The Effect of Age, Diagnosis, and Previous Surgery in Children and Adults Undergoing Heart Transplantation for Congenital Heart Disease

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New York, New York; Atlanta, Georgia; Birmingham, Alabama; Philadelphia, Pennsylvania; Little Rock, Arkansas; and Peoria, Illinois

Objectives
We sought to evaluate the outcomes and identify risk factors for mortality after heart transplantation (HT) for congenital heart disease (CHD) in infants, children, and adults.

Background
CHD is considered a risk factor for mortality after HT, yet this unique group of patients represents a spectrum of complexity.

Methods
There were 488 patients transplanted for CHD from the combined Pediatric Heart Transplant Study (1993 to 2002, n = 367) and the Cardiac Transplant Registry Database (1990 to 2002, n = 121) who were analyzed.

Results
The median age at HT was 12.4 years. Primary diagnosis included single ventricle (36%), d-transposition of the great arteries (12%), right ventricular outflow tract lesions (10%), l-transposition of the great arteries (8%), ventricular/atrial septal defects (8%), left ventricular outflow obstruction (8%), and other (18%). Ninety-three percent of patients had at least 1 operation before HT. Survival at 3 months post-HT was significantly worse in CHD patients versus children with cardiomyopathy, but not adults with cardiomyopathy (86%, 94%, and 91%, respectively). There was no difference in conditional 3-month survival among the 3 groups. Five-year survival was 80%. Risk factors for early mortality were older recipient age, older donors with longer ischemic times, and pre-HT Fontan operations. Predicted survival in Fontan patients was lower (77% and 70% at 1 and 5 years) versus non-Fontan patients (88% and 81% at 1 and 5 years). Risk factors for constant phase mortality included younger recipient age, higher transpulmonary gradient, cytomegalovirus mismatch at HT, and earlier classical Glenn operation.

Conclusions
Patients undergoing transplantation for CHD have a good late survival if they survive the early post-operative period. Risk factors for reduced survival are older age at transplant and a previous Fontan operation. (J Am Coll Cardiol 2009;54:160–5) © 2009 by the American College of Cardiology Foundation

Long-term survival in children and adults with congenital heart disease (CHD) has improved markedly with advances in medical and surgical therapies. Despite these advances, a growing number of patients with complex CHD will ultimately require heart transplantation (HT) for end-stage heart failure. CHD has been identified as a risk factor for 1-year outcome after transplantation (1), but studies identifying specific risk factors for poor outcome after transplantation for CHD in the combined adult and pediatric population have not been performed.

The PHTS (Pediatric Heart Transplant Study) and the CTRD (Cardiac Transplant Research Database) are prospective, event-driven registries that collect information from the time of listing for transplant in patients <18 years of age (PHTS) and the time of transplant in patients >18 years of age (CTRD) (2). The purpose of this study was to use the data available from the PHTS and CTRD registries to generate a combined dataset that would enable evaluation of outcomes after HT in patients of all ages with end-stage CHD and to identify risk factors for mortality after transplantation in this group.
This study is a retrospective multi-institutional analysis of a merged dataset generated from the CTRD and PHTS registries. The CTRD population consisted of 7,345 patients >18 years of age transplanted at 35 centers from January 1990 through December 2002. The PHTS population consisted of 923 patients <18 years of age at the time of listing for HT. A total of 366 patients <6 months of age were excluded to eliminate 291 (80%) of the infants undergoing HT as a primary surgical procedure. Of the remaining 20%, some of whom were listed for transplantation and underwent palliative procedures while awaiting suitable donor organs, all needed transplant <6 months after their last surgical procedure. This unique group of infants was thought not to be generalizable to the entire cohort of pediatric and adult patients with CHD undergoing transplantation. The outcomes of infants with hypoplastic left heart syndrome listed for cardiac transplantation using this same registry data have been published previously (3).

Methods

Patients with the diagnosis of CHD who underwent HT were identified. Multiple recipient and donor variables were examined to identify risk factors for survival after transplantation. Recipient variables included CHD diagnosis, United Network for Organ Sharing status at transplantation, surgical history, and listing hemodynamics. Pulmonary vascular resistance and percent reactive antibody data were not available for analysis. Donor variables included echocardiographic and angiographic data, cause of death, inotropic support, and cytomegalovirus mismatch. Data were analyzed using Kaplan-Meier survival and nonparametric and parametric hazard models. Survival was compared among patients with CHD and those with cardiomyopathy <18 and >18 years of age. Risk factors for death among the patients with CHD were identified using multivariable analysis in the parametric hazard domain.

Results

There were 488 patients (121 of 7,345 [1.6%] patients in the CTRD and 367 of 923 [40%] patients in the PHTS database) with the diagnosis of CHD who underwent HT during the study period. Total patient-years of follow-up were 442 in the adult patients and 1,095 in the pediatric patients. Median follow-up was 2.3 years for the entire cohort and 3.3 years for surviving patients. The age distribution of the patients is represented in Figure 1. The mean age at transplant in the Fontan patients was 15 years. Staged palliation for single ventricle, including the Norwood procedure or variants of the Glenn procedure, was the last operation performed before transplantation in approximately 20% of patients.

Figure 3 compares the Kaplan-Meier post-transplant survival of patients with CHD of any age with adult and pediatric patients with cardiomyopathy. Survival in the CHD patients was significantly worse than survival in pediatric patients with cardiomyopathy (p < 0.01) and no different from that in adults with cardiomyopathy (p = 0.07). Survival at 3 months was 86% for patients with CHD, 91% for adults with cardiomyopathy, and 94% for children with cardiomyopathy. Conditional survival of patients who survived the initial 3 months post-transplant is shown in Figure 4. Conditional 3-month survival was not significantly different among these groups. Five-year survival was approximately 80%.

<table>
<thead>
<tr>
<th>Abbreviations and Acronyms</th>
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<tr>
<td>CHD = congenital heart disease</td>
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<td>HT = heart transplantation</td>
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<tr>
<td>TGA = transposition of the great arteries</td>
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Figure 1. Age Distribution

Age distribution in 488 patients undergoing heart transplantation for congenital heart disease. CTRD = Cardiac Transplant Research Database; PHTS = Pediatric Heart Transplant Study.
In patients with CHD, Kaplan-Meier survival differed among the diagnostic groups. The patients with TGA had the highest survival and patients with atrioventricular canal defect demonstrated the worst survival: 88% versus 62%, respectively (p = 0.02). Survival was significantly worse with increasing ischemic times (p = 0.02). The mean ischemic time was 228 min for patients having 1 to 2 previous sternotomies and 242 min for patients having >3 sternotomies. An interaction was seen among recipient age, donor age, and ischemic time, with the predicted probability of death increasing in the older recipients with respect to older donor age and longer ischemic time. A 40-year-old recipient who received a 50-year-old donor heart and had a 3-h ischemic time had a 15% probability of death within 1 year, compared with a 40% probability of death within 1 year if that donor’s ischemic time was 5 h.

The results of multivariable analysis for risk factors associated with both early and constant phase death in patients with CHD are shown in Table 2. During the early phase after transplantation, older recipient age at transplant (30 years vs. 10 years) had a 1.5-fold increased risk of death, long ischemic time (300 min vs. 180 min for a 20-year-old donor) had a 1.6-fold increased risk, and older donor age in combination with a long ischemic time (35 years vs. 12 years at 300 min) had a 1.4-fold increased risk.

Having a previous Fontan procedure increased the relative risk of death to 8.6. Figure 5 compares the survival post-transplant of Fontan patients with all other patients with CHD having transplantation. One-year survival was 71% in the Fontan patients and 83% in the non-Fontan CHD patients. Five-year survival was 60% in the Fontan patients and 74% in the non-Fontan patients.

In the constant phase, younger recipient age increased the risk of late death post-transplant. Figure 6 shows a stratified actuarial by age. Patients transplanted between the ages of 6

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Table 1 Major Diagnostic Categories for Congenital Heart Disease Patients Undergoing Heart Transplantation

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n</th>
<th>% (of 488)</th>
</tr>
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<tbody>
<tr>
<td>Single ventricle</td>
<td>176</td>
<td>36</td>
</tr>
<tr>
<td>d-transposition of the great arteries</td>
<td>58</td>
<td>12</td>
</tr>
<tr>
<td>Right ventricular outflow tract lesions</td>
<td>49</td>
<td>10</td>
</tr>
<tr>
<td>Ventricular/atrial septal defect</td>
<td>38</td>
<td>8</td>
</tr>
<tr>
<td>Left ventricular outflow tract lesions</td>
<td>38</td>
<td>8</td>
</tr>
<tr>
<td>t-transposition of the great arteries</td>
<td>39</td>
<td>8</td>
</tr>
<tr>
<td>Complete atrioventricular canal defect</td>
<td>37</td>
<td>8</td>
</tr>
<tr>
<td>Other</td>
<td>53</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>488</td>
<td>100</td>
</tr>
</tbody>
</table>

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Figure 2 Last Major Surgical Operation

Last major surgical procedure performed before heart transplantation (n = 488).

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Figure 3 Post-Transplant Survival: CHD Versus Non-CHD by Age

Kaplan-Meier post-transplant survival of patients with congenital heart disease (CHD) of any age compared with adult and pediatric patients with cardiomyopathy. The vertical bars surrounding the survival estimates represent 70% confidence limits.

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Figure 4 Conditional Survival: CHD Versus Non-CHD by Age

Conditional survival of patient who survived the initial 3 months post-transplant. There is no difference among the 3 groups. The vertical bars surrounding the survival estimates represent 70% confidence limits. CHD = congenital heart disease.
and 12 years had a 28% decline in survival in the 6 to 8 years after transplantation; patients >20 years of age at transplant had similar 1-, 3-, and 5-year survival rates. Other risk factors for mortality in the constant phase included a higher systolic transpulmonary gradient, cytomegalovirus mismatch in a negative recipient at the time of transplant, and an earlier classical Glenn operation.

**Discussion**

This large multicenter study evaluated outcomes after HT in 488 children >6 months of age and adults with CHD and identified risk factors for early and constant phase mortality. The ability to undertake cardiac transplantation with complex CHD has been in evolution.

Transplantation for CHD was first reported in 1967 and involved an infant with complex CHD (4). Multiple subsequent reports have addressed the surgical techniques required for transplantation in this setting (5–9). HT is increasingly considered a treatment option for patients with CHD and end-stage heart failure. According to the registry of the International Society of Heart and Lung Transplantation, children with CHD account for 47% of the pediatric patients undergoing HT (1).

This study demonstrated an early difference in survival between patients with CHD who underwent transplantation compared with pediatric patients with cardiomyopathy. Three-month survival post-transplant was significantly worse in the patients with CHD compared with pediatric patients with cardiomyopathy, but not with adults with cardiomyopathy. Analysis from the International Society of Heart and Lung Transplantation also identified CHD as a risk factor for 1-year mortality, but the finding of increased risk in older recipients and Fontan patients was not shown in that dataset. In our analysis, conditional survival in patients who survived the first 3 months after transplant was no different among the groups, indicating that the increased risk of mortality is likely related to peri-transplant issues. Several single-center studies have identified no increased early risk after transplantation for CHD compared with other conditions (7,10,11). However, the power of these analyses was limited by smaller sample sizes.

Although transplantation for adults with acquired heart disease and end-stage heart failure has become routine, experience with HT in adults with CHD is sparse. As survival among patients with CHD improves, more such patients can be expected to present for consideration for HT as a final treatment option. According to the registry of the International Society of Heart and Lung Transplantation, 3% of adults undergoing HTs have CHD as an indication for transplant (12). Experience with adults and CHD has been varied in both the complexity of patients and the

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative Risk</th>
<th>p Value</th>
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<tbody>
<tr>
<td>Early phase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Older recipient age</td>
<td>1.5</td>
<td>0.02</td>
</tr>
<tr>
<td>Previous Fontan operation</td>
<td>8.6</td>
<td>0.003</td>
</tr>
<tr>
<td>Longer ischemic time</td>
<td>1.6</td>
<td>0.002</td>
</tr>
<tr>
<td>Interaction of donor age and ischemic time</td>
<td>1.4</td>
<td>0.0007</td>
</tr>
<tr>
<td>Higher pre-Tx mean RAP (only in patients without previous Fontan)</td>
<td>2.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Constant phase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Younger recipient age</td>
<td>1.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>Higher systolic transpulmonary gradient</td>
<td>2.0</td>
<td>0.01</td>
</tr>
<tr>
<td>CMV donor, CMV recipient</td>
<td>2.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Previous classical Glenn operation</td>
<td>3.1</td>
<td>0.01</td>
</tr>
</tbody>
</table>

CMV = cytomegalovirus; RAP = right atrial pressure; Tx = transplant.

**Table 2**

Multivariable Analysis for Risk Factors Associated With Both Early Phase and Constant Phase Mortality in Patients With Congenital Heart Disease

![Figure 5 Post-Transplant Survival: Fontan Versus Non-Fontan](image)

Kaplan-Meier survival comparing the survival post-transplant of Fontan patients with all other patients transplanted with congenital heart disease. The **vertical bars** surrounding the survival estimates represent 70% confidence limits.

![Figure 6 Post-Transplant Survival: CHD Versus Non-CHD by Age](image)

Kaplan-Meier post-transplant survival of patients with congenital heart disease (CHD) of any age compared with adult and pediatric patients with cardiomyopathy. The **vertical bars** surrounding the survival estimates represent 70% confidence limits.
reported survival rates (8,13,14). Lamour et al. (15) reported results of 24 adult patients with CHD, one-half of whom had single-ventricle anatomy. Survival in this series was 79% at 1 year and 60% at 5 years. In this small series, there was no anatomic or surgical risk factor that could be identified as predictive of death, although 4 of 5 early deaths were in patients who had single-ventricle anatomy. More recently, Chen et al. (16), from the same institution, reported experience with combined pediatric and adult patients with CHD undergoing HT. There was a significant difference in 30-day mortality between CHD patients and the entire cohort. However, the long-term survival of patients with and without CHD was comparable. Since 1990, 1- and 5-year survivals were 82% and 77%, respectively. The majority of deaths were intraoperative or related to bleeding.

A striking finding in this study was the degree of risk found in HT patients with an earlier Fontan procedure. As the number of patients surviving single-ventricle initial palliation and subsequent Fontan procedure increases, the known propensity for late cardiac failure post-Fontan will likely generate a growing subset of transplant recipients. Although cause of death was not analyzed in this study, one can speculate from other smaller studies why this degree of risk was found in our study. Other studies (8,16–18) and in particular, the Fontan analysis within the Pediatric Heart Transplant database (19), underscores the complexity of these patients. These complexities are not only associated with the technical challenges related to individual anatomy and multiple earlier palliative procedures, but also to difficulty in evaluating pulmonary vascular resistance and an increased propensity for infection and bleeding in Fontan patients.

Pulmonary vascular resistance in many complex CHD patients and Fontan patients is difficult to assess and was not analyzed in this study. Anomalies within the pulmonary vasculature or dual supplies of pulmonary blood flow may make accurate calculations of resistance impossible. In addition, patients with sluggish blood flow to the pulmonary arteries or loss of hepatic blood flow are at risk for microemboli and arteriovenous malformations that may change the distribution of flow to the right and left lung. It may be erroneous to assume that because a Fontan patient is alive, the pulmonary vascular resistance is low enough to tolerate an HT (20).

Bernstein et al. (19) noted Fontan patients had a trend toward increased risk of death from infection: 30% versus 21% in CHD patients and 13% in non-CHD patients. Patients with a failed Fontan and, in particular, those with protein-losing enteropathy, are generally cachetic, edematous, and lymphopenic, which predisposes them to infection. This infection risk is increased by the introduction of immunosuppression immediately after transplantation and may explain the increase in infection seen in Fontan patients after transplantation. A trend toward increased early graft failure, hemorrhage, and technical and operative deaths in these Fontan patients was also noted in this study. In the previously cited study by Lamour et al. (15), 4 of 5 early deaths were in Fontan patients. Three of these patients had significant surgical bleeding, resulting in 2 deaths. The presence of aortopulmonary collaterals in some Fontan patients and vascular adhesions after multiple operations may increase the risk for bleeding. In addition, many Fontan patients had some degree of hepatic dysfunction, which could increase the likelihood of postoperative coagulopathy.

Although recipient preformed antibody data were not available, CHD patients with multiple reoperations and transfusions and the possibility of homograft material being used in some repairs increase the risk of pre-sensitization, which could affect early graft function and increase the likelihood of early graft failure (21,22). Neither database identified whether the surgeons performing HT on these CHD patients were trained congenital cardiac surgeons. One could speculate that this might influence surgical outcomes. In addition, associated genetic disorders are not well captured in the databases. Although this population likely represents a small number of patients, this too may influence outcome after HT. As these databases evolve, inclusion of these data fields would improve our dataset and allow these factors to be analyzed in assessing outcome after transplantation in patients with CHD.

The finding of young recipient age as a risk factor in the constant phase contradicts other studies that suggest superior conditional long-term survival in infants <1 year of age (1). When survival is stratified by recipient age at transplant, patients undergoing transplantation between 6 and 12 years of age have a dramatic decrease in survival 6 to 8 years after surgery. Decline in survival of transplant patients when they reach their teen and early adult years has also been reported by others and is likely related to nonadherence. Late rejection after transplantation is associated with nonadherence and poor outcome (23,24).

Conclusions

HT for patients with CHD is an acceptable and encouraging option for patients with end-stage heart failure. Once out of the initial post-operative period, survival is the same as for patients without CHD. Risk factors for poor outcome are older age at transplantation and a previous Fontan operation. New strategies are needed to neutralize the underlying transplant risks unique to the failing Fontan patient.

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REFERENCES


