Marginal Cardiac Allografts Do Not Have Increased Primary Graft Dysfunction in Alternate List Transplantation

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Background—Clinical success with modern heart transplantation (HT) has led to the development of an alternate list (AL) HT strategy, matching marginal cardiac allografts with recipients who do not meet standard criteria for HT. Marginal allografts may be at an increased risk for primary graft dysfunction (PGD), the leading cause of early mortality after HT. The incidence of PGD in AL HT relative to standard list (SL) HT has not been evaluated, and may contribute to the greater mortality associated with AL HT. The objective of this study was to determine the incidence of and predictors for PGD.

Methods and Results—A retrospective analysis was performed on 260 consecutive adult patients undergoing either SL HT (n=207) or AL HT (n=53) at our institution from 1/2000 to 1/2005. PGD was defined by requirement for mechanical circulatory support immediately post-HT or more broadly as the need for either mechanical support or high-dose inotrope (epinephrine ≥0.07 μg/kg/min). Donor hearts allocated to AL recipients were turned down for SL HT for reasons that included coronary disease, left ventricular dysfunction or hypertrophy, and high-dose inotropic requirement. AL HT recipients were significantly older, with a higher proportion of diabetes mellitus and ischemic cardiomyopathy. Both groups experienced a similar incidence of significant rejection, but overall mortality was higher in the AL HT group. The incidence of PGD did not differ between AL and SL HT recipients. Pre-transplant VAD and prolonged total ischemic times (≥4.5 hours) were independent predictors of PGD.

Conclusion—Select marginal donor hearts used in AL HT do not have an increased incidence of PGD. Pre-transplant VAD and prolonged ischemic times are more important determinants of PGD. These data support continued aggressive utilization of marginal donor hearts in AL HT. (Circulation. 2006;114[suppl I]:I-27–I-32.)

Key Words: heart-assist device ■ heart failure ■ surgery ■ marginal donors ■ primary graft dysfunction ■ transplantation

Primary graft dysfunction (PGD) after cardiac transplantation is a poorly understood complication. Reports have cited an incidence of complete allograft failure occurring acutely in five to ten percent of heart transplant recipients. Importantly, this condition represents the most common cause of early mortality, accounting for 40% of deaths occurring during the first thirty postoperative days. Elements which may contribute to this complication include: intrinsic donor organ dysfunction, preservation injury, right heart dysfunction related to increased pulmonary vascular resistance and humoral, or non specific inflammatory mediated, graft injury. Although risk factors which may predict PGD have not been characterized, imperfect donor organs are frequently not utilized due to fear of this unfortunate complication.

Given the donor organ shortage and prolonged waiting times, aggressive cardiac transplantation centers have accepted donor organs with a variety of deficiencies. These deficiencies generally relate to the structure or the function of the heart in the donor prior to harvest. Some of these deficiencies are probably reversible conditions which may improve in the recipient; such potentially reversible conditions include decreased LV systolic function, increased inotrope requirement and even left ventricular hypertrophy (LVH). Other conditions are irreversible and would include coronary artery disease or structural valve lesions. Utilization of such marginal donor hearts has varied from one transplant center to another. Our institution has adopted an alternate list strategy in which recipients who do not meet standard transplant criteria are coupled to marginal donor organs.

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The most typical recipient characteristic for the alternate list is advanced age. Hearts accepted for recipients on the alternate list are turned down by all other centers for the standard transplant recipient list. We recently reported reduced intermediate survival for recipients on the alternate list versus the standard list. In this report, we examine the incidence of PGD for standard list (SL) versus alternate list (AL) transplantation. We sought to determine whether the AL strategy was an independent predictor of PGD by examining factors felt to influence early graft function in a multivariate analysis.

Methods

An alternate list protocol was initiated at our center in January 2000. A retrospective analysis was performed on 260 consecutive adult patients undergoing either SL (n=207) or AL (n=53) heart transplantation at Duke University Medical Center from January 2000 to January 2005. Patients were considered for the alternate list if they had been turned down for cardiac transplantation based on standard criteria (Table 1). All donor organs allocated to AL recipients were had been turned down for cardiac transplantation based on standard donor organ was deemed unsuitable for use in standard heart transplantation for reasons that included coronary disease, left ventricular dysfunction or hypertrophy, high-dose inotropic requirement, positive hepatitis serologies, and/or high-risk donor behaviors (Table 1). Donor left ventricular dysfunction was defined via transthoracic echocardiography demonstrating left ventricular ejection fraction ≤45%. High inotrope requirement for the donor was defined as a sustained need for dopamine ≥10 μg/kg/min. High risk donor behavior was defined as intravenous drug abuse and/or unprotected sex with multiple partners, eg, prostitution. The size mismatch used to define a smaller donor organ was ≥20% reduction in donor versus recipient body surface area. All patients transplanted in AL group provided written informed consent to be transplanted with a marginal donor heart. For the purposes of this analysis, patients receiving heart transplantation on the alternate list during the same time period were used as the control group. Protocols for bridging to transplant (with ventricular assist devices or inotropes) and post transplant care (immunosuppression and rejection surveillance) were the same for both groups. Pediatric patients (age <16 years) and those receiving multi-organ transplants were excluded.

A uniform method of preservation was applied for all donor hearts and consisted of 1 L of cold (4°C) University of Wisconsin solution given antegrade and cold storage (4°C) during transport. During implantation, a single dose of cold blood cardioplegia was also administered for all cases. The implantation technique was bicaval with moderate systemic hypothermia (28°C). A total of 5 donor allografts were identified with single vessel CAD, defined as coronary stenosis ≥75%. In 3 of the 5 cases, the CAD was deemed severe enough to be flow-limiting and thus a concurrent single-vessel coronary artery bypass graft (CABG) of the left anterior descending coronary artery was performed at the time of the heart transplant procedure. Need for post-transplant mechanical or inotropic support was determined by the surgeon and anesthesiologist after a period of adequate reperfusion; this decision was based on intraoperative TEE, visualization of the heart, and hemodynamics.

Data were collected from the medical record by chart review. The study protocol was approved by the Duke University Institutional Review Board. Survival data are 100% complete as of October 2005. Continuous variables were described using means and standard deviations, and dichotomous variables were described as percentages. Baseline characteristics were compared using student’s t-test for continuous variables and likelihood ratio Chi-square test for categorical variables. Non-normally distributed continuous variables were analyzed using non-parametric methods (Wilcoxon rank sum test). Surviving patients were censored at their last known follow-up. Survival data were analyzed using the Kaplan-Meier method and generated survival curves were compared using log-rank test.

PGD was defined by requirement of high-dose inotrope (epinephrine ≥0.07 μg/kg/min) and/or mechanical circulatory support immediately after transplantation. While inotropic support with either dobutamine or milrinone is routinely employed post-transplant at our institution, high dose epinephrine is only utilized for significant graft dysfunction. Patients with PGD were stratified into (1) those that needed only high dose epinephrine support and (2) more severe PGD necessitating some form of mechanical circulatory support. A Cox proportional hazards model was used to determine predictors of PGD requiring mechanical support as well as PGD requiring mechanical or high dose inotropic support. A probability value ≤0.05 was considered statistically significant for all analyses. The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Compared with SL patients, recipients in the AL group were significantly older, with a greater proportion of ischemic cardiomyopathy and pre-transplant diabetes mellitus (Table 2). No intergroup differences were noted with regards to pre-transplant PRA status, prior cardiac surgery, VAD, or wait-list time. The duration of pre-transplant VAD support was significantly reduced in the AL group. Mean total ischemic time was similar for the two groups. The mean donor age was greater for the AL patients. No donor or recipient gender differences were observed between the two groups.

The most common recipient characteristics for assignment to the AL included advanced age, followed by diabetes mellitus with end organ dysfunction (Table 1). Additional AL recipient characteristics included positive hepatitis serologies, peripheral vascular disease, chronic renal insufficiency, and prior stroke with residual deficit. The reasons that led the AL allografts to be turned down for standard transplant included...
coronary artery disease, left ventricular dysfunction, and LVH (Table 1). A significant proportion (19/53) of the AL allografts had no anatomic or functional abnormalities and were turned down for standard transplant due to positive donor hepatitis serologies and/or high risk behaviors.

Both groups experienced an equivalent frequency of acute cellular rejection (ISHLT ≥3a), occurring in 36% of SL patients and 38% of AL patients (P=0.81). Incidence of acute humoral rejection (deposition of complement and Ig on pathologic analysis) was also similar for SL (3%) and AL (9%) patients (P=0.06). Overall survival was greater among SL heart transplant patients (P=0.003, data not shown). However, 30-day (99% versus 96%, P=0.27) and 1-year (90% versus 93%, P=0.14) survival for standard versus alternate list patients were not significantly different.

The incidence of PGD did not significantly differ between SL and AL groups (23% for SL, 26% for AL, P=0.48; Figure 1). There was no difference regardless of whether PGD was defined as need for mechanical support, high dose inotropic support alone, or either mode of treatment (Figure 2). AL recipients of donor allografts with a functional / anatomic abnormality demonstrated a slightly increased incidence of PGD requiring mechanical support compared with SL patients, but this did not reach statistical significance. The exclusion of allografts from only seropositive and/or high risk donors yielded similar incidences of PGD (Figure 1).

Occurrence of PGD had a significantly negative impact on 30-day (Figure 2A), 1-year (Figure 2B), and long-term (Figure 2C) survival in both patient groups. In the absence of PGD, no deaths were observed during the first 30-days post-transplant in either SL or AL recipients. In patients with PGD, 30-day mortality increased to 14% and 16% for SL and AL groups, respectively (Figure 2A). The deleterious effect of PGD on 1-year survival was more severe, leading to decreases from 94% to 79% in SL recipients and from 92% to 57% in AL recipients (Figure 2B).

Cox Proportional Hazards Analysis was utilized to determine predictors of PGD. By univariate analysis, only one clinical variable, total ischemic time, was predictive of the more broadly defined PGD (data not shown). In evaluating PGD necessitating mechanical circulatory support, pre-transplant VAD and total ischemic time were independently predictive by univariate and

### TABLE 2. Preoperative Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Standard List, n=207</th>
<th>Alternate List, n=53</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient age</td>
<td>50±11</td>
<td>61±10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recipient female (%)</td>
<td>53 (28)</td>
<td>8 (17)</td>
<td>0.15</td>
</tr>
<tr>
<td>Diagnosis (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic cardiomyopathy</td>
<td>86 (42)</td>
<td>36 (68)</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td>Idiopathic cardiomyopathy</td>
<td>91 (44)</td>
<td>14 (26)</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Other</td>
<td>30 (14)</td>
<td>3 (6)</td>
<td>0.07</td>
</tr>
<tr>
<td>Pretransplant diabetes mellitus (%)</td>
<td>50 (24)</td>
<td>22 (43)</td>
<td>0.007</td>
</tr>
<tr>
<td>Elevated PRA status (%)</td>
<td>28 (14)</td>
<td>5 (9)</td>
<td>0.38</td>
</tr>
<tr>
<td>Previous cardiac surgery (%)</td>
<td>90 (43)</td>
<td>22 (42)</td>
<td>0.76</td>
</tr>
<tr>
<td>Pulmonary vascular resistance, Wood units</td>
<td>2.9±1.6</td>
<td>2.4±1.1</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td>Wait-List Time, days</td>
<td>179±391</td>
<td>123±263</td>
<td>0.22</td>
</tr>
<tr>
<td>Pretransplant VAD (%)</td>
<td>54 (26)</td>
<td>10 (19)</td>
<td>0.28</td>
</tr>
<tr>
<td>Duration of VAD support, days</td>
<td>66±59</td>
<td>38±30</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td>Total ischemic time, min</td>
<td>205±46</td>
<td>221±49</td>
<td>0.15</td>
</tr>
<tr>
<td>Donor age</td>
<td>34±14</td>
<td>39±13</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Donor female (%)</td>
<td>75 (38)</td>
<td>17 (32)</td>
<td>0.53</td>
</tr>
</tbody>
</table>

PRA indicates panel reactive antibody panel; VAD, ventricular assist device.

Figure 1. Incidence of primary graft dysfunction following cardiac transplantation in standard and alternate list patients. Alternate minus Seropositive excludes marginal donors due only to positive hepatitis serologies and/or high risk donor behaviors. No significant differences were noted between standard and alternate list patient groups.

![Percentage of PGD](http://example.com/figure1.png)

Figure 1. Incidence of primary graft dysfunction following cardiac transplantation in standard and alternate list patients. Alternate minus Seropositive excludes marginal donors due only to positive hepatitis serologies and/or high risk donor behaviors. No significant differences were noted between standard and alternate list patient groups.
multivariate analysis (Table 4). Importantly, alternate status was not predictive of PGD using either definition; even when only alternate donors with anatomic or functional abnormality were considered (Alternate minus Seropositive/High Risk Donor), AL was not predictive of PGD. Other variables which did not significantly predict PGD included prior cardiac surgery, elevated PRA status, PVR, recipient female sex, donor female sex, donor age, and wait list time.

**Discussion**

PGD is the most important postoperative complication associated with heart transplantation. PGD is not well characterized or defined in the literature and etiology is often unclear. Prior reports have not attempted to define clinical predictors. In this report, PGD was defined as the need for either mechanical circulatory support or high dose inotropic infu-
Univariate evidence of primary graft failure was 9.7% with only a 12% aggressive use of inotropic and mechanical support in heart secondary to perhaps a lower threshold at our institution for over, incidence of PGD may appear higher in this series

More-than the higher incidence of PGD observed in this study (23% for SL, 26% for AL recipients) relative to other series.4 More-over, incidence of PGD may appear higher in this series secondary to perhaps a lower threshold at our institution for aggressive use of inotropic and mechanical support in heart transplant patients. In the study by Segovia et al, the incidence of primary graft failure was 9.7% with only a 12% survival of this cohort of patients.4 Survival of PGD patients in our study was vastly improved (Figure 2) and could reflect the combination of less stringent criteria for diagnosing PGD and aggressive support practices.

AL heart transplantation is a strategy designed to offer marginal donor hearts to recipients who do not meet conventional criteria for heart transplantation.2,5 The AL heart transplants at our institution displayed a variety of recipient and donor organ characteristics. The most common recipient characteristic was advanced age. Marginal donor hearts included those with reduced left ventricular ejection fraction, LVH, and presence of coronary artery disease. Donors who

<table>
<thead>
<tr>
<th>TABLE 3. Types of Mechanical Support for Primary Graft Dysfunction</th>
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<tr>
<td>Mechanical Support</td>
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<tr>
<td>---------------------</td>
</tr>
<tr>
<td>SL</td>
</tr>
<tr>
<td>IABP (%)</td>
</tr>
<tr>
<td>VAD (%)</td>
</tr>
<tr>
<td>ECMO (%)</td>
</tr>
</tbody>
</table>

ECMO indicates extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump.

The only predictors for PGD defined in this study were total ischemic time and pre-transplant VAD. A reasonable initial assumption would be that pre-transplant VAD may itself represent a surrogate of prolonged ischemic time since the mediastinal scarring associated with VAD may increase the difficulty of surgical dissection and prolong the explanation. However the donor ischemic times in pre-transplant VAD versus no pre-transplant VAD were similar (204 versus 209 minutes, respectively, P=0.56, data not shown). Furthermore, pre-transplant VAD was independently predictive of PGD by multivariate Cox proportional hazards. Another plausible explanation is that pre-transplant LVAD requires longer cardiopulmonary bypass times which may trigger a greater inflammatory response. The latter may impact on PGD.

The overall importance of ischemic time is also emphasized by the ISHLT registry, which identifies it as an important cause of mortality at one year following cardiac transplantation. Therefore, prolonged ischemic time may contribute both to PGD, early mortality and also to total mortality at one year. Given this identified predictor of PGD, it would seem inappropriate to combine prolonged ischemic times with the use of marginal donor organs which may be more prone to ischemic injury due to coronary artery disease or LVH. This could be in part avoided by utilizing only local marginal hearts with these features. This analysis also reiterates the importance of efforts to improve organ preservation.
One important limitation of this study is the relatively small number of cases of PGD requiring mechanical support for both groups (SL and AL). In addition, marginal donor heart characteristics were very heterogeneous; the impact of any single characteristic (eg, LVH) on PGD cannot be analyzed. Finally, significant bias was introduced in the selection of marginal donors for AL transplantation. For example, not all organs with CAD were accepted. Functionally abnormal hearts from younger donors were probably more likely utilized relative to hearts with similar features from older donors. Bias in selection cannot be accounted for in this analysis, and undoubtedly impacts results.

We have previously shown that overall survival for the AL group is decreased relative to the SL group.2 PGD, however, does not appear to occur more frequently for the AL transplants. Recipients being considered for the AL can be informed that the risk of PGD is not significantly different relative to SL heart transplantation. In general, this analysis supports utilization of the AL strategy. Patients who have end stage heart failure and fail to qualify for standard heart transplant listing, have limited options. Most commonly, intravenous inotropic support is utilized to alleviate symptoms, but this treatment carries up to a ninety percent one year mortality.11 Another option for these patients is destination LVAD therapy; LVAD results are improving but one year mortality is still greater than thirty percent.12,13 Relative to these treatment options, the AL heart transplant strategy appears to provide substantially better results for patients with end stage heart failure and does not appear to be limited by early graft dysfunction.

Disclosures

None.

References

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