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Original Article

Heart transplant after the Fontan operation

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Abstract Although the Fontan operation may provide a durable circulation for some patients with functionally univentricular hearts for several decades, circulatory failure becomes more common over time. Medical and/or surgical interventions can improve the circulation for some period of time; however, many patients will experience end-stage circulatory failure. Heart transplantation may be considered in these patients. This review will cover the indications and evaluation for heart transplantation, management of patients while waiting for heart transplantation and the current outcomes of transplantation in this population.

Keywords: Fontan; heart transplant; heart failure

As detailed in the accompanying manuscripts, the circulation after the Fontan operation is prone to failure. In a recent analysis of data from multiple children's hospital in the United States of America, ~12% of all hospitalisations in children with single ventricles were complicated by heart failure.[1] Although there are multiple medical and surgical interventions that may palliate the circulation allowing for survival with an acceptably good quality of life, a significant number of patients will progress to end-stage disease. Heart transplantation may be considered in these patients.

Indications

The indications for heart transplantation after the Fontan operation are similar to the indications for heart transplantation for other congenital or acquired heart disease or cardiomyopathies: need for ongoing inotropic or mechanical support; abnormal ventricular function or malignant arrhythmia causing severe symptoms unresponsive to treatment; growth failure or unacceptably poor quality of life; and absence of other therapeutic options, which carry lower risk than transplantation.[2] However, as discussed above, there are clinical conditions unique to the Fontan circulation that may deteriorate to the point where transplantation is indicated, despite all medical or surgical attempts to successfully treat the condition. These include protein-losing enteropathy, plastic bronchitis and possibly progressive end-organ function, particularly liver disease. All of these are discussed in detail in another section of this publication. Although development of protein-losing enteropathy is associated with a poor long-term prognosis, its development is not necessarily an absolute indication for heart transplantation. Many children with protein-losing enteropathy have been palliated with medical, transcatheter and/or surgical interventions, and have enjoyed years of transplant-free survival with good quality of life.[3] However, if a patient fails all attempted interventions, especially if the quality of life is poor, heart transplantation may be the only reasonable option. The same can be said for plastic bronchitis in which many patients can be effectively palliated with a variety of interventions. With regard to liver dysfunction, it is our belief at this institution that rarely would the degree of liver disease in and of itself be enough to have a patient undergo heart – and sometimes heart–liver – transplantation if the heart condition would not in and of itself require transplantation.

Another factor that needs to be taken into account when considering optimal timing for heart

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transplant listing in a patient after the Fontan operation who is starting to deteriorate is what options are available for supporting the patient if he or she develops end-stage heart failure and becomes haemodynamically compromised. Some patients after the Fontan operation develop symptomatic heart failure owing to poor systemic ventricular function with or without atrioventricular valve regurgitation. In this setting, inotropic support may benefit and help stabilise the patient as the patient begins the unpredictable and often lengthy wait for an organ. However, a subset of patients after the Fontan operation have reasonable – sometimes normal – ventricular function, but have a failing Fontan circulation because of problems with cardiopulmonary interactions. These patients not only may not respond to the usual inotropic and/or vasodilator support for end-stage heart failure, but are actually at higher risk for complications, including mortality, after heart transplantation than those with poor ventricular function.[4] In addition to planning for options for medical interventions, one has to consider options for mechanical circulatory support. Many patients after the Fontan operation are poor candidates for ventricular assist devices, and may be too small for an artificial heart. This needs to be considered when deciding on timing for listing for heart transplantation; if a patient is not at least a reasonable candidate for inotropic and/or mechanical support, one may move more quickly towards listing for transplantation than one would in a patient with comparable symptoms, but who has good options for inotropic and/or mechanical support.

Evaluation

The evaluation for heart transplantation in those children who have undergone the Fontan operation is similar to other patients, and is well described.[2] However, there are certain areas that require special emphasis when evaluating a patient for heart transplantation who has undergone the Fontan operation. Careful definition of anatomy is critical. Many of these patients have very complex anatomy, and this can complicate the surgical procedure significantly. For those with abnormal venous and/or arterial connections, including situs inversus, it may be necessary to retrieve extended portions of the vena cavae or great arteries from the donor. For instance, in those with bilateral bidirectional cavopulmonary anastomoses, it may be necessary to retrieve extended tissue from the superior vena cava and innominate vein of the donor for appropriate reconstruction of the left-sided superior vena cava in the recipient. Owing to the fact that most of these patients have had multiple surgeries, entry into the chest of the recipient can carry significant risk of cardiac perforation and the need for peripheral canulation for cardiopulmonary bypass. Careful imaging of the veins and arteries of the groin and neck to assure patency of these vessels before transplantation may be necessary. Evaluation of the liver is especially important in children after the Fontan operation who are being considered for heart transplantation. Many modalities of evaluation are possible, each with their own risks and benefits.[5] In some instances, the extent of liver damage may be so severe that heart–liver transplant will be necessary.[6]

Finally, because of the common requirement for multiple heart surgeries in these patients, there are often specific immunologic considerations that need to be taken into account.[7] Patients need to be carefully evaluated for the presence of pre-formed circulating anti-human leukocyte antigen antibodies. These antibodies are commonly present in these patients, often because of exposure to human allograft tissue used at the time of previous heart surgeries.[8] Most attempts to reduce these antibodies before solid organ transplantation have only met with limited success.[9] Thus, many centres, including ours, no longer use the so-called de-sensitisation protocols. Rather, we identify the specific circulating anti-human leukocyte antigen antibodies, in order to anticipate the possibility of having a positive – incompatible – crossmatch of the donor and recipient. Some centres also advocate for either a true or a virtual prospective crossmatch before proceeding with transplantation. A true prospective crossmatch requires exposing donor tissue to recipient serum before transplant to assure compatibility. This is laborious and requires the retrieval of donor tissue before accepting the organ. A virtual prospective crossmatch requires examination of the donor human leukocyte antigen antigens and the recipient anti-human leukocyte antigen antibodies to determine whether there is evidence of cross-reactivity that will accurately predict a positive crossmatch after the transplant. Use of either of these prospective crossmatch strategies will significantly reduce the available donor pool available to a recipient who is sensitised. Owing to this fact, and because of the significant morbidity and mortality associated with waiting on the paediatric heart transplant recipient list, we and many other institutions have adopted a policy of not requiring a prospective crossmatch before accepting an organ for a sensitised recipient.[10,11]

Management of circulatory failure while waiting for heart transplantation

Patients with circulatory failure after the Fontan operation can present management challenges.

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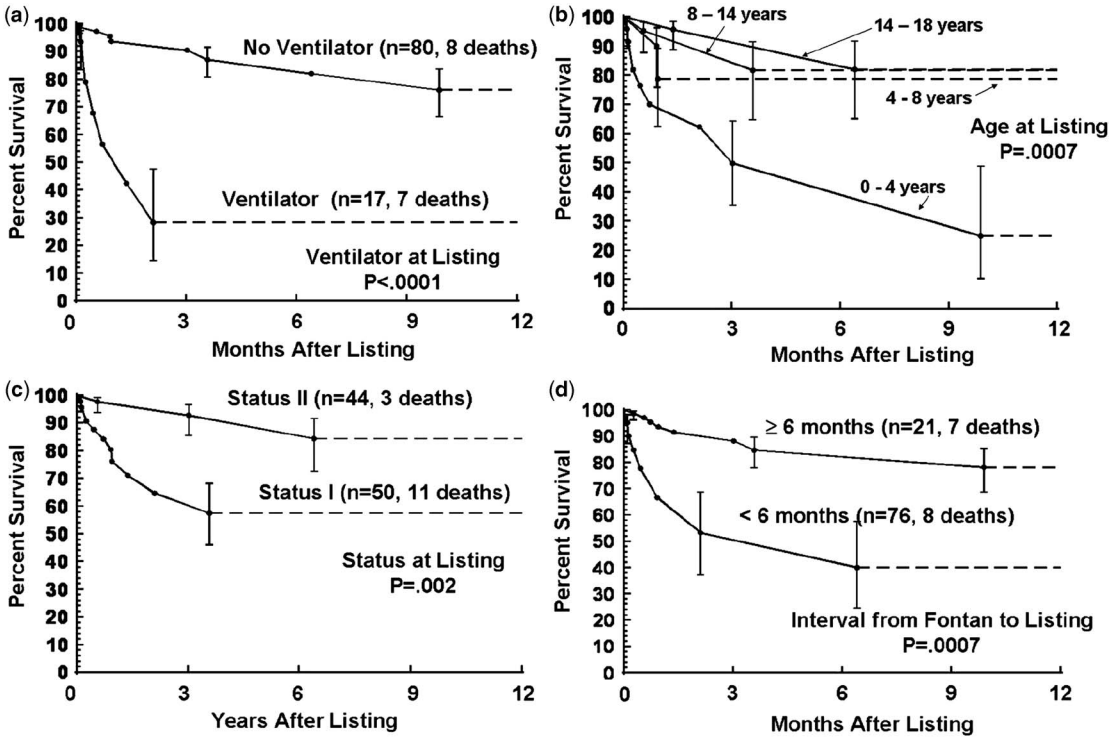

Figure 1.
*Risk factors for death while waiting for heart transplantation among children after the Fontan operation, from the Pediatric Heart Transplant Study Group. (**a**) Patients requiring mechanical ventilation at the time of listing for transplantation. (**b**) Age at listing. (**c**) United Network of Organ Sharing status at listing for transplantation. (**d**) Time interval from Fontan operation to listing for transplantation. Reproduced with permission from Bernstein et al.*[12]

There is a relatively high risk of death after listing for heart transplant, especially among high-risk subgroups such as patients <4 years old, patients listed <6 months after the Fontan operation and patients on mechanical ventilation at the time of listing for transplantation (Fig 1).[12] For patients with severely depressed ventricular function, therapies such as inotropic medications may improve symptoms of heart failure and allow for a period of clinical stability before transplantation.

However, for patients with refractory symptoms on inotropic medications, the options are limited. Successful use of mechanical circulatory support is limited in this population. This is especially true for patients whose main indication for transplantation is protein-losing enteropathy or plastic bronchitis, who often have preserved ventricular function.[4,13] The use of a typical systemic ventricular assist device generally does not achieve the goal of lowering systemic venous pressures and thus may be ineffective in improving the fundamental perturbations that have led to the need for transplantation. Indeed, by increasing the cardiac output, the systemic venous pressures may actually increase and worsen problems such as protein-losing enteropathy and hepatic dysfunction. As such, some have advocated for the use of a total artificial heart in this scenario, which has the theoretical advantage of immediately lowering the systemic venous pressure and increasing the cardiac output.[14,15] Although the use of a total artificial heart for patients with circulatory failure after the Fontan operation is quite limited, successful cases have been performed.[15] Others have attempted placing a single ventricular assist device in the Fontan circuit[16] or two ventricular assist devices, one of the Fontan circuit and one in the systemic ventricle.[17] Dr Rodelfeld has been studying the use of a viscous impeller pump based on the von Kármán viscous pump principle. This could potentially allow for the percutaneous placement of an assist device into the Fontan circulation to lower the venous pressures and improve cardiac output (Figs 2 and 3).[18,19]

Outcomes after heart transplantation

Similar to other patients undergoing heart transplantation, the outcomes of patients undergoing heart transplantation after the Fontan operation may be significantly influenced by the patient's condition at the time of transplantation. Congenital heart disease by itself is a risk factor for worse outcomes compared with patients undergoing transplantation

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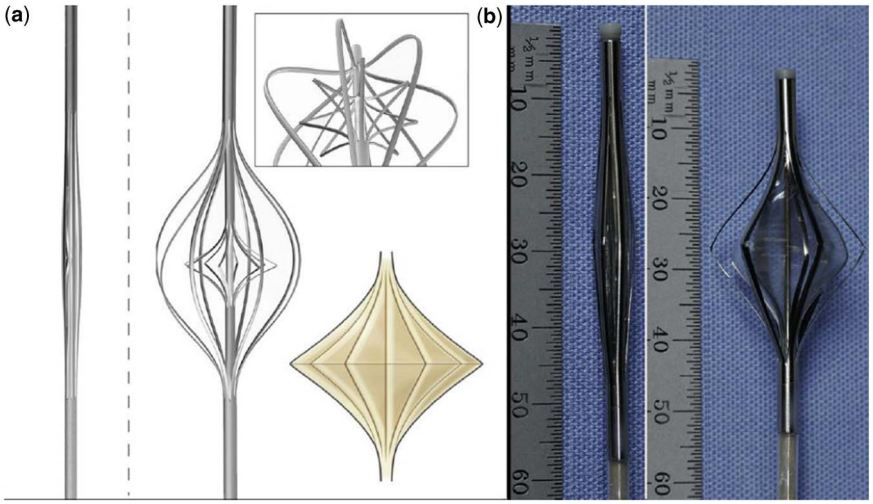

Figure 2.
*Expandable pump based on the von Kármán viscous pump principle. (**a**) Schematic representation. (**b**) Functional scale model. Reproduced with permission from Rodefeld et al.[19].*

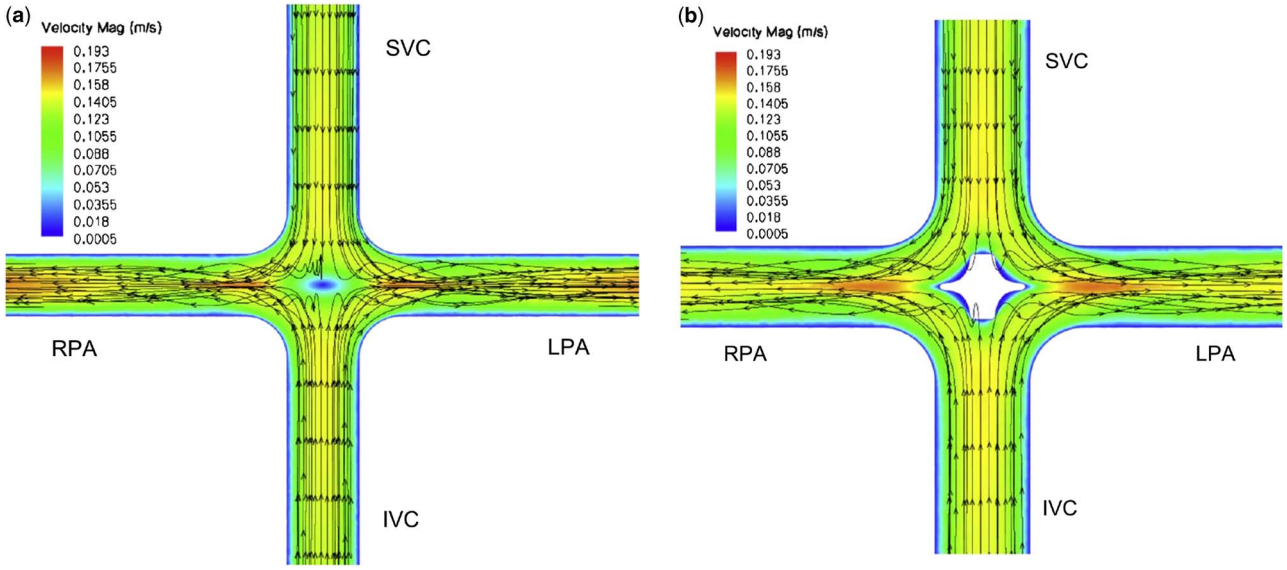

Figure 3.
*Velocity magnitude contour plot in the Fontan circuit. (**a**) Flow in the Fontan circuit without the impeller pump. The flow is irregular at the intersection. (**b**) Flow with the impeller pump. The flow pattern is stabilised with reduced power loss. IVC = inferior caval vein; LPA = left pulmonary artery; RPA = right pulmonary artery; SVC = superior caval vein. Reproduced with permission from Rodefeld et al.[19]*

for cardiomyopathy.[20] The patient after the Fontan operation may have additional high-risk features including elevated anti-human leukocyte antigen antibodies,[21] malnutrition[22] and other organ dysfunction such as kidney or liver disease.[20,23] Successful combined heart–liver transplants have been performed for patients with severe hepatic dysfunction.[6] Patients with early failure of their circulation requiring listing for heart transplantation within 6 months of the Fontan operation and those requiring mechanical ventilation appear to be at particularly high risk of poor outcomes.[12,24]

Several single-centre studies have evaluated outcomes of heart transplantation among patients with a prior Fontan operation. Griffiths et al[4] reviewed their single-centre experience, comparing patients with preserved versus impaired ventricular function at the time of listing for transplantation. The 1-year actuarial survival among patients with impaired ventricular function was 89%, whereas it was 56% among those with preserved ventricular function. Another recent single-centre study reported a high early mortality rate at 35% by 90 days after transplant and <50% survival at 10 years after transplant.[25] Patients undergoing

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transplantation after the Fontan operation fared worse than patients with a biventricular circulation, but morbidities such a protein-losing enteropathy did not influence outcomes. The group from Washington University also reported their experience and found that patients with preserved ventricular function at the time of transplantation were more likely to have protein-losing enteropathy (59 versus 12%), have higher pulmonary vascular resistance (3.7 versus 2.9 WU/m^2), and experience a greater 1-year mortality compared with patients with impaired ventricular function (42 versus 24%).[13]

The multi-institutional Pediatric Heart Transplant Study reported on 97 patients who were listed for heart transplantation after the Fontan operation.[12] Overall, the survival after heart transplantation was 76% at 1 year and 68% at 5 years, which was significantly less than for patients without congenital heart disease. The greatest risk of death among patients with a prior Fontan operation was in the first year after transplant. After the first year, the survival curves among patients with and without a prior Fontan operation were similar. The presence of protein-losing enteropathy was not associated with survival and resolved in all long-term survivors. A more recent report of 269 patients listed for heart transplantation after the Fontan operation from the Pediatric Heart Transplant Study Group reported overall similar survival compared with other forms of congenital heart disease, including the bidirectional Glenn operation.[24] This study also found a significantly greater risk of death after transplantation among patients on a ventilator at the time of transplantation.

Conclusions

The circulation after the Fontan operation is prone to failure with or without significant detriment in systolic ventricular function. This failure can lead to multiple morbidities including hepatic dysfunction, renal dysfunction and protein-losing enteropathy. In the absence of impaired ventricular function, the medical therapy of these patients with severe disease is limited. Heart transplantation offers the possibility of improved survival, although patients in a profoundly moribund state at the time of listing for transplantation are at a high risk of death. Although the long-term outcomes of heart transplantation in the Fontan population are inferior to patients with cardiomyopathies, the greatest risk of death is in the first year after transplant. If patients survive the first year after transplant, morbidities such as protein-losing enteropathy usually resolve, and the survival is similar to other transplant patients.

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Conflicts of Interest

None

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