Review
Heart transplantation after congenital heart surgery: improving results and future goals

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Summary
With growing numbers of children with complex congenital heart disease surviving initial surgical procedures, more patients are presenting in later childhood or early adulthood in cardiac failure. This presents an obvious increased burden on transplant centres, and a further strain on a limited donor pool. Historically, results for heart transplant following congenital heart disease (CHD) have been worse than those following cardiomyopathy. With increased surgical experience and intensive care expertise, the gap between the two aetiologies in our practice is decreasing. This article reviews the current protocols for transplantation in this setting, presenting a large single-centre experience over 20 years, and speculates on possible future advancements in this very challenging field.

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1. Introduction

Historically, transplantation for congenital heart disease (CHD) has had a worse prognosis than that for heart failure of other aetiologies [1]. It has been estimated that between 10 and 20% of children with complex CHD will at some stage require transplantation, and since it accounts for approximately 25% of all heart transplants in the paediatric age group [2] (and, with more and more children with CHD reaching adulthood, a growing number of early adult transplants) it is important to strive to redress this imbalance. Over the 40-year history of heart transplantation, various improvements in preoperative, operative and postoperative care have dramatically improved the immediate and long-term outlook for all transplant recipients. Furthermore, a number of adaptations specific to congenital heart disease recipients have combined to shrink the gap between transplantation for CHD and other indications, and patients transplanted for CHD can now reasonably expect to live for a decade or more. However, CHD remains a highly significant risk factor for 1-year and 5-year mortality in transplant recipients [2,3], and the wide diversity of this group with respect to age, original diagnosis, previous operations and clinical status makes it very difficult to analyse accurately different practices or produce clear formal protocols. This paper reviews the evolution and outcomes for transplantation for CHD in a single centre over almost two decades, and speculates on future advancements in this very challenging field.

2. Particular difficulties

2.1. Pre-transplant assessment and listing for transplantation

Heart transplantation is a complex procedure that requires delicate and insightful understanding of the processes involved in listing for transplantation, preservation of recipient cardiac (and other organ) function, effective use of an increasingly strained donor organ pool, skilful operations, dedicated postoperative intensive care, and careful long-term medical management to prolong graft function. Many of these problems are common to all heart transplantation scenarios, but some are made even more difficult in the CHD population.

2.1. Pre-transplant assessment and listing for transplantation

With demand for donor organs at a premium, and the life of a transplanted graft being limited to approximately 15 years on average, the timing of listing for transplantation must be carefully considered, and cannot be premature. However, prolongation of native cardiovascular function may...
come at the price of other cardiac operations, and potentially additional organ failure, either of which may be detrimental to the success of future transplantation. For instance, post-transplant survival for children with a native single ventricle morphology has been shown to be related to pre-transplant operative stage, and some authors have suggested that listing for transplant with a Glenn shunt in situ rather than proceeding to a sub-optimal Fontan circulation may decrease the formation of lymphocytotoxic antibodies, restrict worsening pulmonary vascular resistance (PVR), and limit post-transplant complications such as diastolic dysfunction and protein-losing enteropathy, resulting in an overall longer, better quality life [4—7]. With improving long-term outlook for transplant recipients, these arguments hold even more influence.

Paradoxically, given the increased importance associated with accurate listing for transplant for CHD, patients are often harder to assess. Specifically, it is important to measure PVR to avoid the potential of donor right heart failure [7]. At our unit, a PVR of ≤6 Woods units (or transpulmonary gradient (TPG) ≤10 mmHg) is considered compatible with a good result post-transplant. A PVR of 7—16 Woods units (TPG 10—20 mmHg) is potentially more difficult, and requires preoperative vasodilator testing with prostacyclin or nitric oxide, with the following inferences:

- PVR ≤ 5 Woods units (TPG ≤ 10 mmHg) — proceed to transplant
- PVR 5—9 Woods units (TPG 10—15 mmHg) — transplantation may convey increased risk
- PVR ≥ 9 Woods units (TPG ≥ 15 mmHg) — heart transplantation contraindicated

However, PVR can be hard to estimate in the Fontan circuit, particularly when there is a fenestration and extensive venous collaterals. If problems with pulmonary vascular resistance are probable, it is wise to avoid undersized hearts and long ischaemic times during the operation [7]. Despite these precautions, post-transplant pulmonary vasodilatation with phosphodiesterase inhibitors, nitric oxide or prostacyclin may be required, as well as, in extreme cases of right ventricular dysfunction, mechanical assistance [8].

2.2. Operative differences

Over the evolution of heart transplantation, the donor and recipient cardiectomy and implantation procedures have become largely standardised. However, specific anatomical abnormalities in the recipient with CHD, such as vascular and cardiac size, position and situs, can necessitate modification of each component. Previously, the most complex anatomies would themselves have contraindicated transplantation, despite an individual clinical scenario that would otherwise have been compatible with a successful operation. Surgical ingenuity has largely overcome anatomical contraindications to heart transplant [9—12], with the possible exceptions of severe pulmonary artery hypoplasia and pulmonary vein stenosis. Crucially, each procedure must be appropriately adapted when considering a recipient with CHD.

With respect to the donor cardiectomy, it is advisable to harvest extended portions of the systemic veins, pulmonary arteries and aorta, in order to facilitate potentially complex anastomoses; graft trimming should be postponed until implantation. Judicious retrieval may limit the need for additional prosthetic material in heart transplantation, but can hamper transplantation of other organs, notably the lungs. The superior and inferior venae cavae can be opened so as to produce a larger right atrial opening in small recipients, and the donor PA can be split open to enable connection with the distorted or undersized recipient pulmonary vasculature.

Dense pericardial and mediastinal adhesions with marked cardiomegaly in those recipients having undergone previous sternotomy can increase the chance of substantial haemorrhage. In addition, the presence of subternal great vessels and conduits may warrant exposure of the femoral vessels prior to sternotomy as a precautionary measure, permitting immediate femoro-femoral cardiopulmonary bypass in emergency situations [13]. In addition, chronically cyanotic patients may have developed collateral vessels which can be troublesome, especially in the posterior mediastinum [14]. It is also prudent to achieve haemostasis prior to implantation of the donor organ.

Pre-implantation, it may be necessary to re-establish normal recipient anatomy with, for instance, a left SVC/innominate vein reconstruction, in the case of bilateral cavo-pulmonary anastomoses. A case of situs inversus requires a spatial rearrangement of the systemic venous drainage, by the formation of a bicaval connection using the donor innominate vein and left-sided SVC [15]; it is also useful to open the left pleural space to accommodate the normally sited donor organ. These extra elements to the operation must be anticipated and corrected in order to synchronise the donor and recipient components of transplantation, and avoid prolonging ischaemic times.

2.3. Postoperative complications

Postoperatively, CHD transplant recipients face the complications common to all heart transplants of, for instance, multi-organ failure, rejection, infection, coronary allograft vasculopathy, and, in the paediatric age group especially, non-compliance [16]. However, specific issues are more problematic in the CHD group. Higher rates of postoperative bleeding, infection and wound dehiscence in those having undergone previous thoracic procedures have been predicted, and, although studies have reported differing relative risks for this population [13,17,4], they must be foreseen in this group. Years of sub-optimal end-organ perfusion also increase the chances of significant postoperative renal failure; our limited experience of extracorporeal support as a bridge to transplant has suggested that this may optimise end-organ function, in the immediate post-transplant phase at least. The effect this has on later function is currently unknown.

2.4. Lymphocytotoxic antibodies

The formation of lymphocytotoxic antibodies in response to repeated blood transfusion [18] or homograft tissue [19] in previous procedures is of particular relevance in the CHD group, and has been linked to increased rejection and worse
actuarial survival post-transplant [20]. If feasible, it is important to limit presensitisation by restricting blood transfusion and homograft use [13] in patients with CHD. Various pre- and post-transplant protective measures, such as immunoglobulins, cytolytics, plasmapheresis, cyclophosphamide and rituximab have been attempted in the event of presensitised patients, with varying success [21—23]. Again, with more transplants being performed on patients with multiple previous operations, this is likely to be a problem that increases over the coming years, and one that needs to be addressed actively.

3. Current results

Since 1988, we have performed heart transplantation in 73 paediatric patients for CHD (aged 0—18 years), out of a total number of 248 first transplants (29.4%). The initial diagnoses are displayed in Table 1. In addition, one patient whose initial diagnosis was tricuspid atresia with VSD was retransplanted 3.6 years after her initial transplant for failing graft. She is currently well, 13.9 years after her second transplant. Only her first transplant is used for this analysis. Transplant management has evolved over the years: for analysis and clarity, transplants were divided into two eras; the Millennium was chosen as an arbitrary time point that created two almost equal groups of TxCHD patients: 38 transplants were performed prior to 2000, and 35 since. The Kaplan—Meier method was used to analyse survival, and Wilcoxon tests were used for comparison between groups.

Fig. 1 displays survival curves of transplantation for CM and CHD divided by the Millennium. One-year survival for TXCHD improved from 66% pre-2000 to 90% post-2000 (p = 0.005). Prior to 2000, 1-year survival for TxCHD was significantly worse than that of TxCM (66% vs 84%, p = 0.036). There was no significant difference in 1-year survival for TxCHD compared to TxCM in the post-2000 era (90% vs 94%, p = 0.756).

Fig. 2 displays survival curves based on univentricular (n = 38) vs biventricular (n = 35) circulations. One-year survival for univentricular circulations was similar to biventricular (75% vs 78%). A total of 8/38 univentricular and 5/35 biventricular patients died within the first 30 days post-transplant (p = 0.450). Table 2 illustrates the repair stage at transplantation of patients with univentricular circulations at the time of their transplant. Of the univentricular deaths there were 4 Fontans, 0 Glenns, 2 Norwoods, and 2 had no operation (Fig. 3; p = 0.052).

Table 1

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<tr>
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<th>Biventricular (35)</th>
<th>Univentricular (38)</th>
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<tbody>
<tr>
<td>TGA</td>
<td>13</td>
<td>14</td>
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<tr>
<td>Aortic disease</td>
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<td>Ebstein’s</td>
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TGA: transposition of the great arteries; HLHS: hypoplastic left heart syndrome; DOV: double outlet ventricle; DIV: double inlet ventricle; HRV: hypoplastic right ventricle; PA: pulmonary atresia; TA: tricuspid atresia.

Fig. 1. Kaplan—Meier curves demonstrating improving graft survival following transplant for CHD, which is comparable to that for cardiomyopathy in the current era.

Fig. 2. Kaplan—Meier curves demonstrating survival following transplantation for univentricular and biventricular anatomies.

Since 2001, we have also been using mechanical support as a bridge to transplant in children, with either extra corporeal membranous oxygenation (ECMO) or Berlin Heart. Although we have successfully used these techniques in many patients with cardiomyopathy, our experience with mechanical support in TxCHD remains limited to two patients. One

Table 2

<table>
<thead>
<tr>
<th>Repair stage</th>
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<tr>
<td>No prior operation</td>
<td>2</td>
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<tr>
<td>Norwood stage 1</td>
<td>8</td>
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<tr>
<td>Glenn</td>
<td>13</td>
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<tr>
<td>Fontan</td>
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Since 2001, we have also been using mechanical support as a bridge to transplant in children, with either extra corporeal membranous oxygenation (ECMO) or Berlin Heart. Although we have successfully used these techniques in many patients with cardiomyopathy, our experience with mechanical support in TxCHD remains limited to two patients. One
was a 6-year-old boy with a diagnosis of double inlet left ventricle who had a total cavo-pulmonary connection performed; the other was a 13-year-old girl who had previously undergone mitral valve repair. Unfortunately, both patients died within 10 days of their operation.

4. Current outlook

There can be little doubt that results for transplantation in the setting of CHD have improved significantly over the last 40 years, and, with many of the difficulties involved in this situation now at least partially remediable, the outlook for these patients is encouraging, similar to that of patients transplanted for dilated cardiomyopathy [13]. We have found the current results at our institution reassuring (Fig. 1) with the historical high early attrition for transplant for CHD [1] no longer present. In addition, transplantation in patients with a failing univentricular circulation was not a survival risk factor in our cohort (Fig. 2).

It is also vital to recognize that a significant proportion of children with CHD will go on to need a transplant after they have been discharged into the care of adult cardiology services. In our experience, a number of adults with congenital heart disease with heart failure or a failing Fontan circulation may not be listed for transplantation. For univentricular anatomies, divided by pre-transplant operative stage. Two patients with hypoplastic left heart syndrome not shown on this graph were transplanted in the neonatal period without previous surgery.

However, the lack of adult cardiac transplant centres with congenital experience on site remains a practical burden.

5. Summary

Despite the problems associated with taking more marginal donors, and operating on more chronically and acutely sick patients, the immediate and long-term outcomes for transplantation for congenital heart disease continue to improve. Noticeably, the historical discrepancy between prognosis following transplantation for CHD and cardiomyopathy is diminishing convincingly. This success is the result of specific advances in the understanding and management of CHD and heart transplantation, and the implementation of these by dedicated surgical, medical and intensive care teams. However, the heterogeneity of this population, even within sub-groups defined by original diagnosis or operative stage, makes it very difficult to perform robust longitudinal studies capable of identifying predictive factors for survival and improving allocation of scarce resources.

References


