Cardiac retransplantation in childhood: Analysis of data from the United Network for Organ Sharing

William T. Mahle, MD,a,b Robert N. Vincent, MD,a,b and Kirk R. Kanter, MD,c

Objective: For children in whom graft failure develops after cardiac transplantation, retransplantation is often considered. Although some centers have reported equivalent results for retransplantation as for primary transplantation, this strategy remains controversial. We sought to examine outcomes after retransplantation in children and to identify risk factors for mortality.

Methods: United Network for Organ Sharing records of heart transplantation for subjects younger than 18 years from 1987 to 2004 were reviewed. Indications for retransplantation and patient characteristics were evaluated. Analysis was performed with proportional hazards regression, controlling for other potential risk factors.

Results: Among the 4227 pediatric heart transplants, there were 219 retransplants. The most common indication for retransplantation was coronary allograft vasculopathy (51%). The mean interval from initial heart transplant to retransplantation was 4.7 ± 3.8 years. Forty-two retransplants (19%) were performed within 180 days of primary transplantation. Survivals at 1, 5, and 10 years after retransplantation were 79%, 53%, and 44%, respectively. In multivariate analysis, retransplantation was associated with significantly higher mortality than primary transplantation (odds ratio 1.67, 95% confidence interval 1.32-2.12, \( P < .001 \)). Patients who underwent retransplantation within 180 days of primary transplantation had a significantly lower 1-year survival than did other retransplant recipients (53% vs 86%, respectively, \( P < .02 \)). Subjects who required mechanical ventilation before retransplantation also had poorer survival (\( P < .03 \)).

Conclusion: Survival after cardiac retransplantation in children is inferior to that after primary transplantation. Although results are acceptable, the impact of retransplantation on the availability of donor hearts requires further consideration.

Heart transplantation plays an important role in the management of children with congenital heart disease and cardiomyopathies. The outcome after pediatric heart transplantation has improved dramatically during the past 20 years, and survival is superior to that reported for adult transplantation.\(^1\,\,^2\) Nonetheless, graft failure occurs in a significant number of children, and the survival half-life in children after heart transplantation is just greater than 12 years.\(^3\) Many centers routinely undertake retransplantation for those children with graft failure. Some single-center reports have suggested that survival after retransplantation is equivalent to that after primary transplantation.\(^4\,\,^5\) Data from adults, however, suggest that retransplantation is associated with significantly poorer outcome than primary transplantation, with fewer than 40% of subjects surviving to 5 years.\(^6\,\,^7\) In this study we examined the data from the United Network for Organ Sharing (UNOS) to analyze the outcome and risk factors for children who undergo retransplantation.
are shown in Table 2. The most common indication for retransplantation was coronary allograft vasculopathy (CAV), accounting for just more than half of the subjects. A significant number of children were also described as having nonspecific graft failure (16%), which in some cases may also have represented CAV. There were 42 subjects (19%) who underwent retransplantation for early primary graft failure (retransplantation within 180 days of primary transplantation). Reported causes of early primary graft failure were primary failure (n = 10), hyperacute rejection (n = 7), nonspecific graft failure (n = 7), acute rejection (n = 7), CAV (n = 2), and other (n = 9).

Patients undergoing retransplantation were more likely to be African American, older, female, allosensitized, and with elevated serum creatinine relative to primary transplant recipients (Table 3). Retransplant recipients had longer waiting times than primary transplant recipients. The median waiting time for retransplant recipients was 37 days.

Retransplantation was associated with poorer overall survival than primary transplantation. The 1-, 5-, and 10-year survivals after retransplantation were 79%, 53%, and 44%, respectively. The 1-, 5-, and 10-year survivals after primary transplantation were 83%, 70%, and 58%, respectively (Figure 1). The survival half-life after retransplantation was 5.6 years, compared with 13.2 years after primary transplantation. When multivariate analysis was undertaken, retransplantation was identified as a significant risk factor for mortality (odds ratio 1.67, 95% confidence interval 1.32-2.12, P < .001). Other variables found to be associated with lower survival were earlier year of transplantation, female sex, African American ethnicity, mechanical ventilation at time of transplantation, congenital heart disease, and older donor age (Table 4). The causes of death after retransplantation were as follows: acute rejection (14%), CAV (14%), infections (13%), nonspecific graft failure (8%), pulmonary disease (7%), primary graft failure (5%), chronic rejection (5%), multiorgan failure (5%), cerebrovascular disease (3%), and all other causes (26%).

We subsequently attempted to identify factors associated with poorer outcome among those subjects who underwent retransplantation. Year of transplantation, need for extracorporeal membrane oxygenation, recipient ethnicity, recipient

<p>| TABLE 1. Variables analyzed for association with survival |</p>
<table>
<thead>
<tr>
<th>Donor</th>
<th>Recipient</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Sex</td>
<td>Year of transplant</td>
</tr>
<tr>
<td>Age</td>
<td>Age</td>
<td>Ischemic time</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>Mechanism of death</td>
<td>Diagnosis</td>
<td></td>
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<tr>
<td>Blood type</td>
<td>Retransplantation</td>
<td></td>
</tr>
<tr>
<td>Clinical infection</td>
<td>ECMO*</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>Mechanical ventilation*</td>
<td></td>
</tr>
<tr>
<td>Inotropic medication*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated creatinine*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRA</td>
<td>Blood type</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Clinical infection*</td>
<td></td>
</tr>
</tbody>
</table>

ECMO, Extracorporeal membrane oxygenation; PRA, panel-reactive antibody. *At time of transplantation.

<table>
<thead>
<tr>
<th>TABLE 2. Indications for retransplantation (n = 219)</th>
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</thead>
<tbody>
<tr>
<td>Acute rejection</td>
</tr>
<tr>
<td>Hyperacute rejection</td>
</tr>
<tr>
<td>Coronary allograft vasculopathy</td>
</tr>
<tr>
<td>Chronic rejection</td>
</tr>
<tr>
<td>Nonspecific graft failure</td>
</tr>
<tr>
<td>Primary failure</td>
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<tr>
<td>Other</td>
</tr>
</tbody>
</table>

Methods
This study was approved by the institutional review board of Children’s Healthcare of Atlanta. Data for this analysis were supplied by UNOS. The data set consisted of the Transplant Candidate Registration form, the Transplant Recipient Registration form, and the Transplant Recipient follow-up form. The follow-up form was administered at repeated intervals. The purpose of the study was to assess the impact of retransplantation on patient survival and to examine recipient and donor-related factors (Table 1) that might influence outcome.

Study Population
This study included all patients younger than 18 years who underwent cardiac transplantation between May 1987 and December 2004. A total of 4227 heart transplants were performed; of these, 219 were retransplants. Subjects undergoing combined heart and lung transplantation were not included in this analysis.

Statistical Analysis
Data are expressed as mean ± SD or median and range as appropriate. Statistical analysis was performed by Fisher exact test, χ² test, Wilcoxon rank sum test, and Student t test. Kaplan-Meier survival curve estimates, log-rank tests to compare survival curves, and Cox proportional hazards model were performed to assess multivariate associations between risk factors and freedom from death. Analysis was performed with STATA version 6.0 (Stata Corporation, College Station, Tex). All P values are 2-sided, and confidence intervals are 95%.

Results
Cardiac retransplantation was performed at a median age of 9.0 years. The mean interval from initial transplantation to retransplantation was 4.7 ± 3.8 years. The ethnic composition of those undergoing retransplantation was as follows: white (n = 132), African American (n = 50), Hispanic (n = 22), Asian (n = 6), mixed (n = 5), American Indian (n = 2), and other (n = 2). The indications for retransplantation

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sex, and age of donor were not associated with survival after retransplantation. Rather, the need for mechanical ventilation at time of retransplantation and early primary graft failure (retransplantation within 180 days of initial transplant) were identified as risk factors for mortality (P < .03 and P < .02, respectively). The 1-year survival for those with early primary graft failure was only 53%, compared with 86% for those who had late primary graft failure (Figure 2). After exclusion of those with early primary graft failure, the 1-year survival for retransplantation did not differ from that of primary transplantation (86% vs. 83%, respectively). However, by 5 years the survival was significantly worse for the retransplant recipients with late primary graft failure compared than for primary transplant recipients (55% vs 70%, P<.001).

**Discussion**

To date, more than 4000 children have undergone heart transplantation in the United States. Intermediate-term survival has improved considerably, although the survival half-life in children is less than 13 years. Retransplantation is considered a reasonable alternative for these children. This study, however, suggests that survival after retransplantation in children is significantly worse than that after primary cardiac transplantation.

A number of institutions have reported promising results for pediatric retransplantation. Dearani and colleagues reported that the 3-year survival for children undergoing retransplantation was 82% and was not significantly different from that of those undergoing primary retransplantation (77%). From our own institution, we reported that 3-year survivals were also similar between retransplantation and primary transplantation (78% vs 73%, respectively). Equivalent survivals in the two groups were noted even though the retransplant recipients were more likely to be UNOS status 1 and to be cared for in the intensive care unit.

In an earlier study, Michler and colleagues reported a 3-year survival of 47% in a cohort of 17 children undergoing retransplantation. In this series as well, the mean graft survival for retransplantation was similar to that of primary transplantation. Conversely, in a recent analysis of the International Society for Heart and Lung Transplantation data.

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**TABLE 3. Patient characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Retransplantation (n = 219)</th>
<th>Primary transplantation (n = 4008)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age at transplantation (y)</td>
<td>9 (0-17)</td>
<td>3 (0-17)</td>
<td>.001</td>
</tr>
<tr>
<td>Female recipient (No.)</td>
<td>113 (51.5%)</td>
<td>1713 (42.7%)</td>
<td>.01</td>
</tr>
<tr>
<td>African American recipient (No.)</td>
<td>50 (22.8%)</td>
<td>667 (16.6%)</td>
<td>.02</td>
</tr>
<tr>
<td>Inotropic medication (No.)*</td>
<td>84 (38.3%)</td>
<td>1559 (38.9%)</td>
<td>.86</td>
</tr>
<tr>
<td>UNOS status 2 (No.)*</td>
<td>62 (29.5%)</td>
<td>1111 (27.8%)</td>
<td>.98</td>
</tr>
<tr>
<td>Elevated serum creatinine (No.)*</td>
<td>16 (8.5%)</td>
<td>87 (3.3%)</td>
<td>.001</td>
</tr>
<tr>
<td>Mechanical ventilation (No.)*</td>
<td>53 (24.2%)</td>
<td>787 (19.6%)</td>
<td>.10</td>
</tr>
<tr>
<td>Extracorporeal membrane oxygenation (No.)*</td>
<td>14 (6.4%)</td>
<td>181 (4.5%)</td>
<td>.26</td>
</tr>
<tr>
<td>PRA ≥20% (No.)</td>
<td>45 (23.6%)</td>
<td>228 (6.9%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Time on waiting list (d)</td>
<td>37 (1-1218)</td>
<td>29 (1-1842)</td>
<td>.04</td>
</tr>
</tbody>
</table>

UNOS, United Network for Organ Sharing; PRA, Panel-reactive antibody. *At time of transplantation. †Serum creatinine ≥2 mg/dL.

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**Figure 1.** Kaplan-Meier survival plot after transplantation stratified by primary transplantation (n = 4008) versus retransplantation (n = 219).

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**TABLE 4. Risk factors for death after transplantation (n = 4227)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio</th>
<th>95% Confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retransplantation</td>
<td>1.67</td>
<td>1.32-2.12</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Female recipient</td>
<td>1.18</td>
<td>1.06-1.32</td>
<td>.003</td>
</tr>
<tr>
<td>Later year of transplant</td>
<td>0.96</td>
<td>0.95-0.98</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Extracorporeal membrane oxygenation*</td>
<td>1.92</td>
<td>1.50-2.48</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mechanical ventilation*</td>
<td>1.30</td>
<td>1.13-1.50</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>African American recipient</td>
<td>1.85</td>
<td>1.44-1.89</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>1.32</td>
<td>1.18-1.50</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Older donor age (effect/year)</td>
<td>1.009</td>
<td>1.004-1.01</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*At the time of transplantation.
Lung Transplantation. Radovancevic and colleagues re-
Research Database and the International Society of Heart
was noted in adults in an analyses of the Cardiac Transplant
retransplantation for late graft failure. A similar association
alive at 1 year, compared with 86% for those undergoing
primary graft failure who underwent retransplantation were
reported that 1-year survival was less than 50% when retrans-
plantation was still significantly less than that for
primary transplantation. The 5-year survival of patients
undergoing retransplantation for late primary graft failure
with indications such as CAV or late nonspecific graft
failure was only 55%, significantly less than that of patients
undergoing primary transplantation during the same era
(70%). The reasons for poorer survival after retransplanta-
tion may be manifold. Children listed for retransplantation
are more likely to be allosensitized. More than 20% of
retransplant recipients in this series had pretransplantation
panel-reactive antibody (PRA) level greater than 20%. Al-
though our analysis did not find high PRA to be associated
with mortality, a recent report from the Pediatric Heart
Transplant Study Group demonstrated that elevated pre-
transplantation PRA was associated with lower survival and
shorter time to first rejection. In addition, other poorly
defined immunologic factors that may have predisposed
toward initial graft loss could lead to the loss of the retrans-
planted graft. Finally, social and environmental factors,
such as medication noncompliance, might be more common
among patients who undergo retransplantation.

An extensive number of recipient and donor factors that
affect survival after pediatric heart transplantation have
been identified. These risk factors include recipient congen-
ital heart disease, recipient elevated PRA, recipient African
American ethnicity, and donor factors such as older age. Because of the relatively small number of children who
underwent retransplantation, analysis of potential risk fac-
tors within this subgroup of retransplant recipients was
limited. We did find that pretransplantation mechanical ven-
tilation was associated with poorer survival. Unlike studies
of adults undergoing retransplantation, we did not find that
later year of retransplantation was associated with improved
survival. It remains to be seen whether improvements in
immunosuppression will result in improved retransplanta-
tion outcomes in coming years.

Given that graft survival after retransplantation is inferi-
or to that after primary transplantation, questions as to the
appropriateness of retransplantation arise. Although wait-
ing times for pediatric heart transplants are less than for
adults, donor organ availability remains a concern. The
competition for such organs may increase in coming years,
because the increased number of pediatric heart transplants
in the early 1990s is likely to result in an increased number
of children, adolescents, and young adults who would be
candidates for retransplantation. It is possible that listing for
retransplantation might be deferred in some cases, particu-

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**Figure 2.** Kaplan-Meier survival plot for patients undergoing re-
transplantation (n = 219) stratified by early (<180 days from
initial transplantation) or late (>180 days from initial transplan-
tation) primary graft failure.
larly children with CAV. Initial reports suggested that the outcome for children diagnosed with CAV was quite poor and that retransplantation would offer the best chance for survival.\textsuperscript{13} Recent reports, however, have suggested improved outcomes once CAV is recognized in children.\textsuperscript{14} In addition, agents such as sirolimus and the use of coronary artery stenting may offer an option to halt or reverse the progression of CAV.\textsuperscript{15-18} Given these findings and the stated limitations of retransplantation, medical interventions may offer an alternative to or a means of delaying the need for retransplantation for subjects in whom CAV develops.

In summary, retransplantation results in reasonable survival for children, although outcomes are inferior to those of primary transplantation. When retransplantation is performed in the setting of early primary graft failure, the results are quite poor, and the appropriateness of this strategy is questionable in light of the limited donor supply. Further data regarding the natural history of CAV and nonspecific graft failure will help in understanding the risks and benefits of retransplantation in children.

We thank Ms Cynthia S. Cors from the UNOS Research Department for assisting in data preparation.

References