Surgical strategies to facilitate heart transplantation in children after failed univentricular palliations: the role of advanced intraoperative surgical preparation†

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Abstract

OBJECTIVES: Heart transplantation in children after univentricular palliation is a technical challenge. As the national referral centre for heart transplantation in children, we review national trends in transplantation and describe technical innovations used in the current era.

METHODS: Children undergoing heart transplantation were separated into patients with (i) structural congenital heart disease (sCHD; subdivided into univentricular and biventricular) and (ii) cardiomyopathy (CM). The operation notes and surgeons’ diagrams were reviewed with particular attention to surgical innovations introduced after 2000.

RESULTS: Between January 1988 and December 2012, 111 primary transplantations were performed: 50 for sCHD (30 univentricular and 20 biventricular) and 61 for CM. Thirty-day mortality for univentricular patients compared to those with CM was significantly higher before 2000 (21 vs 0%, 3/14 vs 0/20, \(P = 0.023\)) and not different after 2000 (8 vs 6%, 3/38 vs 1/16, \(P = 0.852\)). At the same time, the percentage of patients with univentricular physiology increased from 47% (14 of 30 patients) to 80% (16 of 20 patients) versus those with biventricular physiology. After 2000, 12 of 16 patients (75%) with univentricular sCHD required reconstruction of the great vessels. Of these, 8 (50%) patients had reached the stage of Fontan, 5 had reached bidirectional cavopulmonary shunt, 2 had reached Kawashima procedure and 1 had only a Blalock-Taussig shunt. The following techniques were employed in 12 transplantations: aortic arch replacement \((n = 3)\), hilum-to-hilum pulmonary artery (PA) reconstruction \((n = 5)\), PA patch reconstruction \((n = 5)\), reconstruction of the PA bifurcation using donor bifurcation \((n = 2)\) and left superior vena cava (SVC) to donor SVC reconstruction \((n = 3)\).

CONCLUSIONS: In the current era, the majority of children undergoing heart transplantation for sCHD have had univentricular palliation. These patients pose challenges because of prior surgeries and complex anatomy, but the techniques described here in may enable improved outcome.

Keywords: Fontan procedure • Congenital heart disease • Heart transplantation • Retrospective studies

INTRODUCTION

Despite improvements in the results of palliation for univentricular cardiac defects, the proportion of paediatric heart transplantations performed for failed univentricular circulations is increasing [1]. As more patients with previous complex repairs, such as the Norwood procedure, require transplantations, reconstructive techniques that may be used to prepare vascular structures for heart transplantation might be useful. Here, we describe our experience and reconstructive techniques that we found very useful in preparation for successful heart transplantation in patients with complex univentricular anatomy.

MATERIALS AND METHODS

The Royal Children’s Hospital is the national referral centre for paediatric heart transplantation in Australia. All patients \((n = 111)\) who underwent heart transplantation from January 1988 to January 2013 were retrospectively reviewed. Patients were divided into structural congenital heart disease (sCHD) and cardiomyopathy (CM) groups. sCHD patients were further subdivided into those with biventricular and with univentricular physiologies. Focus was made on the univentricular physiology subgroup.

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After 2000, we started to apply advanced surgical preparation of the great vessels to facilitate transplantation. Advanced intraoperative surgical preparation is a strategy for complex surgical reconstruction in advance of arrival of the donor heart. These reconstructions require significant time and thus have to be thoroughly coordinated with the timing of heart procurement to minimize donor ischaemic time. During this period, we also began to coordinate retrieval of the donor heart with the progress of the reconstruction, in order to minimize ischaemic time.

**Statistical analysis**

We compared the all-cause 30-day, hospital and 1-year mortalities between univentricular sCHD and CM in each of the two eras (January 1988 to December 1999 and January 2000 to December 2012) using a $\chi^2$ test. To examine the effect of perioperative care and generic post-transplant care on mortality, we compared 30-day mortality for CM before and after 2000 using a $\chi^2$ test. This was performed with Stata 13.0 (StataCorp, College Station, TX, USA).

**RESULTS**

In total, 112 transplantations were performed: 50 (45%) for sCHD, 61 (55%) for CM and 1 retransplantation in a patient who had previously been transplanted for sCHD. Univentricular anatomy made up 60% (30 of 50 patients) of sCHD. The percentage of patients with sCHD who had univentricular anatomy increased during our experience, from 50% (11 of 22 patients; 1988–94) and 54% (7 of 13 patients; 1995–2002) to 86% (12 of 14 patients; 2003–12), to become the most common anatomical indication for transplantation among children with sCHD (Fig. 1). The characteristics of patients undergoing transplantation for failed single-ventricle palliation are presented in Table 1.

Thirty-day mortality after transplantation for univentricular sCHD was 21% (3 of 14 patients) before 2000, but fell to 6% (1 of 16 patients) after 2000. Hospital and 1-year mortalities for sCHD were the same as 30-day mortality. There were 2 hospital deaths in the CM group, who died after 30 days, at Days 39 and 93 from intracerebral haemorrhage and bronchomalacia. Before 2000, there were 3 hospital mortalities in the univentricular sCHD group: acute rejection in 2 and sepsis in 1. After 2000, the single mortality was because of primary graft failure. This occurred in a patient who had not required any vascular reconstructions and received a donor heart with an ischaemic time of 5 h. After an initial cardiopulmonary bypass run of 3 h, the patient could not be weaned from the pump and despite a second bypass run of 2 h, the patient was supported with extracorporeal membrane oxygenation. In the postoperative period, the patient developed multiorgan failure and sepsis, and died on Day 18.

When 30-day mortality for univentricular patients was compared with CM, it was significantly higher before 2000 (21 vs 0%, 3/14 vs 0/20, $P = 0.023$) and not different after 2000 (8 vs 6%, 3/38 vs 1/16 patients, $P = 0.852$). To examine the effect of perioperative care and intensive care on hospital mortality, we compared 30-day mortality after transplantation for CM before 2000 (9%, 2 of 22 patients) and after 2000 (8%, 3 of 38 patients), and found no difference ($P = 0.197$).

Beyond simple pulmonary artery (PA) patch repair, no patient before 2000 underwent advanced reconstruction of the great vessels. After 2000, 12 of 16 (75%) patients with univentricular sCHD required reconstruction of the aortic arch, pulmonary arteries or systemic veins before transplantation in the fashions described below.

**Intraoperative surgical reconstructive techniques**

The anatomy, indications, reconstructions performed, time to perform reconstructions and outcomes are given in Table 2. The donor ischaemic times are also provided. Later in the series, some patients had donor ischaemic times of <2 h (Patients 14 and 16);

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**Figure 1**: The number of patients undergoing transplantation for sCHD, with the percentage of those who had univentricular sCHD. The number of patients (bars) corresponds to the primary y-axis on the left and is subdivided into univentricular and biventricular. The percentages (lines) correspond to the secondary y-axis on the right.

**Table 1**: Characteristics of patients undergoing transplantation for failed single-ventricle palliation, before and after 2000

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before 1 January 2000 (N = 14)</th>
<th>After 1 January 2000 (N = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at transplantation in years, median (25th–75th percentile)</td>
<td>5.3 (4.3–15.4)</td>
<td>15.4 (8.7–15.7)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>5 (36%)</td>
<td>9 (56%)</td>
</tr>
<tr>
<td>Hypoplastic left heart syndrome, n (%)</td>
<td>0 (0%)</td>
<td>6 (38%)</td>
</tr>
<tr>
<td>Number of prior sternotomies, median (25th–75th percentile)</td>
<td>3 (2–4)</td>
<td>4 (2.8–5.0)</td>
</tr>
<tr>
<td>Reconstruction of the great vessels, n (%)</td>
<td>0 (0%)</td>
<td>12 (75%)</td>
</tr>
<tr>
<td>Donor ischaemia time in minutes, mean (SD)</td>
<td>200 (77)</td>
<td>256 (101)</td>
</tr>
</tbody>
</table>
indications for operation, reconstructive techniques and intraoperative variables for post-2000 era univentricular patients

Table 2: Indications for operation, reconstructive techniques and intraoperative variables for post-2000 era univentricular patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Year</th>
<th>Diagnosis</th>
<th>Age at transplantation (years)</th>
<th>Follow-up time (years)</th>
<th>Donor status</th>
<th>Time to perform repair (min)</th>
<th>Total bypass time (min)</th>
<th>Follow-up status</th>
<th>Aortic arch reconstruction required modification</th>
<th>Non-technical considerations in univentricular structural congenital heart disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2001</td>
<td>Complex isomerism</td>
<td>CCF</td>
<td>18</td>
<td>Alive</td>
<td>6</td>
<td>6</td>
<td>Alive</td>
<td>11.8</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2002</td>
<td>Complex isomerism</td>
<td>LV failure</td>
<td>21</td>
<td>Alive</td>
<td>6</td>
<td>6</td>
<td>Alive</td>
<td>10.6</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2002</td>
<td>DILV-TGA</td>
<td>CCF</td>
<td>11</td>
<td>Alive</td>
<td>6</td>
<td>6</td>
<td>Alive</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2002</td>
<td>Tricuspid stenosis</td>
<td>LV failure</td>
<td>8</td>
<td>Alive</td>
<td>6</td>
<td>6</td>
<td>Alive</td>
<td>9.7</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2003</td>
<td>DORV, PS</td>
<td>CCF</td>
<td>8</td>
<td>Alive</td>
<td>6</td>
<td>6</td>
<td>Alive</td>
<td>9.7</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2004</td>
<td>DORV, PA</td>
<td>CCF</td>
<td>9</td>
<td>Alive</td>
<td>6</td>
<td>6</td>
<td>Alive</td>
<td>8.9</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>2004</td>
<td>HLHS</td>
<td>CCF</td>
<td>15</td>
<td>Alive</td>
<td>6</td>
<td>6</td>
<td>Alive</td>
<td>8.0</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>2005</td>
<td>ccTGA</td>
<td>CCF</td>
<td>17</td>
<td>Alive</td>
<td>6</td>
<td>6</td>
<td>Alive</td>
<td>7.8</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>2006</td>
<td>HLHS</td>
<td>LV failure</td>
<td>15</td>
<td>Alive</td>
<td>6</td>
<td>6</td>
<td>Alive</td>
<td>7.6</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>2006</td>
<td>PA-IVS</td>
<td>Myocardial ischaemia</td>
<td>14</td>
<td>Alive</td>
<td>6</td>
<td>6</td>
<td>Alive</td>
<td>6.3</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>2007</td>
<td>HLHS</td>
<td>CCF</td>
<td>5</td>
<td>Alive</td>
<td>6</td>
<td>6</td>
<td>Alive</td>
<td>5.1</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>2008</td>
<td>Complex isomerism</td>
<td>CCF</td>
<td>16</td>
<td>Alive</td>
<td>6</td>
<td>6</td>
<td>Alive</td>
<td>3.9</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>2008</td>
<td>HLHS</td>
<td>PLE</td>
<td>15</td>
<td>Alive</td>
<td>6</td>
<td>6</td>
<td>Alive</td>
<td>3.2</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>2009</td>
<td>DORV, CoA</td>
<td>LV failure, sepsis</td>
<td>14</td>
<td>Alive</td>
<td>6</td>
<td>6</td>
<td>Alive</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>2010</td>
<td>HLHS</td>
<td>VAD, CCF</td>
<td>5</td>
<td>Alive</td>
<td>6</td>
<td>6</td>
<td>Alive</td>
<td>2.2</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>2012</td>
<td>HLHS</td>
<td>CCF</td>
<td>17</td>
<td>Alive</td>
<td>6</td>
<td>6</td>
<td>Alive</td>
<td>1.2</td>
<td></td>
</tr>
</tbody>
</table>

DORV: double outlet right ventricle; PS: pulmonary stenosis; PA: pulmonary atresia; HLHS: hypoplastic left heart syndrome; ccTGA: congenitally corrected transposition of the great arteries; PA-IVS: pulmonary atresia with intact ventricular septum; CoA: coarctation of the aorta; CCF: congestive cardiac failure; LV: left ventricle; PLE: protein-losing enteropathy; VAD: ventricular assist device. BR: Blalock-Taussig; NA: not available.

Non-technical considerations in univentricular structural congenital heart disease

Beyond routine cardiopulmonary bypass, all 3 patients undergoing aortic arch reconstruction required modified cardiopulmonary bypass considerations. In only 1 of the 3 was selective cerebral perfusion used, while 2 required deep hypothermic circulatory arrest. Additionally, bypass time was prolonged in 2 patients in our experience because of the use of plasmapheresis for the presence of panel-reactive antibodies (PRAs).

Immediately prior to transplantation, 5 of 16 (31%) patients required circulatory support: 4 were admitted to the intensive care unit on inotropes, and 1 was supported with a ventricular assist device. At the conclusion of the transplant procedure, 2
patients required ECMO support. Overt bleeding disorders were not detected preoperatively in any patients, although coagulopathy or anastomotic bleeding requiring massive transfusion was troublesome in 3 (12%) patients, one of whom experienced significant haemoptysis during weaning from bypass.

**DISCUSSION**

Transplantation after failed univentricular palliation is becoming more frequent and more challenging as patients live longer and complex lesions like hypoplastic left heart syndrome (HLHS) are successfully surgically palliated [1, 2]. In our experience, the two most important aspects that represent the biggest challenges when performing transplantation in this population are (i) anatomical reconstruction of vessels prior to transplantation and (ii) reduction of donor heart ischaemic time by accurate timing of heart retrieval according to the progress of the surgical preparation of the recipient. Table 3 summarizes the unique problems encountered in transplantation for failed single-ventricle palliation, and some of the solutions we used or recommend.

Univentricular palliation, particularly prior Fontan operation, has been identified as a risk factor for worse outcomes after heart transplantation [3–5]. The worse outcomes are due, in large part, to the surgical complexity of heart transplantation into recipients with prior multiple cardiac surgeries. Other problems of the failing univentricular circulation also contribute to increased perioperative risk, such as protein-losing enteropathy, pulmonary vascular malformations, elevated pulmonary vascular resistance, as well as a tendency towards bleeding and infection [6]. Finally, patients who have had multiple prior operations are more likely to have high PRA titres, and this may have historically caused worse results among univentricular patients. As a result, operative mortality was initially 29–44% in the 1990s [4, 7, 8] in this group. The initial reports from this era, which described surgically creative techniques to enable transplantation, were in an era when palliative procedures occurred only at an atrial or pulmonary arterial level [7, 9, 10]. Results were poor despite the simplicity of reconstructions required.

In the current era, patients are far more complex. The Norwood procedure for HLHS is now widely performed. There is often a need...
to augment pulmonary arteries to enable successful single-ventricle palliation. Thus, more technically demanding reconstructions are often required at the time of transplantation. Despite the greater complexities, our contemporary series and those of Kanter et al. [11] and Murtuza et al. [12] show that ongoing surgical innovation may result in operative mortality of <10%. The study by Kanter et al. on 27 patients under 18 years of age at a single centre was the first to demonstrate that prior Fontan palliation was no longer a risk factor for mortality. They attributed this to careful patient selection as reflected in the small percentage of patients in their series with a Fontan circulation (14%). Furthermore, the levels of pre-sensitization with PRAs were no different in their series, as patients with pre-sensitization were more likely to die while waiting for a suitably matched heart. Finally, their institution had a liberal policy for retransplantation: among 27 Fontan patients, 5 (18%) received a matched heart. Finally, their institution had a liberal policy for retransplantation: among 27 Fontan patients, 5 (18%) received a matched heart. Kanter et al. [12] showed that ongoing surgical innovation may result in operative mortality of <10%.

The study is limited by its retrospective nature. Any associations between the surgical reconstructions used and reductions in mortality do not prove causation, as causation can only be determined through a prospective study. Non-technical factors may have contributed to the reduction in mortality seen in this study.

**LIMITATIONS**

The study is limited by its retrospective nature. Any associations between the surgical reconstructions used and reductions in mortality do not prove causation, as causation can only be determined through a prospective study. Non-technical factors may have contributed to the reduction in mortality seen in this study.

**CONCLUSIONS**

The increasing complexity of transplantation after failed single-ventricle palliation necessitates techniques to reconstruct the aorta, pulmonary arteries and systemic veins to permit successful transplantation. Advanced surgical preparation may have a role in reconstruction of the great vessels before transplantation to minimize donor ischaemia times.
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Conflict of interest: none declared.

REFERENCES


APPENDIX. CONFERENCE DISCUSSION

Dr M. Griselli (Newcastle upon Tyne, UK): Your group has achieved great results in this difficult group of patients. And I do agree with you that the surgical planning is essential.

I’d like to go further in terms of what other factors may have helped to improve your results in recent years, starting with what you may have changed in terms of donor selection. For example, in this group of patients, we tend to oversize the donor heart because we believe pulmonary vascular resistance may have increased. And the second thing I would like to know is whether you have noticed changes, for example, in your warm ischaemic time, which, as you know, is very important in transplantation, even more than the complete total ischaemic time.

Then, considering patient selection in terms of how we’re looking after the patient before surgery: some of these patients are kept in the hospital nowadays on milrinone, and some on ventilators to optimize the end organ function. Not forgetting what’s happening after transplant, nowadays we have a more refined technique to support these patients to prevent early signs of acute graft failure or acute rejection with or without mechanical cardiac support.

So I would like you to elaborate a little bit on these other factors which are important and may have improved your results.

Dr Iyengar: I agree with you and I believe that all those factors have certainly played a role, and that includes the postoperative care of the patients. In terms of warm ischaemic time, we didn’t study that, but we’ve maintained an attitude of trying to minimize warm ischaemic time to about 60 minutes for most of the series. As for patient selection, I can’t comment on that based on this series, but I might get Yves to.

Dr Y. d’Udekem (Melbourne, Australia): Regarding patient selection, I’m afraid we cannot be too choosy because the donor rate in Australia is half that of the Western world, half that of Europe and North America. So our waiting list is twice as long than in the rest of the world, and we cannot be very picky in terms of donors.

But we are not picky in terms of size, and we still remain quite selective in terms of the quality of the donor. We will not accept a donor above 50 years of age, and we like the patients to be in good condition, and we have a very low threshold to eliminate any comorbidities and cardiovascular risk.

We have no particular management in this patient group. The thing that has arisen in recent years is that we have more and more patients with very high PRA levels, and we have to do a plasma exchange in them. Our strategy is to bring the patient to the theatre, to go on cardiopulmonary bypass and perform the plasma exchange on bypass. And we know it takes about 45 minutes to one hour to do a complete plasmapheresis in these patients before we get the donor heart here, and then we can do the reconstruction at the same time.

Dr Griselli: And just a last question in general. Do you use Trasylol in these cases?

Dr Iyengar: Yes, we have. It’s not Trasylol. It’s a generic name.

Dr Griselli: Aprotinin.

Dr Iyengar: Yes.

Dr D. Anderson (London, UK): I just have one point. Have you noticed any influence of the fact that patients such as those with hypoplastic left heart will have had homograft tissue as a part of their early surgery? Does that have any influence?

Dr Iyengar: No.

Dr Anderson: So we don’t need to give up homograft tissue in reconstruction?

Dr Iyengar: Not from looking at this data, no.

Dr Anderson: Great. I’m glad to hear it.