patients, it has not been validated in univentricular hearts yet. Traditional acquired biventricular heart failure relies heavily on cardiopulmonary exercise testing features, particularly maximal oxygen consumption to supplement clinical data in determining need for heart transplant evaluation [13]. Exercise intolerance and worsening cardiopulmonary testing predicts short-term morbidity, but not mortality, in Fontan palliated patents. In Fontan palliated patients, history of arrhythmias or heart failure symptoms predicts need for hospitalization [14]. Elder et al., in an adult survivor Fontan cohort, describe worsening portal hypertension due to portal venous outflow obstruction (evaluated by the VAS score — 1 point each for varices, ascites, splenomegaly on imaging) as associated with death or need for transplant. In addition, pacemaker placement and decreasing oxygen saturation are also associated with late adverse outcomes [9]. Equally important, patients with a VAS score of zero or one did well over a more than a decade, and theoretically would not have benefited from heart transplantation, where as a VAS score of 2 or 3 was associated with poor outcomes over the same time period. Model for End-Stage Liver Disease excluding international normalized ratio (MELD-XI) is a modification of the Model for End-Stage Liver Disease (MELD) score without including the international normalized ratio (INR), — includes only serum creatinine and bilirubin levels. Although the Model for End-Stage Liver Disease (MELD) score and variations of the Model for End-Stage Liver Disease (MELD) score have been used for organ allocation in patients waiting for liver transplant, as well as to predict risk associated with non-hepatic surgeries, Kim et al. used Model for End-Stage Liver Disease (MELD) and Model for End-Stage Liver Disease excluding international normalized ratio (MELD-IX) to evaluate patients for heart transplantation. Higher scores were associated with decreased survival in heart failure patients [15]. Assenza et al. applied the Model for End-Stage Liver Disease excluding international normalized ratio (MELD-IX) to Fontan patients and discovered higher scores (≥18) correlated with increased risk of death or transplantation [16], although in this study the score was largely driven by elevated creatinine, suggesting MELD-XI in the Fontan may be a surrogate marker for poor renal perfusion. A validated risk assessment tool is needed to accurately identify patients in need of orthotropic heart transplantation (OHT), and to identify those who will most likely benefit.

5. Organ Allocation in the United States: Implications for the Single Ventricle Patient on the Waiting List

Adults with congenital heart disease spend a longer time on the transplant waiting list compared to adults without congenital heart disease [17]. Coronary atherosclerotic heart disease and cardiomyopathy are the most common indications for heart transplant in the adult population, with congenital heart disease (CHD) as an indication for only 3% of all adult heart transplants, although a more common indication in the young adult population (11% of the 18–39 year olds) [18]. For adult heart transplant candidates, organ allocation and priority listing status are determined primarily by treatment requirements, and apply primarily to treatments for the more common indications of acquired biventricular systolic heart failure, such as need for inotropes or mechanical circulatory support (Table 1). Single ventricle patients often do not benefit from, or are not candidates for, many of these treatments that determine priority status on the United Network for Organ Sharing (UNOS) waitlist [19]. Patients with univentricular circulations and Fontan palliation may have a poor prognosis even in the presence of normal ventricular function and pressures — a pure "right heart failure" problem in the absence of a sub-pulmonary ventricle that does not respond to treatments developed for left heart failure. While exception status may be requested for status 1A and 1B listings, initial and periodic review is required, and the request may be denied. Advanced therapies for this unique and rare type of circulatory failure are lacking, and validated risk scores to predict short-term survival have not yet been developed, further complicating wait-list management of the patient with univentricular heart. Thus univentricular heart transplant candidates face longer wait-list times [17], further increased in the setting of human leukocyte antigen (HLA) sensitization related to prior surgeries and blood transfusions.

Support options for the critically ill decompensated wait-listed Fontan patient are limited. Intra-aortic balloon pump support has been described in 21 reported cases of Fontan palliated patients, all under age 21 years, and most in the immediate postoperative period following the Fontan operation. Eight patients survived [20]. Case series describing congenital heart patients requiring extracorporeal membrane oxygenation (ECMO) report limited survival, about 30% after cannulation. Predictors of death were failing Fontan and adult sized patients [21]. Continuous positive pressure mechanical ventilation

Table 1
Adult heart transplant listing status criteria.

Status 1A — Hospitalized at transplant center
Total artificial heart
Intra-aortic balloon pump
Extracorporeal membrane oxygenation
Continuous mechanical ventilation
Requires continuous infusion of a single high-dose, or multiple inotropes, and continuous hemodynamic monitoring of left ventricular filling pressures
Status 1A — Hospitalization not required
Has one of the following mechanical circulatory support devices in place (30 days of 1A time):
Left ventricular assist device (LVAD)
Right ventricular assist device (RVAD)
Left and right ventricular assist devices (BiVAD)
Mechanical circulatory support device with significant device-related complications including thromboembolism, device infection, mechanical failure, or life-threatening ventricular arrhythmias.
Status 1B
Left ventricular assist device (LVAD)
Right ventricular assist device (RVAD)
Biventricular assist devices (BiVAD)
Continuous infusion of intravenous inotropes
Status 2: Active but does not meet Status 1A or 1B criteria

Modified from http://optn.transplant.hrsa.gov [19].