The impact of gender on heart transplantation outcomes: a single center experience

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Heart transplantation; Rejection; Sex; Survival.

Background. **According to the data of the Registry of the International Society for Heart and Lung Transplantation, donor and recipient female gender is a significant risk factor for mortality after heart transplantation. It has also been reported that donor-recipient gender mismatch is a determinant of post-transplant morbidity and mortality. To examine the effect of gender on the early and mid-term outcomes, we retrospectively reviewed data of a consecutive group of heart transplant recipients at our Institution.**

Methods. **The study population comprised 99 patients undergoing heart transplantation between 1996 and 1998. This population was divided into four groups on the basis of donor and recipient matching. Group A consisted of 61 men who received male donor hearts, group B of 12 women who received female donor hearts, group C of 9 women who received male donor hearts, and group D of 17 men who received female donor hearts. Standard heart transplantation protocols were applied to all patient groups [graft preservation with Celsior solution, Shumway surgical technique, donor-recipient size matching ≥ 1.0, induction therapy with polyclonal antithymocyte globulins, triple immunosuppressive therapy (neoral, azathioprine, steroids)].**

Results. **The study groups were found to be homogeneous with regard to the major preoperative risk factors (etiology, status at transplantation, donor and recipient age, total ischemic time). Donor gender, recipient gender and donor-recipient gender mismatching did not significantly modify the short and mid-term survivals, functional recovery and freedom from rejection.**

Conclusions. **Even though previous reports suggest that gender negatively affects survival, this factor proved to have no influence on the outcomes of the present series. These results can be explained by a correct donor-recipient size matching. The well-documented female recipients tendency to more frequent and fatal rejection was not confirmed in our experience. The patient's age at transplantation, the routine use of induction therapy and an aggressive immunosuppressive regimen may be the substrate of these findings.**

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Introduction

The limited number of donor hearts mandates the judicious application of heart transplantation to appropriate recipients. Despite many advances, the factors influencing short- and long-term survivals are still being defined. In particular, the effect of donor gender, recipient gender, and donor-recipient gender matching on heart transplantation outcomes has not been definitely established. Several clinical studies have reported an increased risk of death and rejection in female heart transplant recipients, with conflicting reports on the effect of donor-recipient gender matching. Other investigators have implicated the use of female donor hearts as a risk factor for rejection[1-5]. The fifteenth annual data report of the International Society of Heart and Lung Transplantation (ISHLT) confirmed the role of a female donor as a statistically significant risk factor increasing the 1- and 5-year mortality rates after transplantation[6]. More recently, the 2001 annual report indicated that the donor-recipient gender mismatch (i.e. transplantation of a female graft into a male recipient) constitutes an independent risk factor for the 1-year mortality. In order to elucidate this issue further, we attempted to separately and retrospectively examine the effects of donor gender, recipient gender, and donor-recipient gender matching by reviewing data of a consecutive group of heart transplant recipients at our Institution.

Methods

The study population comprised 99 patients undergoing heart transplantation between 1996 and 1998. This population was divided into four groups. Group A consist-

ed of 61 men who received male donor hearts, group B consisted of 12 women who received female donor hearts, group C consisted of 9 women who received male donor hearts, and group D consisted of 17 men who received female donor hearts.

Patient management. All recipients underwent transplantation in the hands of the same group of surgeons who performed the atrial anastomotic technique. Triple-drug immunosuppression therapy with methylprednisolone, azathioprine and neoral cyclosporine was standard practice. Intravenous methylprednisolone administration was initiated at a dosage of 500 mg during the operation and followed in the postoperative period by 125 mg every 8 hours for 2 days. After patient extubation, oral prednisone (1 mg/kg tapered to 0.1 mg/kg daily) was begun and azathioprine administration was initiated at a dosage of 2 mg/kg daily and adjusted to keep the white blood cell count between 4×10^3 and 6×10^3/ml. Oral cyclosporine (3 mg/kg) was begun only after hemodynamic stabilization and normalization of the renal function. The dosage was adjusted to achieve, during the first 12 months, blood levels of 300 ng/dl (as measured by a whole blood radioimmunoassay). All patients were given induction therapy consisting of a 5-day course of continuous intravenous infusion of polyclonal antithymocyte globulin (12.5 mg/10 kg).

Rejection episodes were treated with 1 mg of methylprednisolone sodium succinate administered intravenously for 3 consecutive days. Steroid-resistant rejection episodes with severe hemodynamic instability were treated with a 9-day course of OKT3.

Following hospital discharge, patient follow-up included endomyocardial biopsies performed weekly for 2 months, then every 2 weeks during the third month. Further endomyocardial biopsies were dictated by the patient's clinical needs.

Data collection. Preoperative data including etiology, age, weight and United Network of Organ Sharing (UNOS) status were collected for each patient. Each donor's age, total ischemic time and level of inotropic support at graft harvesting were also registered. In particular, high inotropic support was defined as a dobutamine or dopamine dosage > 10 μg/kg/min, and/or the use of norepinephrine regardless of the dose. The incidence of primary donor heart failure (right ventricular failure, left ventricular failure, and biventricular failure) along with the need of high inotropic support (dobutamine or dopamine > 10 μg/kg/min and/or epinephrine > 8 μg/kg/min and/or milrinone ≥ 0.7 μg/kg/min) were examined in order to better characterize the effect of donor gender on the early postoperative outcomes. In particular, the persistence of the following hemodynamic parameters despite high inotropic support and intra-aortic balloon counterpulsation led to the diagnosis of primary donor heart failure: 1) right ventricular failure, with a central venous pressure > 20 mmHg, a right ventricular end-diastolic pressure > 15 mmHg, a pulmonary capillary wedge pressure < 15 mmHg, a mean pulmonary artery pressure > 20 mmHg, and a cardiac index < 1.5 l/min/m^2 ; 2) left ventricular failure, with a pulmonary capillary wedge pressure > 25 mmHg and a cardiac index < 1.5 l/min/m^2. The number of rejection episodes (severity ≥ 1B) as well as the mortality rates during the first year of transplantation were examined. The results of echocardiographic screening for left and right ventricular function (ejection fraction) at 1 year along with the NYHA class were also analyzed.

Statistical analysis. Clinical and laboratory data were retrospectively entered in a computerized database. No patient was lost to follow-up. Data were expressed as means ± SD. Categorical variables were compared using the Pearson exact test whereas continuous variables were compared using the univariate ANOVA test with Bonferroni correction for *post hoc*. The analyses of survival and event-free survival (rejection) were performed with the Kaplan-Meier method. Differences between the groups regarding actuarial analysis were studied using log-rank tests. The level of statistical significance was established at 95% ($p < 0.05$). The analysis was performed using the SPSS 10.0 statistical program (SPSS, Chicago, IL, USA).

Results

Recipient and donor data. The recipients in all groups were homogeneous with regard to age, UNOS status, and pulmonary vascular resistance. Coronary artery disease was the main cause of heart failure in male patients (30.8%), while idiopathic dilated cardiomyopathy was the most common underlying disease in female patients (85.7%). At antibody screening, no significant difference in the percentage of pre-transplant reactivity was found between the groups. The weight and body surface area of male recipients were significantly greater than those of their female counterparts (Table I).

The donor age was found to differ significantly between the groups ($p = 0.01$). The causes of death and the total post retrieval cold ischemia time, percentage of high inotropic support at harvesting, pre-harvesting intensive care unit stay, and the ratio of donor to recipient body surface area were similar. The use of marginal donors was also found to be homogeneous (Table II).

Outcomes. The overall hospital mortality rate was 9.1%. The causes of hospital mortality included graft failure in 6 cases, multiorgan failure in 2, and pneumonia in 1. No statistically significant difference emerged among the groups. The 1-year actuarial survival was 91.8%. At 1 year the overall freedom from

Table I. Preoperative characteristics of heart transplant recipients.

	Group A (n=61)	Group B (n=12)	Group C (n=9)	Group D (n=17)	p
Age (years)	44.8 ± 1.7	46.7 ± 4.9	44.4 ± 3.9	50 ± 2.2	0.52
Weight (kg)	75.1 ± 1.7	60.6 ± 1.9	60.4 ± 3.8	73.3 ± 5.1	0.0001
BSA (kg/m^2)	2.01 ± 0.7	1.65 ± 0.2	1.66 ± 0.1	1.88 ± 0.2	0.03
UNOS status 1	16 (26.2%)	4 (33.3%)	–	4 (23.5%)	0.314
LVAD	3 (4.91%)	–	–	1 (5.88%)	0.415
Marginal donor usage/status I	8 (50%)	1 (25%)	–	2 (50%)	0.325
Mean PRA	0.02	0.04	0.04	0.03	0.56
PVRI value	3.04	3.61	2.35	2.83	0.487
PVRI > 5	7 (11.5%)	1 (8.3%)	1 (11.1%)	2 (11.8%)	0.991

BSA = body surface area; LVAD = left ventricular assistance device; PRA = panel reactive antibodies; PVRI = pulmonary vascular resistance index; UNOS = United Network for Organ Sharing.

Table II. Characteristics of the heart donors.

	Group A (n=61)	Group B (n=12)	Group C (n=9)	Group D (n=17)	p
Age (years)	29.8 ± 1.4	37.6 ± 2.8	26.8 ± 3.7	37.5 ± 2.6	0.01
Donor/recipient BSA ratio	1.07 ± 0.007	1.07 ± 0.002	1.08 ± 0.002	1.07 ± 0.001	0.932
Marginal donors usage	33 (54%)	4 (33%)	3 (33%)	6 (35.3%)	0.721
High inotropic support	19 (31.1%)	3 (25%)	2 (22.2%)	3 (17.6%)	0.737
Cause of death					
Trauma	35 (57.4%)	2 (16.6%)	1 (11.1%)	8 (47%)	0.125
Cerebrovascular/stroke	20 (32.8%)	7 (58.3%)	6 (66.6%)	8 (47%)	0.360
Other	6 (9.8%)	3 (25%)	2 (22.2%)	1 (6%)	0.251
Pre-harvesting ICU stay (hours)	60.04	46	55.83	47.28	0.75
Cold ischemia time	156.9 ± 43.9	136.7 ± 35.5	141.6 ± 44.1	136.6 ± 31.7	0.17

BSA = body surface area; ICU = intensive care unit.

rejection reached 76%. In none of the patients did steroid-resistant rejection or rejection with severe hemodynamic instability occur. The 3-year actuarial survival was 91.8%. The causes of delayed mortality included accelerated graft coronary artery disease in 7 cases, multiorgan failure in 1, pneumonia in 1, Kaposis's sarcoma in 1, and pancreatitis in 1. No statistically significant difference emerged among the groups. As reported in table III, no statistically significant difference was found in the hospital mortality, the 1-year survival and the freedom from rejection of each study group. As far as primary donor heart failure was concerned, this complication developed in 3 patients in group A and in 3 in group D (p = 0.132) and was lethal in all cases. The need for early postoperative high inotropic support proved similar among the study groups. The post-transplant functional recovery was usually good and 93% of the patients were in NYHA class I at 1 year of follow-up. Concordantly, echocardiographic screening at 1 year showed normal left and right ventricular functions (mean ejection fraction 51 ± 5.2%). No difference emerged in either functional or hemodynamic recovery.

Donor gender, recipient gender and donor-recipient gender matching effect. Neither donor gender nor recipient gender exerted a significant effect on heart transplantation outcomes. Donor-recipient gender mismatch did not exert a significant effect on heart transplantation outcomes; nevertheless, fatal graft failure occurred in 3 out of 17 gender mismatched male recipients (Table IV).

Discussion

The objective of applying selection criteria to organ donors is to allow recipients the highest probability of successful transplantation. Several reports on human and animal models suggest that female heart transplant recipients have a decreased survival compared with matched male controls. Similarly, in the literature there is evidence that female recipients experience more frequent and severe rejections. The Registry of the ISHLT reports that female donor is a statistically significant risk factor for increased 1- and 5-year mortality rates. In order to elucidate this issue further, we attempted to separately examine the effects of donor-gender, recipi-

Table III. Effects of gender on early heart transplant outcomes.

	Group A (n=61)	Group B (n=12)	Group C (n=9)	Group D (n=17)	p
Graft failure	3 (4.9%)	–	–	3 (17.6%)	0.132
High inotropic support	14 (22.95%)	3 (25%)	–	3 (17.6%)	0.430
Hospital mortality	6 (9.8%)	–	–	3 (17.6%)	0.297
1-year survival (%)	92.4 ± 0.04	91.7 ± 0.08	100	83.9 ± 0.1	0.690
1-year freedom from rejection (%)	77.6 ± 0.06	66.7 ± 0.13	88.9 ± 0.1	71.4 ± 0.12	0.636
3-year survival (%)	87.63 ± 0.05	91.67 ± 0.08	100	83.92 ± 0.1	0.68

Table IV. Effects of recipient gender, donor gender and donor-recipient gender matching on heart transplant outcomes.

	Recipient gender			Donor gender			Donor-recipient gender		
	Male (n=78)	Female (n=21)	p	Male (n=70)	Female (n=29)	p	Matched (n=73)	Mismatched (n=26)	p
Hospital mortality	9 (11.5%)	–	0.1	6 (8.6%)	3 (10.3%)	0.52	6 (8.2%)	3 (11.5%)	0.44
Graft failure	6 (7.7%)	–	0.23	3 (4.3%)	3 (10.3%)	0.24	3 (4.1%)	3 (11.5%)	0.18
1-year cumulative survival (%)	90.8 ± 0.04	95.2 ± 0.05	0.37	93.5 ± 0.03	87.6 ± 0.07	0.69	92.3 ± 0.03	90.7 ± 0.06	0.85
1-year freedom from rejection (%)	76.3 ± 0.5	76.4 ± 0.09	0.97	79.1 ± 0.05	68.8 ± 0.09	0.26	75.4 ± 0.05	78.3 ± 0.09	0.90
3-year cumulative survival (%)	76.95 ± 0.05	95.2 ± 0.05	0.068	81.6 ± 0.05	78.6 ± 0.08	0.70	80.9 ± 0.05	80.2 ± 0.08	0.90

ent-gender and donor-recipient gender matching on the outcomes of heart transplantation.

In our series, the hospital mortality was 9.1% while the 1-year survival was 91.9%, regardless of donor and recipient gender. These percentages are consistent with those of larger series from major centers.

A greater right ventricular mass is usually thought to be the substrate of male donor heart superiority, especially in high-risk patients. Although in this report the effect of male donor heart transplantation in a recipient with pulmonary hypertension was not stratified, our data, concerning a large group of heart transplantation recipients, suggest that this parameter did not bear any influence on the final outcomes. This finding may be justified by a strict donor-recipient size matching, which in our experience was always ≥ 1.0. Similar evidence derives from a recent report from the Cardiac Transplant Research Database which reviewed data on more than 5000 heart transplants[7]. Placing the heart of a smaller female donor (body surface area < 1.5 m^2) into a larger male recipient proved to be a statistically significant risk factor for death (p = 0.003). The 3 deaths attributable to graft failure, in the group of 17 male recipients of gender mismatched hearts, may be explained by the high UNOS status at the time of transplant (2 out of 3 patients), the presence of pulmonary hypertension (2 out of 3 patients) and the occurrence of massive intraoperative bleeding (1 out of 3 patients). The statistically significant differences in donor age that emerged between the groups are to be carefully evaluated taking into account that all the donors in our study were < 45 years old. Nevertheless, further studies are needed in order to identify specific subsets of recipients for whom donor gender may turn out to be an important parameter.

In accordance with the results of Fabbri et al.[8] and with those of Prendergast et al.[9], even in our study population recipient gender alone did not significantly influence the heart transplantation outcomes.

Organ rejection is another issue in which recipient and donor gender has been believed to play a major role. In the literature there is considerable evidence that female recipients experience more frequent and fatal episodes of graft rejection. Several factors may play a role in this enhanced rejection response: 1) the presence of increased antigenic stimuli consequent to pregnancy, 2) the presence of higher levels of circulating immunoglobulins, 3) the immunomodulating properties of estrogens, 4) the relatively low tissue sensitivity to androgens, 5) the lower age at the time of transplantation, and 6) the higher incidence of idiopathic dilated cardiomyopathy, a condition related to immune disorders. On the other hand, it has been reported that gender mismatch is a major risk factor for rejection, especially in female recipients. In our series, female recipients experienced a similar freedom from rejection to that of male recipients. These results may depend on the relatively high mean age at the time of transplantation, comparable to that of male recipients, and on the routine use of induction therapy in the context of an aggressive immunosuppressive protocol. Prendergast et al.[9] have reported similar results. Lack of gender mis-

match significance on the incidence of rejection in our series may be based on the aggressiveness of the immunosuppressive protocol. These findings are consistent with the results of Keogh et al.[10] who stated that more aggressive maintenance immunosuppression (triple drug regimen) decrease the propensity to rejection in gender mismatched heart recipients.

In conclusion, more intense immunosuppression and correct donor-recipient size matching seem to provide good results in higher-risk patient groups even though enhanced donor-recipient gender matching strategies must come to terms with the severe shortage of donor organs.

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