Impact of Donor-to-Recipient Weight Ratio on Survival After Heart Transplantation

Analysis of the United Network for Organ Sharing Database

Nishant D. Patel, BA; Eric S. Weiss, MD; Lois U. Nwakanma, MD; Stuart D. Russell, MD; William A. Baumgartner, MD; Ashish S. Shah, MD; John V. Conte, MD

Background—Generally accepted donor criteria for heart transplantation limit allografts from donors within approximately 20% to 30% of the recipient’s weight. We analyzed the impact of donor-to-recipient weight ratio on survival after heart transplantation.

Methods and Results—Adult heart transplant recipients reported to the United Network for Organ Sharing from 1999 to 2007 were divided into 3 groups based on donor-to-recipient weight ratio: <0.8, 0.8 to 1.2, and >1.2. Kaplan–Meier methodology was used to estimate survival. Propensity-adjusted Cox regression modeling was used to analyze predictors of mortality. A total of 15,284 heart transplant recipients were analyzed; 2078 had weight ratio of <0.8, 9684 had 0.8 to 1.2, and 3522 had >1.2. Kaplan–Meier survival was not statistically different between groups at 5 years (P=0.26). Among patients with weight ratio <0.8, 5-year survival was lower for recipients with high pulmonary vascular resistance (>4 Woods units; P=0.02). Among recipients with high pulmonary vascular resistance, 5-year survival was similar for those with weight ratio 0.8 to 1.2 and >1.2 (P=0.44). Furthermore, male recipients with elevated pulmonary vascular resistance who received hearts from female donors had a significantly worse survival than males who received hearts from male donors (P=0.01). Propensity-adjusted multivariable analysis demonstrated that weight ratio <0.8 did not predict mortality (hazard ratio, 1.09; 95% CI, 0.94 to 1.27; P=0.21). Five-year survival after propensity matching was not statistically different between those with weight ratio <0.8 versus ≥0.8 (P=0.37).

Conclusions—Weight ratio did not predict mortality after heart transplantation. However, recipients with elevated pulmonary vascular resistance who received undersized hearts had poor survival. Furthermore, in the setting of high pulmonary vascular resistance, male recipients who received hearts from female donors had worse survival than those who received hearts from male donors. Extending donor criteria to include undersized hearts in select recipients should be considered. (Circulation. 2008;118[suppl 1]:S83–S88.)

Key Words: heart transplantation ■ heart failure ■ donor criteria

Heart transplantation is a successful therapy for patients with end-stage heart failure. In the 2007 International Society of Heart and Lung Transplantation report, Taylor and colleagues reported 50% survival at 10 years for over 70,000 adult and pediatric heart transplant recipients.1 Despite the improvements in early survival, antirejection therapy as well as refinements in surgical technique and perioperative management, donor organ shortages have resulted in long waiting list times and high mortality rates for those awaiting heart transplantation.1

Because of the donor organ deficit, efforts have been made to use marginal donors in an attempt to increase the donor organ pool and reduce waiting list mortality.2–7 These attempts include the use of hearts from older donors8–11 and hearts that have been subjected to longer ischemic times,12–16 both of which have led to conflicting results in the literature.

Generally accepted transplant criteria limit the use of cardiac allografts from donors to within approximately 20% of the recipient’s weight. Previous studies have evaluated the impact of donor-to-recipient size on outcomes after heart transplantation with varying results.1,2,17 These have largely been small single-institution studies. To our knowledge, no large multicenter study focusing on donor-to-recipient size mismatch has been performed. Lacking this, we felt the next best option would be to investigate this issue using data from the United Network for Organ Sharing database.

Methods

Study Design and Patient Population

We retrospectively reviewed all reported data to the United Network for Organ Sharing/Organ Procurement and Transplantation Network
(UNOS/OPTN) registry for adult patients who underwent primary heart transplantation from January 1999 to January 2007. A total of 26,563 adult transplant recipients were reviewed. All patients who had retransplantation (n=605), those who had combined heart and lung transplantation or lung transplantation (n=9368), and those with missing donor or recipient weight data (n=1306) were excluded from analysis; our final study cohort consisted of 15,284 adult primary heart transplant recipients. All primary adult heart transplant recipients were then divided into 3 groups based on donor-to-recipient (DR) weight ratio: 0.8 to 1.2 (or within 20% of the recipient’s weight; current accepted criterion), <0.8 (or greater than 20% undersized), and >1.2 (or greater than 20% oversized). The UNOS/OPTN Standard Transplant Analysis and Research (STAR) files provided deidentified data, so waiver of consent was granted by our Institutional Review Board.

Statement of Responsibility
The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Statistical Analyses
STATA version 9.0 (Stata Corp, College Station, Texas) software package was used for statistical computations. Continuous variables are presented as mean±SEM. Categorical variables are expressed in percentages of the total number of data points available within the database. Analysis of variance and χ² analyses were used to compare continuous and categorical variables among groups, respectively. Survival was assessed by the Kaplan–Meier method and compared between groups using the Mantel-Cox log rank test.

Mortality was first assessed for all risk factors using a univariate analysis. Significant predictors of mortality were included into a Cox proportional hazards regression model to assess for predictors of cumulative mortality. Only well-represented variables (less than 20% missing in the registry) were included in the Cox regression model. In addition, propensity scores were calculated for each patient to control for potential selection bias for a recipient to receive a heart from an undersized donor. Variables included in the propensity score model were recipient age, donor age, recipient male gender, donor-to-recipient gender match, recipient black race, pulmonary vascular resistance, human leukocyte antigen mismatch level ≥5, ischemic time, baseline creatinine, baseline cardiac output, and year of transplant. Propensity scores were then analyzed using the regression adjustment technique in which the propensity scores and study groups were included in a Cox regression model. Finally, once propensity scores were calculated, they were used to create matched pairs of recipients with DR weight ratio <0.8 versus ≥0.8. Kaplan–Meier survival of matched groups was compared with the Mantel-Cox log rank test.

Results
Patient Demographics
A total of 15,284 adults underwent primary heart transplantation during the study period. Of the 15,284 recipients, 9684 (63.4%) had a DR weight ratio of 0.8 to 1.2, 2078 (13.6%) had weight ratio <0.8, and 3522 (23.0%) had weight ratio >1.2. The annual number of adults undergoing primary heart transplantation has remained relatively stable over the time course of our study (Figure 1).

Pertinent baseline characteristics were dissimilar between groups (Table 1). Of note, the number of recipients older than 70 years of age, the number of black recipients, and the number male recipients were all significantly different among the 3 groups. Furthermore, a diagnosis of dilated cardiomyopathy, a history of hypertension, a history of diabetes, and intensive care unit stay before transplant were also significantly different among the 3 groups.

Postoperative Data
Postoperative complications are listed in Table 2. The need for dialysis postoperatively was found to be significantly different among the 3 groups, although the incidence of postoperative stroke, reoperation, infection, and pacemaker placement were similar. The rate of graft failure was also similar among the 3 groups (21.5% versus 21.0% versus 23.5%; P=0.08): causes of primary graft failure were primary nonfunction (47.5% versus 41.4% versus 50.0%), acute rejection (29.1% versus 35.0% versus 30.8%), and chronic rejection (23.4% versus 23.6% versus 19.2%).

Survival and Regression Analyses
Thirty-day mortality was highest for those with weight ratio <0.8 but did not reach statistical significance. Thirty-day mortality was 5.8% for recipients with DR weight ratio of 0.8 to 1.2, 5.5% for those with weight ratio >1.2, and 6.5% for those with weight ratio <0.8 (P=0.32). There was a trend toward a higher 1-year mortality for recipients with weight ratio <0.8 (13.7%) when compared with those with weight ratio 0.8 to 1.2 (11.9%) and >1.2 (12.3%). Kaplan–Meier survival approached 70% for all 3 groups at 5 years, which was not statistically significant (P=0.26; Figure 2). The most common causes of mortality were multigorgan failure (10.7%), sepsis (8.0%), cardiac arrest (7.6%), acute rejection (7.3%), and primary failure (7.1%).

We also assessed survival for recipients with high pulmonary vascular resistance (>4 Woods units) stratified by DR weight ratio (Figure 3). Kaplan–Meier survival was not found to be significantly different when comparing all 3 groups. However, as expected, when comparing survival for recipients with high pulmonary vascular resistance, those who had DR weight ratio <0.8 had a significantly worse survival than those with weight ratio >1.2 (P=0.04).

Kaplan–Meier analysis also demonstrated statistically significant differences in survival when assessing recipients with DR weight ratio <0.8 stratified by pulmonary vascular resistance (Figure 4). Among those with weight ratio <0.8, recipients with the low pulmonary vascular resistance (<2 Woods units) had the best survival out to 5 years followed by recipients with pulmonary vascular resistance of 2 to 4 Woods units. As expected, among those with weight ratio <0.8, recipients with the highest pulmonary vascular resistance (>4 Woods units) had the worst survival.

Donor-to-recipient gender mismatch was also analyzed to assess the impact of a surrogate variable for size on survival (Figure 5). Among those with high pulmonary vascular
resistance (>4 Woods units), male recipients who received hearts from male donors had a significant survival advantage out to 5 years compared with male recipients who received hearts from female donors ($P=0.01$).

Cox regression analysis identified that donor-to-recipient gender match and recipient male gender were both significantly protective. Recipient history of diabetes, donor age, ischemic time, recipient baseline creatinine, and donor history of diabetes were all significantly predictive of cumulative mortality (Table 3). Weight ratio <0.8 and weight ratio >1.2 as well as pulmonary vascular resistance were not found to be significant predictors of mortality in our model.

We calculated propensity scores to control for selection bias and included them in our Cox regression model. After controlling for propensity, DR weight ratio <0.8 was not significantly associated with mortality (hazard ratio, 1.07; $P=0.28$; 95% CI, 0.94 to 1.23). Propensity scores were then used to create matched pairs of recipients with DR weight ratio <0.8 to recipients with weight ratio ≥0.8. A total of 1261 recipients with DR weight ratio <0.8 were matched with 7044 recipients with weight ratio ≥0.8; Kaplan–Meier survival out to 5 years was 74% and 75%, respectively, which was not found to be significantly different on the Mantel-Cox log rank test ($P=0.37$).

**Comment**

Heart transplantation is the gold standard surgical treatment for patients with end-stage heart disease. The International Society of Heart and Lung Transplantation 2007 annual report found excellent long-term survival for adult heart transplant recipients. Nevertheless, the shortage of donor organs and high waiting list mortality remain sobering statistics for patients with heart failure.

### Table 1. Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Weight Ratio &lt;0.8</th>
<th>Weight Ratio 0.8–1.2</th>
<th>Weight Ratio &gt;1.2</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years</td>
<td>50.7±0.3</td>
<td>51.2±0.2</td>
<td>46.6±0.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Recipient age &gt;70 years</td>
<td>0.7% (2078)</td>
<td>1.5 (9684)</td>
<td>1.1 (3522)</td>
<td>0.01</td>
</tr>
<tr>
<td>Male (no. available)</td>
<td>78.7% (2078)</td>
<td>76.5% (9684)</td>
<td>62.6% (3522)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Black (no. available)</td>
<td>17.8% (2078)</td>
<td>14.6% (9684)</td>
<td>16.0% (3522)</td>
<td>0.001</td>
</tr>
<tr>
<td>Recipient weight, kg</td>
<td>94.0±0.5</td>
<td>80.1±0.2</td>
<td>63.0±0.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>84.7% (2078)</td>
<td>80.7% (9684)</td>
<td>69.4% (3522)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>4.8% (2078)</td>
<td>6.4% (9684)</td>
<td>3.9% (3522)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>2.1% (2078)</td>
<td>2.2% (9684)</td>
<td>2.1% (3522)</td>
<td>0.84</td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>1.3% (2078)</td>
<td>1.8% (9684)</td>
<td>2.1% (3522)</td>
<td>0.10</td>
</tr>
<tr>
<td>PVR &lt;2 Woods units</td>
<td>43.1% (2078)</td>
<td>35.7% (9684)</td>
<td>23.7% (3522)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>42.6% (2078)</td>
<td>38.2% (9382)</td>
<td>26.6% (3401)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>24.2% (2045)</td>
<td>19.9% (9562)</td>
<td>12.4% (3473)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HLA mismatch level 6</td>
<td>17.1% (2078)</td>
<td>17.1% (9684)</td>
<td>17.3% (3522)</td>
<td>0.97</td>
</tr>
<tr>
<td>Baseline creatinine, mg/dL</td>
<td>1.4±0.02</td>
<td>1.4±0.01</td>
<td>1.2±0.02</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pretreatment ventilatory support</td>
<td>3.7% (2078)</td>
<td>3.9% (9684)</td>
<td>9.1% (3522)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ICU before transplant</td>
<td>29.1% (2078)</td>
<td>31.1% (9684)</td>
<td>42.6% (3521)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Donor age, years</td>
<td>29.4±0.3</td>
<td>31.0±0.2</td>
<td>30.3±0.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Donor male (no. available)</td>
<td>68.5% (2078)</td>
<td>70.5% (9684)</td>
<td>65.4% (3522)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Donor gender match (no.</td>
<td>70.8% (2078)</td>
<td>70.7% (9684)</td>
<td>61.3% (3522)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Donor weight, kg</td>
<td>68.2±0.4</td>
<td>77.7±0.2</td>
<td>88.3±0.7</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

PVR indicates pulmonary vascular resistance; HLA, human leukocyte antigen; ICU, intensive care unit.

### Table 2. Operative and Postoperative Data

<table>
<thead>
<tr>
<th></th>
<th>Weight Ratio &lt;0.8</th>
<th>Weight Ratio 0.8–1.2</th>
<th>Weight Ratio &gt;1.2</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic time, hours</td>
<td>3.2±0.03</td>
<td>3.1±0.01</td>
<td>3.1±0.03</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Days on waiting list</td>
<td>260±11</td>
<td>233±5</td>
<td>161±7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total length of stay, days</td>
<td>19.1±0.7</td>
<td>18.8±0.3</td>
<td>20.2±0.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Dialysis (no. available)</td>
<td>9.6% (2004)</td>
<td>9.3% (9463)</td>
<td>7.8% (3463)</td>
<td>0.01</td>
</tr>
<tr>
<td>Stroke (no. available)</td>
<td>1.9% (1999)</td>
<td>2.6% (9432)</td>
<td>2.4% (3448)</td>
<td>0.18</td>
</tr>
<tr>
<td>Pacemaker (no. available)</td>
<td>3.2% (2004)</td>
<td>3.6% (9476)</td>
<td>2.8% (3463)</td>
<td>0.06</td>
</tr>
<tr>
<td>Infection (no. available)</td>
<td>24.1% (1995)</td>
<td>24.0% (9422)</td>
<td>25.5% (3449)</td>
<td>0.20</td>
</tr>
<tr>
<td>Reoperation (no. available)</td>
<td>10.8% (2003)</td>
<td>11.4% (9451)</td>
<td>10.5% (3461)</td>
<td>0.35</td>
</tr>
<tr>
<td>Graft failure (no. available)</td>
<td>23.5% (2074)</td>
<td>21.5% (9668)</td>
<td>21.0% (3518)</td>
<td>0.08</td>
</tr>
</tbody>
</table>
Efforts have been made to use marginal donor organs to expand the donor pool and reduce waiting list mortality. Current donor and recipient criteria limit the use of hearts to donors who are within approximately 20% of the recipient’s weight or a DR weight ratio of 0.8 to 1.2. Previous studies analyzing the impact of donor-to-recipient size have done so from an institutional perspective or as a subanalysis of a larger study. Most recently, Taylor and colleagues in their 2007 International Society of Heart and Lung Transplantation annual report found that decreasing donor-to-recipient body mass index ratio was a significant predictor of mortality at 5 years for those recipients surviving the first posttransplant year. Body mass index ratio was not associated with mortality within 1 year posttransplant and mortality at 10 years. In an institutional report assessing the impact of donor characteristics on short- and long-term transplant outcomes, Chen and colleagues stated that body mass index mismatch >20% was associated with mortality on univariate and multivariate analysis; importantly, only recipients who received hearts that were >20% undersized had a higher risk of mortality. Unfortunately, hard data and analyses were not available in the results section of their article. Furthermore, although the discussion states that body mass index mismatch >20% was found to be significant on multivariate analysis, the authors only report donor weight as a significant predictor in the abstract and results section of the article.

On the other hand, an institutional report from Sethi and colleagues from the University of Arizona specifically assessed the clinical significance of weight difference between donor and recipient. The authors reviewed 200 transplant recipients; 27 of these received an undersized heart (>30% undersized). The authors found similar early and late survival for the recipients who received undersized versus normalized hearts. Freedom from rejection and infection as well as postoperative ejection fraction was also similar. Based on their findings, the authors reported that extension of the donor criteria to include undersized hearts is safe. Although others have assessed the impact of donor-to-recipient size mismatch on heart transplant outcomes, a more recent focused analysis on this issue is not currently available. Furthermore, other reports on heart transplantation outcomes have only included size mismatch as a subanalysis, and those that have specifically assessed the issue have been limited by institutional reviews with relatively low power. Moreover, there is a paucity of data on the impact of oversized hearts on transplant outcomes. To overcome some of these limitations, we used the UNOS/OPTN registry to assess primary heart transplant recipients in a contemporary era.

We wanted to assess undersized and oversized donor hearts and so divided all patients into 3 groups based on donor-to-recipient weight ratio. Despite differences in baseline characteristics on short-term transplant outcomes, the authors only report donor weight as a significant predictor in the abstract and results section of the article.
statistically significant. Various subanalyses, however, shed some light on the relationship between weight ratio and pulmonary vascular resistance. Recipients who received undersized hearts had a significantly worse survival when pulmonary vascular resistance was >4 Woods units versus recipients who received undersized hearts in the setting of normal or low pulmonary vascular resistance. When analyzing all recipients with elevated pulmonary vascular resistance (>4 Woods units), the transplantation of an undersized heart portended a worse outcome, as would be expected. Finally, male recipients with pulmonary vascular resistance >4 Woods units who received hearts from male donors had significant survival advantage over male recipients who received hearts from female donors. Others have found similar results when analyzing the impact of donor gender on transplant outcomes.\(^\text{17–19}\)

Multivariable analysis demonstrated that weight ratio <0.8 and weight ratio >1.2 were not associated with mortality in the overall population after controlling for known risk factors. Risk factors that were associated with overall mortality in our model were ischemic time, baseline creatinine, diabetes, donor age, donor history of diabetes, recipient gender, and gender match. We attempted to correct for potential selection bias for one recipient to receive an undersized heart over another recipient using propensity scores in our Cox regression model. After controlling for propensity score, weight ratio <0.8 and weight ratio >1.2 were not associated with mortality. We also matched recipients with weight ratio <0.8 to those with weight ratio ≥0.8 based on propensity score. Kaplan–Meier survival out to 5 years was similar for the matched pairs.

This study has limitations consistent with retrospective analyses and the use of a national multiscene database. Some important variables have considerable missing data that prevented their incorporation into our Cox regression and propensity score models. We avoid including variables into either model that are less than two thirds complete to avoid inadequate representation of the patient population in the data set.

Nevertheless, the UNOS/OPTN registry has provided a large sample size to assess the impact of donor-to-recipient weight ratio on outcomes after heart transplantation in the current era. Weight ratio did not predict mortality after heart transplantation after controlling for known risk factors, propensity score adjustment, and propensity score matching.

Although undersized allografts in recipients with normal/low pulmonary vascular resistance did not adversely affect survival, using undersized hearts probably does portend some ill-defined increased risk. The implantation of undersized hearts in recipients with high pulmonary vascular resistance should be avoided because there is clearly defined increased risk. Oversized allografts in recipients with high pulmonary vascular resistance did not provide survival advantage over normal-sized allografts. Undersized hearts from female donors should be used with great trepidation in male recipients with high pulmonary vascular resistance. Extending donor criteria to include undersized hearts in recipients without elevated pulmonary vascular resistance and with gender match may be considered to expand the donor organ pool and reduce mortality rates for patients on the waiting list.

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### Disclosures

None.

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