The Impact of Donor-Recipient Sex Matching on Survival After Orthotopic Heart Transplantation
Analysis of 18 000 Transplants in the Modern Era

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Introduction—Single-institution series have suggested that men receiving orthotopic heart transplantation from female donors have decreased survival. No multi-institutional series has comprehensively addressed the issue of donor and recipient sex matching for both male and female orthotopic heart transplantation recipients.

Methods and Results—We used data from the multi-institutional prospectively collected United Network for Organ Sharing open transplantation cohort to review 18 240 adult patients who received orthotopic heart transplantation from 1999 to 2007. Four donor recipient strata were identified (male donor/male recipient, N = 10 750; female donor/female recipient, N = 2201; male donor/female recipient, N = 2121; and female donor/male recipient, N = 3168). The primary end point of all cause posttransplant mortality was compared among groups using a Cox proportional hazard regression model with additional propensity adjustment. Female recipients, irrespective of donor sex, had 3.6% lower overall survival at 5 years posttransplant (P = 0.003). Men who received organs from male donors had the highest cumulative survival at 5 years (74.5%). Men receiving female hearts had a 15% increase in the risk of adjusted cumulative mortality (hazard ratio, 1.15; 95% CI, 1.02 to 1.30; P = 0.02). No significant increase in the relative hazard for death occurred for women receiving opposite sex donor organs (1.24; 0.92 to 1.35; P = 0.31).

Conclusions—The United Network for Organ Sharing data set has provided a large sample examining donor recipient sex pairing in orthotopic heart transplantation. Men receiving organs for same sex donors have significantly improved short- and long-term survival. No survival advantage was seen for women with same sex donors. (Circ Heart Fail. 2009;2:401-408.)

Key Words: transplantation ■ sex ■ UNOS ■ outcomes ■ heart failure

Despite its place as the gold standard treatment for end-stage heart failure, orthotopic heart transplantation (OHT) remains constrained by limitations in donor organ supply, long-term allograft vasculopathy, and complications associated with immunosuppression. For these reasons, substantial interest continues to exist in identifying factors portending increased survival and improved organ utilization.

Clinical Perspective on p 408

For many years, investigators have remained unsure to what extent donor and recipient sex influence outcomes in OHT. Several early studies identified female donor sex to be an independent predictor of mortality. Complicating the issue, however, is the fact that unlike other solid organs, >75% of OHT recipients have traditionally been male. Thus, it may well be the interplay between donor and recipient sex (rather than the sex of the donor or recipient individually) that most influences outcomes.

Along these lines, a few single-institution series have focused on whether male recipients have increased mortality when receiving hearts from female donors. The general consensus from these reports is that men who receive female hearts have decreased short- and long-term posttransplant survival. An association between donor sex mismatch and mortality for female recipients has been neither convincingly demonstrated nor extensively studied.

There are several potential mechanisms by which donor/recipient sex mismatch might affect outcomes in transplantation. Included among these are the minor histocompatibility antigen present on the Y chromosome, antigen development during normal pregnancy in women, and differing hormonal composition between the sexes. Unique to the heart is the importance of physical size both for provision of adequate perfusion and to ensure adequate functional reserve. As it is known that female hearts are smaller relative to men, size discrepancy has emerged as an important consideration when...
clinicians contemplate providing a male recipient with a female heart.

Although several studies have examined donor and recipient sex in OHT, they have been conducted in single centers with small patient numbers and are thus inherently prone to confounding and single center biases. Multi-institutional series such as those from the International Society for Heart and Lung Transplantation registry have not thoroughly addressed the issue. As 30% of donor hearts are recovered from women, definitive guidelines are needed to aid clinicians and enhance organ utilization. With this background, we aimed to comprehensively evaluate the effect of sex matching for both male and female recipients on mortality after OHT using data from the multi-institutional prospectively collected United Network for Organ Sharing (UNOS) open transplantation cohort.

Methods

Data Source
We used a Standard Transplant Analysis and Research file with follow-up data provided to us by UNOS. No patient identifiers were included in this analysis and therefore, the study was exempt from institutional review board approval at our institution. The data set comprised a prospectively collected open cohort of all US patients receiving heart transplantation from 1987 to 2007 with follow-up through May 2008.

Study Design
We retrospectively examined a cohort of adult patients (>17 years) receiving first time OHT over a 10-year period (January 1998 to January 2007). We divided this group by donor and recipient sex to create 4 separate strata (male donor with male recipient, female donor with female recipient, male donor with female recipient, and female donor with male recipient).

Variables Examined and Outcome Measures
The data set used contains 433 unique preoperative, intraoperative, and postoperative variables. In addition, 119 follow-up variables are provided. We focused our analysis on potential clinically pertinent variables. Specifically studied were demographic factors (age, sex, race, education level, and insurance type), comorbidities (hypertension, diabetes mellitus, body mass index [BMI], and preoperative hematocrit levels), transplant variables (ischemic time, human leukocyte antigen mismatch, panel reactive antibody level year of transplant, and wait list times), and measures of recipient support (hospitalization status, intensive care unit treatment before transplant, use of intra-aortic balloon counter pulsation before transplant, UNOS status, and use of inotropic agents before OHT). We also examined donor variables including donor age, race, sex, and BMI. Finally, important hemodynamic measurements before transplant such as mean pulmonary artery pressure, pulmonary vascular resistance (PVR), cardiac index, and transpulmonary gradient were included in the analysis.

The primary end point was all cause cumulative mortality during the study period. We also examined short-term mortality including 30-day, 90-day, and 1-year mortality.

Statistical Analysis
We compared baseline characteristics among the 4 donor/recipient sex strata by 1-way ANOVA (for continuous variables) and the \( \chi^2 \) test (categorical variables). For significant associations, post hoc pairwise comparisons between strata were performed using the Tukey-Kramer method (continuous variables) and univariate logistic regression (categorical variables).

Cumulative survival was estimated using the Kaplan-Meier method focused on time intervals with adequate follow-up. Censoring occurred for those individuals lost to follow-up and those alive at the end of study time (administratively censored).

Multivariable analysis was performed by use of a Cox proportional hazards regression model with censoring occurring for loss to follow-up, and administrative reasons. Independent covariates with potential for confounding based on clinical, biological, or hospital-based factors were first evaluated in a univariate model. Those reaching statistical significance (\( P<0.05 \)) were incorporated into the multivariable model in a stepwise fashion using the likelihood ratio test for significance. The final model incorporated the following covariates relating to the recipient: race, age >60 years, BMI, creatinine, mechanical ventilation before transplant, history of diabetes, intensive care unit before transplant, panel reactive antibody >20%, <2 human leukocyte antigen match, and PVR >4 woods units and the following relating to the donor: age, cigarette use, diabetes mellitus, and ischemic time >6 hours.

A propensity score estimating the likelihood of receiving an organ from a same sex donor was created using logistic regression based on 21 potential predictors. Risk of mortality by sex matching strata was further assessed in a second multivariable model incorporating ordinal quintiles of the propensity score to serve as a sensitivity analysis.

For all analyses, a \( P \) value of <0.05 (2-tailed) was considered significant. Means are presented with standard deviations, medians with interquartile ranges, and all hazard ratios (HRs) are presented.
Table 1. Baseline Characteristics Stratified by Donor-Recipient Sex Pairing

<table>
<thead>
<tr>
<th>18 240 Patients</th>
<th>Male Donor, Male Recipient, (N=10 750)</th>
<th>Female Donor, Female Recipient, (N=2201)</th>
<th>Male Donor, Female Recipient, (N=2121)</th>
<th>Female Donor, Male Recipient, (N=3168)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recipient demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>53.0 (±11.3)</td>
<td>49.1 (±12.9)†</td>
<td>47.8 (±12.9)†</td>
<td>53.4 (±12.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age ≥65 y</td>
<td>3413/10750 (31.8)</td>
<td>494/2201 (22.4)†</td>
<td>395/2121 (18.6)†</td>
<td>1143/3168 (36.1)†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>White</td>
<td>8420/10715 (78.6)</td>
<td>1539/2189 (70.3)†</td>
<td>1385/2108 (65.7)†</td>
<td>2431/3153 (77.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Black</td>
<td>1395/10715 (13.0)</td>
<td>447/2189 (20.4)†</td>
<td>505/2108 (24.0)†</td>
<td>384/3153 (12.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hispanic</td>
<td>657/10715 (6.1)</td>
<td>142/2189 (6.5)</td>
<td>164/2108 (7.8)†</td>
<td>224/3153 (7.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>Other</td>
<td>243/10715 (2.3)</td>
<td>61/2189 (2.8)</td>
<td>54/2108 (2.6)</td>
<td>114/3153 (3.6)†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Recipient insurance</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Private insurance/self-pay</td>
<td>6576/10720 (59.0)</td>
<td>1346/2194 (61.4)</td>
<td>1276/2116 (60.3)</td>
<td>1945/3156 (61.6)</td>
<td>0.79</td>
</tr>
<tr>
<td>Medicare</td>
<td>2608/10720 (24.3)</td>
<td>445/2194 (20.3)†</td>
<td>401/2116 (19.0)†</td>
<td>764/3156 (24.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medicaid</td>
<td>975/10720 (9.1)</td>
<td>325/2194 (14.8)†</td>
<td>348/2116 (16.5)†</td>
<td>302/3156 (9.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other</td>
<td>561/10720 (5.2)</td>
<td>78/2194 (3.6)†</td>
<td>91/2116 (4.3)</td>
<td>145/3156 (4.6)</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Recipient education level</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>College or graduate</td>
<td>4162/8081 (51.5)</td>
<td>707/1604 (44.1)†</td>
<td>721/1579 (45.7)†</td>
<td>1037/2253 (46.0)†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Precollege</td>
<td>3919/8081 (48.5)</td>
<td>897/1604† (55.9)</td>
<td>858/1579† (54.3)</td>
<td>1216/2253† (53.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Recipient comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>2485/10750 (23.5)</td>
<td>396/2201 (18.4)†</td>
<td>383/2121 (18.4)†</td>
<td>629/3168 (20.4)†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HTN</td>
<td>4023/9560 (42.1)</td>
<td>655/1962† (33.3)</td>
<td>627/1909† (32.8)</td>
<td>1164/2881 (49.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.4 (±0.9)</td>
<td>1.2 (±0.8)†c</td>
<td>1.2 (±1.0)</td>
<td>1.4 (±1.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>27.0 (±4.5)</td>
<td>25.1 (±5.1)†</td>
<td>26.1 (±5.7)†</td>
<td>25.4 (±4.3)†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UNOS status 1‡</td>
<td>8394/10476 (78.1)</td>
<td>1402/2198 (63.8)‡</td>
<td>1574/2120 (74.3)‡</td>
<td>2361/3168 (74.5)‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Recipient support</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IABP before transplant</td>
<td>568/10750 (5.3)</td>
<td>114/2201</td>
<td>103/2121 (4.9)</td>
<td>190/3168 (6.0)</td>
<td>0.3</td>
</tr>
<tr>
<td>Inotropes before transplant</td>
<td>5032/10750 (46.8)</td>
<td>975/2201 (44.3)†</td>
<td>1027/2121 (48.4)</td>
<td>1590/3168 (50.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ventilator before transplant</td>
<td>251/10750 (2.3)</td>
<td>63/2201 (2.9)</td>
<td>84/2121 (3.9)†</td>
<td>105/3168 (3.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICU before transplant</td>
<td>3593/10750 (33.4)</td>
<td>655/2201 (29.8)†</td>
<td>768/2121 (36.2)†</td>
<td>1127/3168 (35.6)†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hospitalized</td>
<td>5752/10750 (53.5)</td>
<td>1021/2198 (46.5)†</td>
<td>1162/2121 (54.8)</td>
<td>1771/3168 (56.0)†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Days on wait list</td>
<td>239 (±387)</td>
<td>184 (±328)†</td>
<td>176 (±303)§</td>
<td>204 (±346)§</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Recipient hemodynamics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PA pressure</td>
<td>29.2 (±10.4)</td>
<td>27.3 (±10.0)†</td>
<td>28.3 (±9.7)†</td>
<td>28.8 (±10.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PVR</td>
<td>2.4 (±2.0)</td>
<td>2.8 (±2.0)†</td>
<td>2.7 (±1.6)†</td>
<td>2.5 (±1.9)†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>2.3 (±0.8)</td>
<td>2.4 (±1.2)</td>
<td>2.4 (±0.8)</td>
<td>2.3 (±0.8)</td>
<td>0.03</td>
</tr>
<tr>
<td>TPG</td>
<td>9.6 (±5.7)</td>
<td>9.5 (±5.6)</td>
<td>9.8 (±5.3)</td>
<td>9.3 (±6.3)</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Donor variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donor age, y</td>
<td>30.2 (±11.9)</td>
<td>34.4 (±13.6)†</td>
<td>27.2 (±11.7)†</td>
<td>36.2 (±13.0)†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Donor BMI</td>
<td>26.2 (±4.8)</td>
<td>25.3 (±6.1)†</td>
<td>24.1 (±4.3)†</td>
<td>27.5 (±6.5)†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Donor-to-recipient BMI ratio</td>
<td>1.0 (±0.2)</td>
<td>1.0 (±0.3)†</td>
<td>1.0 (±0.2)†</td>
<td>1.1 (±0.3)†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Donor-to-recipient BSA ratio§</td>
<td>0.9 (±0.08)</td>
<td>1.0 (±0.1)†</td>
<td>1.0 (±0.1)†</td>
<td>0.9 (±0.08)†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ischemic time, h</td>
<td>3.2 (±1.0)</td>
<td>3.1 (±1.0)</td>
<td>3.0 (±1.0)</td>
<td>3.2 (±1.0)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are presented as mean (±SD) or n/N (%). HTN indicates hypertension; IABP, intra-aortic balloon pump; ICU, intensive care unit; PA, pulmonary artery; PVR, pulmonary vascular resistance (defined by mean PA pressure [mPAP] – pulmonary capillary wedge pressure [PCWP]/cardiac output); CI, cardiac index (defined as cardiac output variable present in the data set/BSA [as calculated by DuBois and DuBois12 method]); TPG, transpulmonary gradient (defined by mPAP-PCWP). *P value based on results of either 1-way ANOVA (for continuous variables) or χ² test for categorical variables. †Post hoc pairwise comparison P<0.05 (compared with reference of male donor-male recipient) by Tukey-Kramer method (for continuous variables) or univariate logistic regression for categorical variables. ‡UNOS status 1 refers to patients listed as status 1a, status 1b, or older UNOS status 1. §BSA in square meter based on the method of DuBois and DuBois.12

with 95% CIs. Incidence rates are calculated as the number of patients who died during the interval of interest divided by the total person time at risk during the interval (standardized to 100 person-years). Statistical analyses were performed with the aid of STATA software (version 9.2 SE, StataCorp LP, College Station, Tex).

Results

Cohort Statistics

From 1998 to 2007, 20,923 patients receiving OHT were followed within the UNOS registry. After exclusion of
patients with previous transplants (n=779), children (n=2677), and patients with inadequate data (n=6), the final study population was 18,240. The mean age of the cohort was 52.0±12 years with 23.7% women (n=4322). The median time spent on the waitlist was 2.9 months (interquartile range, 0.9 to 8.2) and 75% (n=4503) were listed as UNOS status 1. A total of 4732 patients died during the follow-up period for an overall incidence rate of 7.0 deaths/100 person-years. The median follow-up time was 37.0 months (interquartile range, 12.1 to 72.6).

Stratification by donor and recipient sex provided the following groups: male donor with male recipient, n=10,750 (58.9%); female donor with female recipient, n=2201 (12.1%); male donor with female recipient, n=2121 (11.6%); and female donor with female recipient, n=3168 (17.4%). During the study period, this distribution did not differ substantially, with male donor/male recipient pairs comprising >50% of the sample in each year (range, 55.3% to 64.0%; Figure 1). Among female recipients, donor sex was evenly distributed overall and yearly throughout the study period. Finally, the total number of adult OHTs remained constant throughout the 10-year study period ranging from 1671 to 2016 per year.

Baseline Characteristics
Examination of baseline characteristics revealed differences by donor and recipient sex. Specifically, male recipients tended to be older, with a greater percentage of patients older than 65 years (Table 1). In addition, men were more likely to be white than women, whereas female recipients had higher percentages of blacks than men. The majority of all patients were self-paid or possessed private insurance and this did not differ among the 4 sex strata. Male recipients who received organs from male donors had the highest level of recipients completing an advanced degree (college or graduate work, 51.5%). Male recipients who received male donor organs had the greatest number of comorbidities. Specifically, the male donor/male recipient group had the highest rates of diabetes mellitus, highest creatinine levels, greatest BMI and had the highest percentage of patients listed as UNOS status 1 at transplant (Table 1). There were significant differences in levels of support among the 4 groups including differences in rates of preoperative intra-aortic balloon pump use, rates of intensive care unit care, hospitalization, and preoperative mechanical ventilation. Hemodynamic variables such as cardiac index, PVR, mean pulmonary artery pressure, and transpulmonary gradient differed among groups statistically, but absolute differences from a clinical perspective were small.

Survival
Female recipients, irrespective of donor sex, had lower overall survival as compared with men (3.6% lower cumulative survival at 5 years, P=0.003 by log rank test; Figure 2). On risk adjustment, this corresponded to a HR of 1.11 (95% CI, 1.0 to 1.26).

After stratification by donor sex, men who received organs from male donors had the highest cumulative survival at 5 years (74.5%; Figure 3). The incidence rate for death in this group was 6.6 deaths/100 person-years. By contrast men receiving hearts from female donors had a mortality incidence of 7.7 deaths/100 person-years (P<0.001). Men receiving hearts from men additionally had improved short-term survival demonstrating the highest survival rates at 30 days, 90 days, 1 year, and 2 years when compared with the other 3 strata (Table 2). By contrast, women did not demonstrate differences in short- or long-term survival based on donor sex (P=0.77; Figure 4) with mortality incidence rates of 7.5 and 7.7 deaths per 100 person-years in the female donor-female recipient and male donor-female recipients groups, respectively.

Multivariable Analysis
After risk adjustment, with multivariable analysis, men who received organs from male donors continued to demonstrate the greatest survival after transplantation (Table 3). Men who received male hearts had a 15% increase in the risk of adjusted cumulative mortality as compared with men who received male hearts (HR, 1.15; 95% CI, 1.02 to 1.30; P=0.02). The incremental effect of female gender and opposite sex transplant resulted in a 25% increase in the risk of cumulative mortality when compared with the reference group of men receiving male organs (HR, 1.25; 1.07 to 1.43; P=0.003). Examination of female recipients alone revealed no significant increase in the relative hazard for death.
between those receiving same versus opposite sex donor organs (1.24; 0.92 to 1.35; \( P = 0.31 \); Figure 4). Additional predictors of mortality on multivariable analysis included age >60 years, black race, BMI, recipient diabetes mellitus, mechanical ventilation before transplant, intensive care unit before transplant, age of donor, panel reactive antibody >20%, and 5 or 6 human leukocyte antigen mismatch.

### Propensity Adjustment

The propensity score generated ranged from 0 to 0.61 (median, 0.29). Individuals receiving organs from opposite sex donors had higher propensity scores (0.31 versus 0.29, \( P < 0.001 \)) as expected. The sensitivity analysis provided results consistent with that previously mentioned (Table 4). After propensity score quintiles were included in a separate multivariable analysis, men receiving organs from female donors continued to demonstrate increased risk of cumulative mortality when compared with the male donor-male recipient groups (HR, 1.2; 1.08 to 1.34; \( P < 0.001 \)).

### Survival Stratified by UNOS Status

Male recipients were stratified by UNOS status that served as a surrogate for clinical acuity (Figure 5). For men who were listed for transplant as UNOS status 1a, 1b, or older UNOS status 1, receiving organs from female donors continued to demonstrate decreased survival (HR, 1.19; 1.03 to 1.37; \( P = 0.02 \)). Interestingly, this association did not persist when examining those male patients listed as UNOS status 2 (1.01; 0.79 to 1.26; \( P = 0.94 \)). When female recipients were stratified in a similar manner, no association between donor sex and survival existed for either acuity strata.

### Discussion

In this study, we have presented multi-institutional UNOS data from a decade of OHT to aid clinicians in discerning differences in outcomes based on donor and recipient sex. Similar to previous reports, we have observed that female recipients had an 11% increase in the risk of cumulative mortality irrespective of donor sex. Among male recipients, those receiving hearts from a male donor had a 2.7% and 3.6% increase in their cumulative survival at 1 and 5 years, respectively. This strong association persisted after risk adjustment for potential confounding variables (ie, donor age, recipient acuity, and size matching).

An important finding of this study is that despite their overall lower survival, female recipients were not at increased risk for death when receiving a heart from a male recipient. Differences in survival for female recipients based on donor sex were not different at any time point, and this lack of association remained after risk adjustment. Although not observing an association does not prove equivalence, given our study parameters, the sample size of 4322 female recipients provides adequate statistical power to detect approximately a 6% increase in the relative hazard of death.

We further examined differences among patients transplanted after being listed as UNOS status 1 versus 2 as a surrogate for clinical acuity. For female recipients, this stratification did not alter the primary findings that no differences in mortality were observed based on donor sex. For men, however, the association between donor sex and mortality disappeared when examining those patients listed as status 2. This suggests that receiving organs from male donors may be especially important in male recipients of high clinical acuity.

As has been previously reported, male heart transplant recipients strongly outnumbered women in this series. With the American Heart Association reporting equal prevalence rates for heart failure in men and women, the reasons for this discrepancy were not entirely clear. Some have speculated earlier heart failure diagnosis in men, which may be a contributing factor. In this present cohort, male recipients were on average 5 years older than women, implying that age is not a strong predicting factor. Implicated as well is that female heart failure patients may be up to 3 times more likely to refuse heart transplantation than men. Finally, some series have suggested that when compared with men, women

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**Table 2. Unadjusted Kaplan-Meier Estimates of Short-Term Cumulative Survival**

<table>
<thead>
<tr>
<th>Survival Time</th>
<th>Male Donor, Male Recipient (N=10 750)</th>
<th>Female Donor, Female Recipient (N=2201)</th>
<th>Male Donor, Male Recipient (N=2121)</th>
<th>Female Donor, Male Recipient (N=3168)</th>
<th>( P^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 d</td>
<td>94.5 (94.1–95.0)</td>
<td>93.4 (92.2–94.4)</td>
<td>93.6 (92.4–94.5)</td>
<td>92.2 (92.2–93.1)†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>90 d</td>
<td>92.0 (91.5–92.5)</td>
<td>89.9 (88.5–91.1)†</td>
<td>90.3 (89.9–91.5)</td>
<td>89.4 (88.3–90.1)†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1 y</td>
<td>87.5 (86.8–88.1)</td>
<td>85.1 (83.5–86.6)†</td>
<td>84.9 (83.2–86.4)†</td>
<td>84.5 (83.3–85.8)†</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2 y</td>
<td>83.6 (82.9–84.3)</td>
<td>80.1 (79.0–82.5)†</td>
<td>80.1 (79.1–82.6)†</td>
<td>77.8 (76.3–79.3)†</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are presented as % (95% CI).

\( ^* P < 0.05 \) based on results of Mantel-Cox log rank test.

\( ^† P < 0.05 \) relative to reference: male donor/male recipient (adjusted for post hoc multiple comparisons).
with advanced heart failure of nonischemic etiologies may have improved survival without transplantation.15,16

**Previous Work**

Initial work examining donor and recipient sex in OHT supported female donor sex to be an independent risk factor for mortality.9 This belief has been supported in both single-institution series1,2,4 and multi-institutional data.3 The major limitation of these studies is that they failed to stratify patients by both donor and recipient sexes. With >70% of OHT recipients male, investigation of the role of donor sex and mortality only should include separate examinations for

### Table 3. Univariate and Multivariable Predictors of Mortality After OHT

<table>
<thead>
<tr>
<th>Variables of Interest</th>
<th>Univariate Analysis</th>
<th>Multivariable Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Donor-recipient sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male donor, male recipient</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Female donor female recipient</td>
<td>1.14 (1.05–1.25)</td>
<td>0.003</td>
</tr>
<tr>
<td>Male donor female recipient</td>
<td>1.16 (1.06–1.27)</td>
<td>0.001</td>
</tr>
<tr>
<td>Female donor male recipient</td>
<td>1.19 (1.1–1.28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex mismatch (combined males and females)</td>
<td>1.15 (1.07–1.22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Additional variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1.42 (1.31–1.45)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.11 (0.98–1.25)</td>
<td>0.09</td>
</tr>
<tr>
<td>Other</td>
<td>1.06 (0.88–1.29)</td>
<td>0.05</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>1.01 (1.01–1.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age, &gt;60 y</td>
<td>1.20 (1.13–1.27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recipient creatinine</td>
<td>1.05 (1.04–1.07)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recipient diabetes mellitus</td>
<td>1.23 (1.15–1.32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Recipient HTN</td>
<td>1.13 (1.07–1.20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PVR (&gt;4 woods units)</td>
<td>1.08 (0.98–1.19)</td>
<td>0.1</td>
</tr>
<tr>
<td>Recipient diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dilated CM</td>
<td>1.13 (1.06–1.21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ischemic CM</td>
<td>1.44 (1.21–1.72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Congenital</td>
<td>1.06 (0.98–1.15)</td>
<td>0.12</td>
</tr>
<tr>
<td>Acuity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU before transplant</td>
<td>1.22 (1.15–1.29)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>2.36 (2.07–2.71)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Inotropes at time of OHT</td>
<td>1.07 (1.01–1.14)</td>
<td>0.01</td>
</tr>
<tr>
<td>IABP at time of OHT</td>
<td>1.27 (1.13–1.43)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UNOS status 1†</td>
<td>1.16 (1.09–1.25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Donor and immunology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRA &gt;20%</td>
<td>1.25 (1.08–1.43)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HLA mismatch (0 or 1 antigens matched)</td>
<td>1.12 (1.05–1.19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age of donor, y</td>
<td>1.01 (1.01–1.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Donor cigarette use</td>
<td>1.17 (1.11–1.25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Donor/recipient BMI ratio &lt;0.75</td>
<td>1.18 (1.04–1.34)</td>
<td>0.008</td>
</tr>
<tr>
<td>Ischemic time &gt;6 h</td>
<td>1.39 (1.05–1.85)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*P value based on multivariable Cox proportional hazards regression. The final model incorporated the following covariates significant on univariate analysis and passing the likelihood ratio test for significance. Recipient: race, age >60 years, BMI, creatinine, mechanical ventilation before transplant, history of diabetes, ICU before transplant, PRA >20%, <2 HLA antigen match, PVR >4 woods units. Donor/organ: age, cigarette use, diabetes mellitus, and ischemic time >6 hours.

†UNOS status 1 refers to patients listed as status 1a, status 1b, or older UNOS status 1.

HTN indicates hypertension; PVR, pulmonary vascular resistance; CM, cardiomyopathy; ICU, intensive care unit; IABP, intra-aortic balloon pump; PRA, panel reactive antibody; HLT, human leukocyte antigen.
male and female recipients. To address this issue more fully, 2 series have been published, which stratified both male and female recipients by the sex of the donor heart. Prendergast et al reviewed 174 OHT patients at a single institution between 1992 and 1994. Among all recipients, the investigators noted an 18% lower 1-year survival for sex-mismatched transplants. In addition, among male recipients, 84.8% survived to 1 year when receiving a male heart versus 66.7% of those with female hearts (P=0.003). With only 39 female recipients, the study was not large enough to allow through assessment of donor/recipient sex mismatching in women.

An important study on this subject was conducted by Al-Khaldi et al who reviewed 869 consecutive OHTs at the Stanford University Medical Center. Similar to the study by Prendergast et al, male recipients receiving hearts from female donors had reduced 1-, 5-, and 10-year survivals when compared with sex-matched pairs. The investigators stratified the group by recipient age and found the association to hold only for those recipients older than 45 years. No association between donor sex and outcomes was observed for the 213 female recipients in the series.

Our study builds on the work of these investigators by using a multi-institutional modern cohort. This series provides a snapshot of the modern practice of heart transplantation in the United States and shows that men assume an increased risk of death when receiving hearts from female donors.

### Donor-to-Recipient Size

Clinical studies like this and those mentioned previously cannot definitively address the question of why sex mismatch leads to decreased survival in men only. There have been many mechanisms postulated. Chief among these is the belief that the smaller mass of the female heart may not have functional reserve required to supply the male body. In the study by Al-Khaldi et al, the authors make note of the fact that donor-to-recipient body surface area (BSA) ratio can serve as a surrogate for identifying hearts, which may be prone to fail. Because of practice patterns at their institution, the series reports similar donor-to-recipient BSA ratios in all 4 of their donor/recipient sex strata. Our data reported also suggests that similar matching occurs broadly in the United States. Likely resulting from the large sample size, statistically significant differences in donor-to-recipient BSA and BMI ratios occurred among groups, although the absolute differences were quite small and unlikely to be of clinical significance.

From the present analysis, however, the importance of size matching remains unclear. In our series, neither donor-to-recipient BSA nor BMI ratio (continuously) was found to be predictors of mortality using either univariate or multivariable regression. Donor-to-recipient BMI ratio of <0.75 was associated with increased mortality for men (univariate analysis only), which did not persist on multivariable analysis. Furthermore, we failed to demonstrate a significant interaction between size mismatch and PVR in the cohort. It should be noted, however, that practice patterns among clinicians limit smaller donors for recipients with high PVR, and the absolute number of mismatched patients fitting this profile was too small to draw meaningful conclusions (n=36). Other potential mechanisms requiring further investigation include the role of the minor histocompatibility antigen on the Y chromosome, differences in hormonal composition between the sexes, and unknown immunologic factors.

### Table 4. Cox Proportional Hazards Regression Analysis, Adjusted by Propensity Score Quintiles

<table>
<thead>
<tr>
<th>Donor-Recipient Sex</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male donor, male recipient</td>
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<td>1.07 (0.94-1.22)</td>
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</tr>
<tr>
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<td>1.14 (1.0-1.29)</td>
<td>0.05</td>
</tr>
<tr>
<td>Female donor male recipient</td>
<td>1.20 (1.08-1.34)</td>
<td>0.001</td>
</tr>
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<td>Sex mismatch (combined males and females)</td>
<td>1.14 (1.08-1.22)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Table 5. Kaplan-Meier estimates of survival for males who received their OHT from same versus opposite sex donors, stratified by UNOS status 1 (A) versus UNOS status 2 (B). Status 1 refers to patients listed as status 1a, status 1b, or older UNOS status 1. MD/MR indicates male donor/male recipient; FD/MR, female donor/male donor (based on OPTN data, May 2008).

### Figure 5.

A UNOS Status 1

- Male Donor/Male Recipient
- Female Donor/Male Recipient
- Adjusted HR for death 1.19 (1.03-1.37), p<0.02

B UNOS Status 2

- Male Donor/Male Recipient
- Female Donor/Male Recipient
- Adjusted HR for death 1.01 (0.97-1.06), p=0.94

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Limitations

Our study is limited by the retrospective cohort approach. As we have relied on UNOS for data collection, we did not have control of the variables selected. Therefore, we acknowledge that there are variables of interest for heart transplant programs unaccounted for in this data set. Furthermore, there may well be important confounding variables which we have consequently failed to include in our analysis. The UNOS data set is limited by incomplete follow-up and in some cases missing data. We cannot confirm that errors in coding do not exist, although we have made the assumption that these in general are random and unlikely to bias the results. Finally, using this approach, we are unable to delineate the mechanism by which sex mismatching may lead to increased mortality for male OHT recipients. Although some information on rejection and transplant coronary disease is present, it is incomplete and the data set does not provide the comprehensive data to draw appropriate conclusions regarding the “why” behind mortality.

Conclusions

Despite these limitations, we have presented a modern cohort of patients receiving OHT to study outcomes based on donor and recipient sexes. More than 3 quarters of OHT male recipients have superior outcomes when paired with male donor hearts. Female recipients have decreased survival irrespective of whether they receive hearts from male or female recipients. These data support the conclusion that men should receive hearts from male donors when feasible.

Sources of Funding

This work was supported in part by Health Resources and Services Administration contract 234-2005-370011C and by a Ruth L. Kirschstein National Research Service Award (NIH Services Administration contract 234-2005-370011C and by a Ruth L. Kirschstein National Research Service Award (NIH

References


CLINICAL PERSPECTIVE

Limited data has suggested that men who receive heart transplantation from female donors may have decreased survival. In our study, it is believed that women receiving heart transplantation may have lower overall survival irrespective of donor sex. Our study aimed to comprehensively address outcomes associated with donor and recipient sex in heart transplantation using a multi-institutional sample from the United Network for Organ Sharing database. We present the outcomes of >18,000 heart transplantation patients in the modern era and show that male recipients derive a substantial benefit from receiving their heart from a male donor. For females, however, donor sex does not seem to influence mortality. It is noteworthy that overall, women had lower survival than men irrespective of donor sex (3.6% lower at 5 years). The clinical relevance of the study lies primarily in the data surrounding the male recipients. Men should receive hearts from male donors whenever possible because of the substantial mortality benefit with sex matching. In addition, more data regarding how donor and recipient sex influence outcomes in heart transplantation is needed.
The Impact of Donor-Recipient Sex Matching on Survival After Orthotopic Heart Transplantation: Analysis of 18 000 Transplants in the Modern Era

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