Outcome After Orthotopic Cardiac Transplantation in Adults With Congenital Heart Disease

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Background—Advances in surgical and medical management have greatly improved long-term survival rates in patients with congenital heart disease (CHD). As these patients reach adulthood, myocardial dysfunction can occur, leading to cardiac transplantation.

Methods and Results—We reviewed the pretransplantation and posttransplantation courses of 24 patients ≥18 years old (mean age, 26 years; range, 18 to 56 years) with CHD who received a transplant between January 1985 and September 1998. The relation between preoperative and perioperative risk factors for complications and death was assessed. Single ventricle was the pretransplantation diagnosis for 12 patients (50%), and d-transposition of the great vessels was the diagnosis for 4 patients (16%). Twenty-two patients had a mean of 2 previous operations. At cardiac transplantation, additional surgical procedures were required to correct extracardiac lesions in 18 patients (75%). Refractory heart failure was present in 22 patients, significant cyanosis was present in 7, and protein-losing enteropathy was present in 4. There were 5 early deaths due to bleeding (n=3) and infection (n=2). The Kaplan-Meier survival rate after cardiac transplantation was 79% at 1 year and 60% at 5 years. No anatomic or surgical risk factor was predictive of death. The outcome of patients with CHD who received a transplant was compared with that for patients without CHD (n=788). Mean bypass and ischemic times were significantly longer in patients with CHD than in patients without CHD (P=0.83). Survival rates after transplantation did not differ significantly between patients with and those without CHD. The purpose of our study was to describe the pretransplantation and posttransplantation courses of adults with CHD, with an outcome similar to that of patients without CHD. A detailed assessment of cardiac anatomy and careful surgical planning are essential to the pretransplantation and posttransplantation management of these patients. (Circulation. 1999;100[suppl II]:II-200–II-205.)

Conclusions—Successful cardiac transplantation is obtainable in adults with complex CHD, with an outcome similar to that of patients without CHD. A detailed assessment of cardiac anatomy and careful surgical planning are essential to the pretransplantation and posttransplantation management of these patients. (Circulation. 1999;100[suppl II]:II-200–II-205.)

Key Words: transplantation ■ heart defects, congenital ■ risk factors

Advances in surgical and medical management have greatly improved the long-term survival rates of patients with congenital heart disease (CHD); however, late myocardial dysfunction can occur after palliative or corrective surgery and is the most common cause of decline and death in patients with CHD. Penkoske et al estimated that of all patients with CHD, 10% to 20% will be potential candidates to receive a heart or heart-lung transplant at some time during their lifetime. This group of patients presents multiple unique surgical and medical challenges owing to their complex anatomy, prior palliative and corrective procedures, and overall debilitated condition. Elevated pulmonary vascular resistance due to years of long-standing congestive heart failure may further complicate cardiac transplantation, increasing the risk of donor right heart failure. Although there have been multiple publications reporting the outcomes in children with CHD after cardiac transplantation, few reports in the literature have focused on transplantation in the adult with complex CHD.

The purpose of our study was to describe the pretransplantation and posttransplantation courses of adults with CHD who undergo cardiac transplantation, to assess potential risk factors for a poor outcome, and to compare the posttransplantation outcome of adult patients with CHD with that of adult patients without CHD.

Methods

Patients

Eight hundred two patients underwent primary orthotopic cardiac transplantation at our institution between January 1985 and September 1998. Twenty-four (3%) were ≥18 years old and had CHD. Pretransplantation variables that were assessed included anatomic diagnosis, previous surgical and catheterization interventions, indications for transplantation, United Network for Organ Sharing (UNOS) status, and pulmonary vascular resistance. Operative and
postoperative variables included additional surgery at the time of transplantation, bypass time, ischemic time, time on mechanical ventilation and receiving inotropic support, and length of stay. In addition, the age, ischemic time, and bypass time for the 788 patients without CHD were obtained.

Morbidity and Mortality
The timing and cause of complications and death were identified in patients with CHD. Early death was defined as death before discharge from the hospital. Potential risk factors were identified for early death: age at transplantation, a diagnosis of single ventricle, number of prior operations, years from last operation to transplantation, cross-clamp time, and ischemic time.

Statistical Methods
The Kaplan-Meier product-limit estimate was used to estimate the survival functions for (1) patients with CHD versus all others, (2) patients with CHD versus matched controls (by age, sex, race, and year of transplantation), and (3) decade of transplantation (1985 to 1990 versus 1991 to 1998). The log-rank test was used to compare the survival distributions. Student’s t test was used to compare continuous variables, and the χ² and Fisher’s exact tests were used to compare groups for discrete data. Data were analyzed with the use of SAS system software (SAS Institute Inc).

Results
Patient Population
The mean age of the patients with CHD was 26 years (range, 18 to 56 years). There were 17 men and 7 women. As shown in Figure 1, 19 (79%) of 24 adults underwent cardiac transplantation for CHD at our institution within the past 7 years. During the study period, 788 patients underwent transplantation due to other cardiac diseases; the mean age of this group was 51 years. There were 33 patients in the matched control group (mean age, 31 years; 28 men and 5 women). The patients were matched for race and year of transplantation.

Indications for Transplantation in Patients With CHD
The anatomic diagnosis and previous operations for each patient are shown in Table 1. The most common diagnosis was single ventricle (12 patients [50%]). Nine of these patients had previously undergone a Fontan procedure 11.5 ± 3.3 years before transplantation; 7 patients had rhythm disturbances, and 1 patient had complete heart block requiring a pacemaker early after the Fontan procedure. Six patients had a tachyarrhythmia; all were medically managed, but 1 of these patients required a pacemaker for sick sinus syndrome. Three patients, all with poor ventricular function, had a rapid progression in heart failure once they presented with an arrhythmia. Although contributory, arrhythmia was not the primary indication for transplant listing in these patients who had undergone a Fontan procedure. Two patients had a combination of a Glenn shunt and aortopulmonary shunts. One patient had multiple aortopulmonary shunts as the only palliative procedure before transplant referral. The second most common diagnosis was d-transposition of the great vessels (4 patients [16%]) all of whom had Mustard operations). Two patients, both of whom had congenitally corrected transposition of the great vessels, had not undergone cardiac surgery before transplantation. Twenty-two patients underwent a median of 2 operations per patient (range, 1 to 5) (Figure 2).

Eleven patients (46%) had specific interventions in an attempt to improve clinical condition before transplant referral. A pacemaker was implanted in 10 patients (42%) for either complete heart block or sick sinus syndrome. Six patients (25%) had interventional catheterization procedures performed: coil embolization of aortopulmonary collaterals (n=2), coil embolization of Blalock-Taussig shunt (n=1), pulmonary artery angioplasty (n=1), stent placement in an obstructed Mustard baffle (n=1), and device closure of a ventricular septal defect (n=1). Two patients had Harrington rods placed for severe scoliosis.

The indication for transplantation in all patients with double-ventricle anatomy was systemic ventricular failure refractory to medical therapy. In the 12 patients with a single ventricle, 9 had had an unsuccessful Fontan procedure, with poor ventricular function in 7. Significant cyanosis and severe protein-losing enteropathy were also present in patients with a single ventricle, contributing to exercise intolerance. Twenty-two patients were UNOS status 1 and 2 patients were status 2 (criteria established by the United Organ Donor Network). All status 1 patients were hospitalized on inotropic support. Only 1 patient required mechanical ventilation and a biventricular assist device before transplantation secondary to acute decompensation related to a pulmonary infection.

Although all patients had cardiac catheterizations, 15 were available for review. Overall, pulmonary vascular resistance (PVRI) in the patients with CHD was 4.4 U/m². However, increased PVRI (mean, 8 U/m²) was found in 5 (30%) of 15 patients. All patients with elevated PVRI responded to nitroprusside in the catheterization laboratory and were maintained on pulmonary vasodilators while they awaited transplantation. Two patients had surgically created discontinuous pulmonary arteries with isolated left pulmonary artery hypertension (mean, 43 to 50 mm Hg) and Glenn shunts supplying blood flow to the right lung (mean, 12 mm Hg).

Perioperative Data
Two patients had preformed antibodies that were considered significant (>20% reactivity to a standard antigen panel).
However, neither of these patients had prospective cross-matching, and therefore it did not interfere with the timing of an appropriate donor organ. Eighteen (75%) of 24 patients required additional significant surgical reconstruction at the time of transplantation, including takedown of a Fontan or Glenn anastomosis (12 patients) and reconstruction of pulmonary arteries (42%) (Table 2). The bypass time for patients with CHD was 4.7 ± 2 hours, which was significantly longer than the time (3 ± 1.2 hours) for patients without CHD ($P < 0.001$). The ischemic time was also significantly longer in those with CHD (4.2 ± 2 hours) than in those with other cardiac disease (3.2 ± 1.2 hours) ($P < 0.001$). The median intubation time for those with CHD undergoing cardiac transplantation was 2 days (range, 1 to 65 days). The median time on inotropic support was 5 days (range, 0 to 35). The median length of stay was 22 days (range, 9 to 92 days).

**Mortality and Morbidity**

There were 5 early deaths and 4 late deaths. Four of 5 early deaths occurred in patients for whom the Fontan procedure was unsuccessful. Three patients for whom the Fontan procedure was unsuccessful had significant surgical bleeding, resulting in 2 deaths. One patient required reoperation for a kinked pulmonary artery and later developed *Staphylococcus aureus* infection. The fifth early death and the oldest patient with CHD died of an intracerebral hemorrhage 1 day after transplantation at age 56. There were no anatomic or surgical risk factors identified as predictive of early death (Table 3). The causes of late death were acute rejection (n = 2) and graft arteriosclerosis (n = 2); late death occurred 13 to 123 months after transplantation. Significant complications occurred in 7 (30%) of 24 patients, accounting for the prolonged length of stay in 5 of 7 patients. Infection was the most common cause and included mediastinitis, infection of the graft at the cannulation site, and sepsis. One patient required reoperation for a kinked pulmonary artery and later developed *Staphylococcus aureus* infection.

### Table 1. Diagnosis and Surgical History in 24 Study Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Diagnosis</th>
<th>Age, y</th>
<th>Survival, mo</th>
<th>Status</th>
<th>Prior Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>d-TGV, tricuspid atresia, pulmonary atresia</td>
<td>26</td>
<td>77</td>
<td>Alive</td>
<td>Ao-PA shunt, Glenn shunt, Fontan</td>
</tr>
<tr>
<td>2</td>
<td>d-TGV, hypoplastic right ventricle, PS</td>
<td>23</td>
<td>0.03</td>
<td>Dead</td>
<td>Ao-PA shunt, Glenn shunt, Fontan, excision of PA aneurysm</td>
</tr>
<tr>
<td>3</td>
<td>Heterotaxy syndrome, SV</td>
<td>20</td>
<td>68</td>
<td>Alive</td>
<td>Ao-PA shunt, Fontan/Mustard</td>
</tr>
<tr>
<td>4</td>
<td>Tricuspid atresia</td>
<td>18</td>
<td>65</td>
<td>Alive</td>
<td>Ao-PA shunt, Glenn shunt, Fontan</td>
</tr>
<tr>
<td>5</td>
<td>Double-outlet right ventricle, straddling AV valve</td>
<td>26</td>
<td>54</td>
<td>Alive</td>
<td>Fontan</td>
</tr>
<tr>
<td>6</td>
<td>Tricuspid atresia</td>
<td>20</td>
<td>0.0</td>
<td>Dead</td>
<td>Ao-PA shunt, Glenn shunt, Fontan</td>
</tr>
<tr>
<td>7</td>
<td>Heterotaxy syndrome, SV</td>
<td>20</td>
<td>28</td>
<td>Alive</td>
<td>Ao-PA shunt ×2, right Glenn shunt, left Glenn shunt</td>
</tr>
<tr>
<td>8</td>
<td>Pulmonary atresia, intact ventricular septum</td>
<td>21</td>
<td>1.1</td>
<td>Dead</td>
<td>Ao-PA shunt ×3</td>
</tr>
<tr>
<td>9</td>
<td>DILV, PS</td>
<td>31</td>
<td>0.3</td>
<td>Dead</td>
<td>Ao-PA shunt, Glenn shunt, Fontan, reop Fontan</td>
</tr>
<tr>
<td>10</td>
<td>Tricuspid atresia</td>
<td>22</td>
<td>1</td>
<td>Alive</td>
<td>Ao-PA shunt ×2, septectomy, Glenn shunt, ligation RSVC-RA fistula</td>
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<tr>
<td>11</td>
<td>DILV</td>
<td>30</td>
<td>13</td>
<td>Dead</td>
<td>PAB ×2, Fontan</td>
</tr>
<tr>
<td>12</td>
<td>SV, d-TGV, PS</td>
<td>39</td>
<td>2</td>
<td>Alive</td>
<td>Glenn shunt</td>
</tr>
<tr>
<td>13</td>
<td>d-TGV</td>
<td>18</td>
<td>2</td>
<td>Alive</td>
<td>Mustard operation</td>
</tr>
<tr>
<td>14</td>
<td>d-TGV</td>
<td>19</td>
<td>14</td>
<td>Alive</td>
<td>Mustard operation</td>
</tr>
<tr>
<td>15</td>
<td>d-TGV</td>
<td>25</td>
<td>24</td>
<td>Alive</td>
<td>Mustard operation</td>
</tr>
<tr>
<td>16</td>
<td>d-TGV, VSD</td>
<td>28</td>
<td>3</td>
<td>Alive</td>
<td>PAB, Mustard/Glenn shunt</td>
</tr>
<tr>
<td>17</td>
<td>l-TGV, VSD</td>
<td>18</td>
<td>77</td>
<td>Alive</td>
<td>PAB, VSD repair</td>
</tr>
<tr>
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<td>l-TGV</td>
<td>18</td>
<td>112</td>
<td>Alive</td>
<td>None</td>
</tr>
<tr>
<td>19</td>
<td>l-TGV</td>
<td>56</td>
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<td>Dead</td>
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</tr>
<tr>
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<td>Tetralogy of Fallot</td>
<td>43</td>
<td>123</td>
<td>Dead</td>
<td>Repair</td>
</tr>
<tr>
<td>21</td>
<td>Tetralogy of Fallot</td>
<td>21</td>
<td>38</td>
<td>Dead</td>
<td>Ao-PA shunt, repair</td>
</tr>
<tr>
<td>22</td>
<td>VSD</td>
<td>23</td>
<td>142</td>
<td>Alive</td>
<td>Repair, resection subPS, Ao valve replacement</td>
</tr>
<tr>
<td>23</td>
<td>Heterotaxy syndrome, VSD</td>
<td>28</td>
<td>42</td>
<td>Dead</td>
<td>PAB, VSD repair</td>
</tr>
<tr>
<td>24</td>
<td>Pulmonary stenosis, ASD</td>
<td>25</td>
<td>129</td>
<td>Alive</td>
<td>PA valvotomy, ASD repair</td>
</tr>
</tbody>
</table>

VSD indicates ventricular septal defect; Ao, aorta; PS, pulmonary stenosis; ASD, atrial septal defect; PA, pulmonary artery; PAB, pulmonary artery band; AV, atrioventricular; RSVC-RA, right superior vena cava to right atria; TGV, transposition of the great vessels; SV, single ventricle; and DILV, double-inlet left ventricle.
pericarditis. Two patients with single-ventricle anatomy had high output failure as a result of significant left-to-right shunting via aortopulmonary collateral arteries and underwent coil embolization with resolution. Three patients, both with multiple previous operations, had paralysis of a hemidiaphragm after cardiac transplantation. One patient with a prior Mustard repair, who had required mechanical ventilation and a biventricular assist device before transplantation, was severely debilitated, necessitating a tracheostomy and prolonged ventilatory support. This patient developed mediastinitis, which responded to an extensive course of antibiotics. One patient with congenitally corrected transposition with prior pulmonary artery banding and ventricular septal defect closure had severely elevated pulmonary vascular resistance before transplantation; he required continuous general anesthesia and a right ventricular assist device for 1 week due to significant pulmonary hypertension and donor right heart failure. Two patients who survived surgery had resolution of protein-losing enteropathy.

Outcome
The actuarial survival rate for patients with CHD was 79% at 1 year and 60% at 5 years. This was not significantly different from the rate for patients undergoing transplantation for other cardiac disease. There was no difference in survival rate compared with controls matched for age, sex, race, and year of transplantation (Figures 3 and 4). The decade of transplantation also did not change the survival rate.

Discussion
The present study describes the outcome of transplantation in adults with CHD and ventricular failure. It has been well established that children with CHD, outside the infant group, do as well as children undergoing transplantation for other cardiac disease. The number of adults with CHD who undergo evaluation and transplantation has been increasing in the past several years. Seven have received a transplant at our institution within the past 13 months (30%).

Heart transplantation was performed successfully in 19 (79%) of 24 adults with CHD, with a survival rate of 79% at 1 year and 60% at 5 years. This was not significantly different from our overall transplant survival rate or from that for matched controls and has not varied based on year of transplantation. Compared with the most recent registry data of the International Society for Heart and Lung Transplantation, our overall survival rate is not considerably different from that previously reported (1 year, 80%; 5 years, 63%). These rates are only slightly different from those reported in the registry during 1991 through 1997 (1 year, 82%; 5 years, 68%).

Figure 3. Kaplan-Meier survival rates for adults with CHD who underwent transplantation (n=24) and all other adult heart transplant recipients (n=788). From Columbia-Presbyterian Medical Center (January 1985 through October 1998).

Experience with transplantation in adults with CHD has been varied in both the complexity of patients and the reported survival rate. Hasan et al reported on 7 adults who had received a transplant, of whom 3 had no prior operations. One patient who had undergone a Fontan procedure, who was <18 years old, died after surgery. The early mortality rate in their series was 43%. Carrel et al reported a 100% survival rate in 7 patients >18 years old who underwent transplantation for CHD. However, 3 of these patients had had no prior operations, and none had undergone a Fontan procedure. More recently, Speziali et al reported their experience with 11 patients, all of whom had had prior operations. There were 2 patients who had undergone a Fontan procedure in this series, but they were both <18 years old. They reported no postoperative deaths, with a 1-year survival rate of 86%.
In the present study, heart transplantation was successful in 8 of 12 patients with single-ventricle anatomy, but 4 of 5 early deaths occurred in patients with single-ventricle anatomy, of whom 3 had undergone an unsuccessful Fontan procedure. This group of patients seems to be at an increased risk for death and have a higher mortality rate than patients with CHD who have double-ventricle anatomy. Patients with single-ventricle anatomy and, in particular, an unsuccessful Fontan procedure, are more difficult to evaluate after transplantation. They are at risk for the development of pulmonary arteriovenous malformations, which may be responsible for increased cyanosis, and can have aortopulmonary collateral arteries, which may contribute to heart failure. Aortopulmonary collateral arteries were present in 25% of our patients. Two patients underwent embolization of aortopulmonary collaterals before transplantation, and 2 underwent coil embolization after transplantation secondary to high output failure after allograft implantation. The passive flow physiology of patients who had undergone a Fontan procedure increases the possibility of ventilation-perfusion mismatch. Protein-losing enteropathy is present in a significant number of these patients, contributing to their exercise intolerance that sometimes occurs in the presence of preserved ventricular function. Four of our patients who had undergone a Fontan procedure had significant protein-losing enteropathy that resolved after successful transplantation; however, there were 2 deaths in this group.

The ability to undertake cardiac transplantation in patients with complex CHD has been in evolution, with the first reported transplantation involving an infant occurring in a child with CHD in 1967 and multiple subsequent reports that outlined the surgical approach and addressed issues of extracardiac repair. Preplanning is essential when the possibility is entertained of cardiac transplantation for this group of patients. Each patient who presents with end-stage CHD is unique and challenging. In general, attempts are made to use native tissue (donor and recipient) for reconstruction; therefore, at donor procurement, additional lengths of aorta, pulmonary artery, and pericardium may have to be harvested. Previous surgery may make reentry to the chest difficult; the lack of standard access, as a result of multiple prior invasive procedures, may make the use of cardiopulmonary bypass challenging. Surgical improvisation based on anatomic findings at the time of transplantation may be necessary. Because the majority of our patients had multiple prior palliative or corrective surgery, reconstructive surgery was necessary in 75%; thus, bypass and ischemic times were longer. Others have suggested that anatomic complexities may add to allograft ischemic time, which may compromise the result.

As our experience increases, so does the level of physiological complexity we are considering for transplantation. Other challenges to the postoperative course in these patients include increased risk of bleeding, potential of donor right heart failure, and increased risk of infection. We have learned how to identify and address issues of increased pulmonary vascular resistance in these patients undergoing cardiac transplantation. Thirty percent of our patients had high pulmonary vascular resistance; despite this, no patient died of donor right heart failure. Even in the context of CHD, elevated pulmonary vascular resistance is not a contraindication to cardiac transplantation. Two patients in the past year have undergone a “physiological” cardiac transplantation to 1 lung. As mentioned in the results, both of these patients had discontinuous pulmonary arteries as a result of a previous classic Glenn anastomosis with pulmonary hypertension present in the left pulmonary artery. When initially evaluated several years ago, both patients were considered potential heart-lung candidates. Both patients underwent successful cardiac transplantation with reanastomosis of the right and left pulmonary arteries. Both patients had benign postoperative courses and are alive and well, despite the presence of the majority (>95%) of flow going to 1 lung.

Conclusions
Heart transplantation offers the possibility of excellent short- and medium-term survival rates with a variety of complex congenital heart lesions in adults and should be considered a therapeutic option in the patients with end-stage disease. A successful outcome can be achieved with detailed assessment of cardiac anatomy and careful surgical planning.
References
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