Duration of Graft Cold Ischemia Does Not Affect Outcomes in Pediatric Heart Transplant Recipients

Albertus M. Scheule, MD; Grenith J. Zimmerman, PhD; Joyce K. Johnston, RN; Anees J. Razzouk, MD; Steven R. Gundry, MD; Leonard L. Bailey, MD

Background—Utilizing donor hearts with prolonged graft ischemia may extend the donor pool.

Methods and Results—The medical records of 363 infants and children, aged 1 day to 17 years, transplanted at Loma Linda University between November 1985 and March 2001, were retrospectively reviewed. Fourteen children received organs with prolonged ischemic times (>8 hours)(PIT) compared with 14 with short ischemic times (≤90 minutes)(SIT). There were no significant differences when comparing donors for gender, age, weight, cause of death, or duration of cardiopulmonary resuscitation. Preoperative donor shortening fraction (%), as determined by echocardiography, was significantly higher in the SIT group (44.5 versus 36.5%; P=0.006). There were no significant differences between PIT and SIT recipients when comparing age at transplant, weight at transplant, waiting time, weight mismatch, postoperative days on ventilator, duration of inotropic support, and hospital stay. Cardiopulmonary bypass time was significantly longer in the PIT group (140.5 versus 80.5 minute; P=0.001). Median length of follow-up for both groups was approximately 5 years. Five grafts were lost in the PIT group; 7 were lost in the SIT group, with 1 early graft loss in each group. Significant posttransplant coronary artery disease was diagnosed in 2 recipients in each group (PIT: 80 and 42; SIT: 84 and 67 months posttransplant). There was no significant difference between groups in actuarial graft survival. Number of rejection episodes and hospital readmissions during the first posttransplantation year did not differ significantly between groups.

Conclusion—Late outcomes were not adversely affected by donor hearts preserved by single dose cold crystalloid cardioplegia with greater than 8 hours of cold ischemia. (Circulation. 2002;106[suppl I]:I-163-I-167.)

Key Words: pediatrics • transplantation • surgery • ischemia

The shortage of cardiac allografts is a major limiting factor for heart transplantation. In an effort to maximize the donor supply, several centers, including ours, have expanded conventional limits for ischemic times, with good early graft survival. In adult heart transplantation, there is evidence that ischemic times greater than 4 hours affect late survival if donor age is greater than 50 years. In a previous study at this institution, we looked at ischemic times above and below 4 hours with no apparent difference in outcomes between groups. In this study, we compared early and late outcomes of children receiving grafts with extremely prolonged preservation time (more than 8 hours) with children receiving grafts from local donors with preservation times of 90 minutes or less.

Methods

The medical records of 363 infants and children, aged 1 day to 17 years, who underwent primary heart transplantation at Loma Linda University between November 1985 and March 2001, were retrospectively reviewed. Fourteen children receiving organs with prolonged ischemic times (PTI) (>8 hours; median 503, range 481 to 608 minutes) were compared with 14 children with short ischemic times (SIT) (≤90 minutes; median 76, range 49 to 90 minutes). These children represent all patients in our experience within these extreme parameters of long and short ischemic times. Approval for this study was obtained from the Institutional Review Board (IRB) at Loma Linda University.

Data Collection

Hospital charts, echocardiographic data, and the transplantation database were reviewed. Recipient and donor demographic variables included age, gender, and weight at transplantation. Other donor variables recorded were cause of death, duration of cardiopulmonary resuscitation, normal or abnormal electrocardiogram (EKG), duration of inotropic support and cardiac function as evidenced by echocardiography. Other recipient variables were donor/recipient weight mismatch, waiting time, cardiopulmonary bypass time, and circulatory arrest time. Postoperative variables included duration of mechanical ventilation, duration of inotropic support, length of postoperative hospital stay, number of rejection episodes, hospital readmissions, and cause of death. Donor and recipient data are summarized in Tables 1 and 2, respectively. Techniques of donor procurement have been previously described. Gravity fed Roe’s solution was utilized for cardioplegia consisting of NaCl 27 mEq/, KCl 20 mEq/, Solu-Medrol 250 mg/, MgSO4 3mEq added to 1 L of D5W with a pH adjusted to 7.40. No additional cardioplegia was utilized.
Nonparametric statistics were used because of the small sample sizes and the skewed variable distributions. The groups were compared using chi-square tests for qualitative variables and Mann-Whitney tests for quantitative variables. Multivariate analysis involving risk factors was not possible because of small sample size.

**Results**

**Donors**

Donor information for the 2 groups is summarized in Table 2. Donors for the 2 groups did not differ in terms of gender ($P=0.71$), cause of death ($P=0.67$) or normal/abnormal EKG ($P=0.32$). All abnormal EKGs showed a prolonged QT-interval. Donors for the PIT group had a median age of 33.4 months (0.1 to 123 months) and median weight of 13 kg (3.3 to 26 kg), while donors for the SIT group had a median age of 15.5 months (0 to 100 months) and median weight of 9.1 kg (2.1 to 30 kg). These differences were not statistically significant because of the extreme variability within each group. Donors in the PIT group required a median of 2.5 minutes (0 to 40 minutes) of cardiopulmonary resuscitation, while those in the SIT group required a median of 0 minutes (0 to 120 minutes). Shortening fraction (%) as determined by echocardiography immediately before organ procurement was significantly higher in the SIT group (44.5% versus 36.5%; $P=0.006$). In both groups, the majority of donors (8/14 for PIT; 9/14 for SIT) required inotropic support (dopamine) for a median of 24 hours (PIT: 8 to 48 hours; SIT: 12 to 96 hours). In the PIT group, 2 donors did not require inotropic support; 4 required a combination of dopamine and...
dobutamine. In the SIT group 4 donors had no inotropic support and 1 required a combination of dopamine and dobutamine.

**Recipients**

The PIT group, 7 males and 7 females, had a median age at transplantation of 3.8 months (0.3 to 192.1 month), median weight at transplantation of 4.7 kg. (2.8 to 33.0 kg), and a median waiting time of 19.3 days (3.4 to 260.8 days). The SIT group, 11 males and 3 females, had a median age at transplantation of 1.9 months (0.2 to 77.5 months), median weight at transplantation of 4.5 kg. (2.2 to 15.9 kg), and a median waiting time for an organ of 10.3 days (0.8 to 57.5 days). There were no statistically significant differences between the groups in terms of recipient gender, age, median weight or median waiting time (see Table 1). The median ischemic time for the PIT group was 503 minutes (481 to 608 minutes); the median ischemic time for the SIT group was 76 minutes (49 to 90 minutes). Median weight mismatch for both groups was approximately 0.55. The PIT group had a significantly longer duration of cardiopulmonary bypass than the SIT group (140.5 minutes versus 80.5 minutes; \( P < 0.001 \)); the circulatory arrest time between the groups, however, was not significantly different (see Table 1).

**Graft Survival**

Figure 1 compares the actuarial graft survival for the 2 groups. There was no significant difference between groups at 5 years (PIT 64%; SIT 62%). There was 1 cardiac related early death in each group. The early cardiac related death (4th post-operative day) in the PIT group was attributed to a technical management failure, caused by an oversized donor heart (donor’s weight more than 3 times recipient’s weight) and sepsis which resulted in graft failure. In the SIT group, the operative cardiac related death at 14 days posttransplant was the result of acute graft failure in the face of fixed pulmonary hypertension. Later graft loss in the PIT group was related to presumed posttransplant coronary artery disease (no autopsy) in 1 child at 9 years; chronic rejection with posttransplant coronary artery disease at 3.4 years; acute rejection at 6 months posttransplant and pulmonary hemorrhage following presumed rejection at 14 months posttransplant. Later graft loss in the SIT group was caused by acute rejection at 22 months; posttransplant coronary artery disease at 7 years. There were 2 cases of posttransplant lymphoproliferative disease at 21 months and 8.3 years. In addition, there was 1 early noncardiac death (12th posttransplant day) because of a ruptured duodenal ulcer. These data are summarized in Table 3.

### Table 2. Comparison of Donor Information by Ischemic Time Group

<table>
<thead>
<tr>
<th>Ischemic Time</th>
<th>Donor gender</th>
<th>Donor cause of death</th>
<th>EKG</th>
<th>Donor age (months)</th>
<th>Donor weight (kg)</th>
<th>Cardio-pulmonary resuscitation time (min)</th>
<th>Shortening fraction by echocardiography</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤90 Min</td>
<td>Male 7 (50)</td>
<td>Anorexia 6 (43)</td>
<td>Normal 12 (92)</td>
<td>15.5 (0, 100)</td>
<td>9.1 (2.1, 30)</td>
<td>0 (0, 120)</td>
<td>44.5 (35, 68)</td>
</tr>
<tr>
<td></td>
<td>Female 7 (50)</td>
<td>Cerebrovascular 1 (7)</td>
<td>Abnormal 1 (8)</td>
<td>33.4 (1, 123)</td>
<td>13 (3.33, 26)</td>
<td>2.5 (0, 40)</td>
<td>36.5 (12, 47)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Head trauma 7 (50)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>≥8 hrs</td>
<td>Male 8 (67)</td>
<td>Anorexia 4 (40)</td>
<td>Normal 11 (79)</td>
<td>33.4 (1, 123)</td>
<td>13 (3.33, 26)</td>
<td>2.5 (0, 40)</td>
<td>36.5 (12, 47)</td>
</tr>
<tr>
<td></td>
<td>Female 4 (33)</td>
<td>Cerebrovascular 2 (20)</td>
<td>Abnormal 3 (21)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Chi square tests.
†Independent t-test.

Comparison of cardiac graft survival between pediatric grafts with short (≤90 min) versus those with prolonged (≥8 hours) cold ischemic times. There is no significant difference in graft survival to 5 years.
TABLE 3. Cause of Death by Ischemic Time Group

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Time Between TX and Death (days/ys)</th>
<th>Autopsy</th>
<th>Cause of Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short ischemic time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>14</td>
<td>Yes</td>
<td>Acute graft failure (pulmonary hypertension)</td>
</tr>
<tr>
<td>2</td>
<td>46</td>
<td>Yes</td>
<td>Infection (pneumonia)</td>
</tr>
<tr>
<td>3</td>
<td>667/1.8</td>
<td>Yes</td>
<td>Acute rejection</td>
</tr>
<tr>
<td>4</td>
<td>636/1.7</td>
<td>Yes</td>
<td>Post-transplant-lymphoproliferative disease</td>
</tr>
<tr>
<td>5</td>
<td>3062/8.4</td>
<td>Yes</td>
<td>Post-transplant-lymphoproliferative disease</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>Yes</td>
<td>Ruptured duodenal ulcer</td>
</tr>
<tr>
<td>7</td>
<td>2592/7.1</td>
<td>Yes</td>
<td>Acute rejection, post-transplant coronary artery disease</td>
</tr>
<tr>
<td>Prolonged ischemic time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>Yes</td>
<td>Acute graft failure (oversized donor heart)/sepsis</td>
</tr>
<tr>
<td>9</td>
<td>3304/9.1</td>
<td>No</td>
<td>Presumed post-transplant coronary artery disease</td>
</tr>
<tr>
<td>10</td>
<td>1252/3.4</td>
<td>Yes</td>
<td>Chronic rejection, Posttransplant coronary artery disease</td>
</tr>
<tr>
<td>11</td>
<td>204</td>
<td>Yes</td>
<td>Acute rejection</td>
</tr>
<tr>
<td>12</td>
<td>438/1.2</td>
<td>Yes</td>
<td>Pulmonary hemorrhage after presumed rejection</td>
</tr>
</tbody>
</table>

Discussion

Heart transplantation is limited by the shortage of donors. To maximize the use of this limited resource, organs are frequently procured over long distances. Two retrospective studies from the pediatric transplantation group at Loma Linda University have analyzed myocardial function using echocardiographic measurements as well as assessing myocardial damage by cardiac myosin light chain efflux. Patients who received donor hearts with long ischemic times demonstrated diminished cardiac function in the first postoperative week, with functional recovery after the second week. Serum levels of cardiac myosin light chain were higher during the first posttransplant week in patients who received donor hearts with prolonged ischemia; significant differences were not evident beyond the first posttransplant week in patients with either long or short graft ischemia. In both studies, long graft ischemic time was defined as more than 4 hours and short ischemic time was defined as less than 4 hours. The influence of graft ischemic time is controversial in the adult cardiac transplantation population. Multicenter studies have shown that prolonged ischemic time has a negative effect on early survival. Single center studies reported that short and long term outcomes were not adversely affected by graft ischemic times longer than 4 hours.

In this study, we focused on the limits of graft ischemic time, comparing recipients with ischemic times of more than 8 hours with those less than 90 minutes. Accepting prolonged graft ischemic times has permitted organ procurement throughout the Northeast United States and into Nova Scotia, Canada. In the Southeast, procurement has included Puerto Rico. Loma Linda University is located in the Southwest of the United States. We found no difference in the outcome of the 2 groups. Interestingly, the length of inotropic postoperative support did not differ between groups. Only the duration of cardiopulmonary bypass was longer in patients receiving a graft with long ischemic time; this was because of planned longer reperfusion time. We can only speculate as to why extremes of pediatric graft cold ischemic times have not appeared to jeopardize early or late outcomes. While there were no differences in donor-recipient weight ratio between the PIT and SIT groups, in general, donors were larger and older than recipients in both groups. These donor hearts may make up in stroke volume what is lost acutely in contractility after prolonged cold ischemia. Another possible factor is that it is standard practice, at our institution, for a senior cardiac surgeon to accompany procurement of all donor hearts. This is done to ensure a smooth procurement and transition of the graft from donor to recipient.

Several investigators have reported the central pathogenic role of ischemia in cardiac allograft vasculopathy. Ischemia induced endothelial cell injury may induce chronic rejection. Knight and colleagues demonstrated in an animal model that the immunological process of chronic vasculopathy is accelerated by the ischemic insult to the allograft. Ott and coworkers demonstrated in a clinical study, which compared patients receiving allografts from high risk donors to those from low-risk donors, that the early and late mortality did not differ between these groups. However, there was a higher incidence of posttransplant vasculopathy in the high-risk group. In the present study, we found no evidence of increased incidence of coronary artery disease as seen by angiography in either of these groups. At our institution, routine surveillance for posttransplant coronary artery disease involves annual coronary angiography in all patients with intravascular ultrasonography in children older than 6 years of age. Five-year actuarial graft survival for all children (n=363) who received heart transplants at Loma Linda University is 74% (Personal communication with Richard E. Chinnock, MD). Neither group in this study achieved this result (PIT: 64%; SIT: 62%). Donor organs with long ischemic time had significantly decreased shortening fractions as revealed by echocardiographic examination before procurement.

Our study was limited by the small number of patients in each group, weakening the power of the statistical tests.
In summary, early and late recipient outcomes were not adversely affected by donor hearts preserved by single dose cold crystalloid cardioplegia with greater than 8 hours of cold ischemia. Organ donation and distribution, therefore, becomes a national and international resource unencumbered by limitations of local and regional networks. Long distance procurements in pediatric heart transplantation may increase the utilization of all available donor organs.

References
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