Gender-Based Analysis of Outcome After Heart Transplantation

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Abstract

Objectives: **Gender differences between donors and recipients might have an effect on outcome after heart transplantation. Literature and registries reveal controversial results. We reviewed 1000 heart transplantations at our center focusing on the influence of gender differences on short- and long-term outcome after heart transplantation.**

Materials and Methods: **We performed a retrospective analysis of 1000 (960 primary and 40 redo-heart transplantations) between August 1981 and July 2008. In contrast to other studies, the data for gender differences (donor gender and recipient gender) were evaluated for recipient survival and survival conditional to early mortality.**

Results: **Female donors are significantly older than male donors (females, 36.5 ± 14.5 years; males, 31.2 ± 13.8 years). One-year survival was significantly inferior in male recipients receiving female donor hearts (mR/fD: 73.7%) compared to females receiving male donor organs (fR/mD: 90.9%) (*P* = .045). Univariate analysis revealed that, for recipients who survived > 1 year, survival at 10 years was significantly greater for female donors and female recipients (90%) than it was for male donors and male recipients (72%; *P* = .034). Multivariate analysis showed that the gender combination with female donors and female recipients was an independent indicator for greater long-term survival (*P* = .04).**

Conclusions: **The gender combination of female donors and male recipients had a greater risk for early mortality after heart transplantation, and the combination of male donors and female recipients resulted in favorable short-term outcomes. In long-term follow-up, recipients of hearts from female donors had better survival, especially female recipients.**

Key words: *Transplantation, Cardiomyopathy, Organ donation, Allocation, Gender medicine*

Introduction

There are differences in clinical presentation and survival between men and women after heart transplantation and their clinical presentations before transplantation are different.[1, 2, 3] Treatment and response to treatment may vary between the sexes.[4, 5] Gender differences of donors and recipients may have a major effect on survival after a heart transplantation.[1-3, 6]

Most heart transplant recipients are men. According to the registry data of the International Society for Heart and Lung Transplantation, the frequency of heart transplantation that were done in female recipients between 1992 and 2001 was 20%, and between 2002 and 2009 was 23%.[6] The underrepresentation of women as heart transplant recipients may occur because men develop heart failure at a younger age and have higher heart failure mortality than women. Furthermore, there may be referral bias, selection bias, lower access to care, and lower acceptance of heart transplantations among women.[1-3, 7] Other gender differences may include

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heart size and the frequency of vasculopathy after a heart transplant.[6, 8]

Although the surgical procedure does not differ between sexes, we suspected gender-specific differences in outcome. Therefore, we studied the outcomes of heart transplant recipients at a single transplantation center to evaluate possible gender-based differences in short- and long-term results in male and female heart transplant recipients. We hypothesized that gender-differences have an effect on outcome after heart transplantation.

Materials and Methods

Study population

We retrospectively reviewed the data of 1000 heart transplantations, including 38 second- and 2 third heart transplantations, who underwent heart transplantation between August 1981 and July 2008 at the Medical Center of the University of Munich, Grosshadern University Hospital for treatment of end-stage heart disease. All protocols were approved by the ethics committee of the institution before the study began, and the protocols conformed with the ethical guidelines of the 1975 Helsinki Declaration. Written, informed consent was obtained from patients or their guardians.

Surgical technique

In most patients, surgery was performed with a bi-atrial technique except for 2 patients who had an atrial switch operation.[8, 9] Furthermore, 74 patients were bridged to a heart transplantation by implantation of a ventricular assist device.

Follow-up

The following criteria were recorded: age, gender, height, and weight of donor and recipient, indications for heart transplantation; ischemia time; and type and amount of cardioplegic solution used during surgery. Every patient underwent regularly detailed examinations to evaluate for acute or chronic rejection and infectious complications; these examinations included chest radiography, coronary angiography, endomyocardial biopsy, echo - cardiography, and laboratory tests including trough level testing for immunosuppressive drugs and testing for *cytomegalovirus*. All patients received cholesterol-lowering medication after the heart transplantation, but this medication was stopped in some patients because of muscle toxicity. Cardiovascular risk factors such as hyperlipidemia and diabetes mellitus were monitored. Mortality at 30 days, 1 year, and 10 years was recorded.

Statistical analyses

Data analyses were performed with SPSS software (SPSS: An IBM Company, version 19.0, IBM Corporation, Armonk, New York, USA). Values of continuous variables are expressed as means ± standard deviation (SD); discrete data are summarized as frequencies and group percentages. Linear and logistic regression models were used to test for gender differences. Statistical analysis of all data included Kaplan-Meier survival, log rank test, Mann-Whitney *U* test, and chi-square test. Data for gender differences were calculated with respect to actuarial and conditional survival (without 30-day or 1-year mortality). For Kaplan-Meier heart transplantation survival analysis, 4 subgroups were formed: male donors and male recipients; male donors and female recipients; female donors and male recipients; and female donors and female recipients. The probability values were calculated with the log rank test. For survival according to donor gender, the Gehan-Wilcoxon or Breslow test was used to place a greater weight on earlier events. For multivariate analysis, a Cox proportional hazard model was used. Statistical significance was defined as $P \leq .05$.

Results

Most heart transplant donors and recipients were male, and the most common indication for a heart transplantation was dilative cardiomyopathy (Table 1). Male recipients were significantly older than female recipients (Table 1). Male donors and recipients had significantly greater body weight and height than did female donors and recipients (Table 1). Male donors were significantly younger than female donors were (Table 2).

There was no significant difference in long-term survival between female and male recipients (not corrected for the higher life expectancy in females) (Figure 1). There was no significant difference in long-term survival between recipients who received hearts from either female or male donors (Figure 2). For heart transplant recipients who survived > 30 days after transplantation, long-term survival of

Table 1. Clinical Characteristics of Donors and Recipients of Heart Transplantations*

	Male	Female	$P \leq$
Number of patients (%)			
Recipients	819 (82%)	181 (18%)	
Donors	665 (67%)	335 (33%)	
Diagnosis			
Dilative cardiomyopathy	430	110	.05
Ischemic cardiomyopathy	250	25	.0001
Other†	130	55	.003
Age of heart transplant recipients (y)			
All	48 ± 15	41 ± 20	.0001
Other indications†	39 ± 20	20 ± 19	.003
Donor gender			
male	569	60	
female	218	117	
Donor height (cm)	177 ± 10	167 ± 12	.0001
Donor weight (kg)	76 ± 12	65 ± 13	.0001
Recipient height (cm)	176 ± 8	163 ± 9	.0001
Recipient weight (kg)	73 ± 12	61 ± 12	.0001

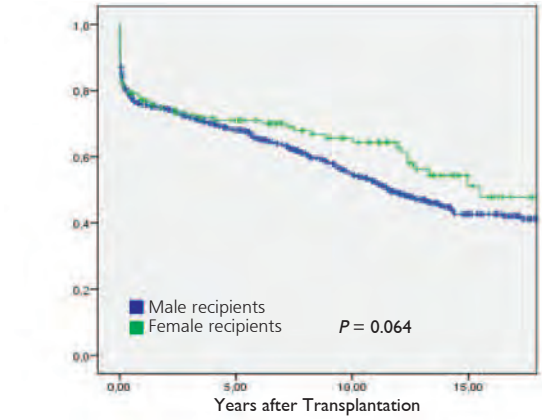
*n=1000 heart transplantations. Data are reported as number (%) patients or mean ± SD.
†Other indications: congenital heart disease, cardiac tumors, advanced valvular heart disease, or restrictive or hypertrophic cardiomyopath

Table 2. Relation Between Heart Transplant Donor and Recipient Gender and Age

Donor Gender Recipient Gender	Male Male	Male Female	Female Male	Female Female	$P \leq$
Donor age (y)*	32 ± 13	25 ± 18	37 ± 14	36 ± 15	.001
Recipient age (y)	48 ± 14	33 ± 22	47 ± 16	46 ± 17	.001

*Predominant causes of donor death: male donors, trauma; female donors, cerebrovascular accident. Mean age of all male donors was 31 ± 14 y and all female donors was 37 ± 15 y ($P \leq .01$)

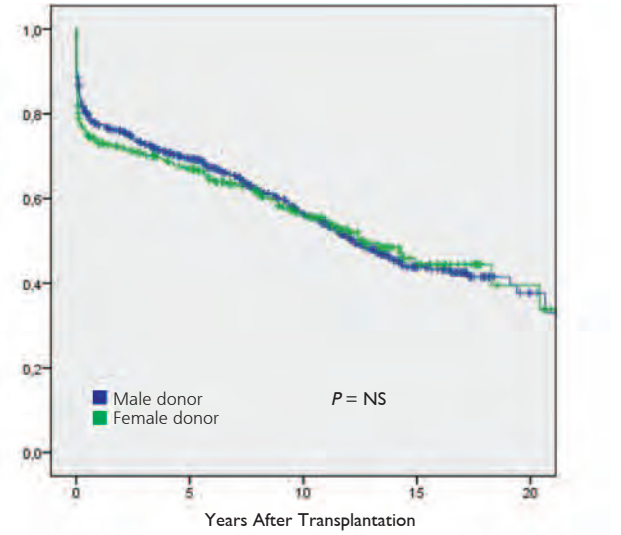
Figure 1. Survival Depending on Recipient Gender



Relation between cumulative survival of 1000 heart transplant recipients, including 40 revision transplantations in 38 patients, and recipient sex. Survival at 10 years was 65% in women and 55% in men. These values were not corrected for the higher life expectancy in women.

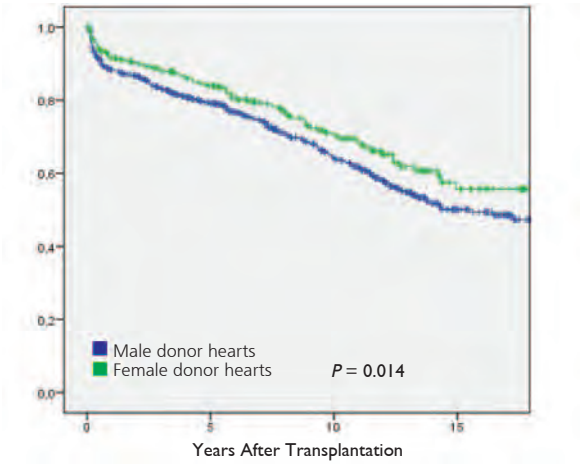
recipients of hearts from female donors was significantly greater than recipients of hearts from male donors (Figure 3). Survival of recipients at 1 year after transplantation was significantly greater for the subgroup of male donors and female recipients than the subgroup of male donors and

Figure 2. Survival Depending on Donor Gender



Relation between cumulative survival of 1000 heart transplant recipients, including 40 revision transplantations in 38 patients, and donor gender. Survival at 1 year was 73% with female donors and 77%, with male donors. Survival at 10 years was 57% with female donors and 56% for male donors.

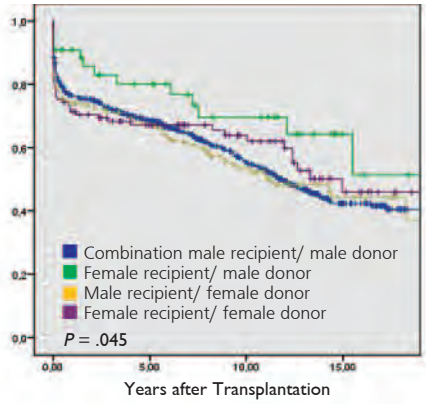
Figure 3. Conditional Survival Depending on Donor Gender (Without 30-Day Mortality)



Relation between cumulative survival and donor gender for recipients who survived > 30 days after heart transplantation. Long-term survival of recipients with hearts from female donors was significantly longer than from male donors; survival at 10 years was 80% in recipients with hearts from female donors and 72% in recipients with hearts from male donors ($P = .014$).

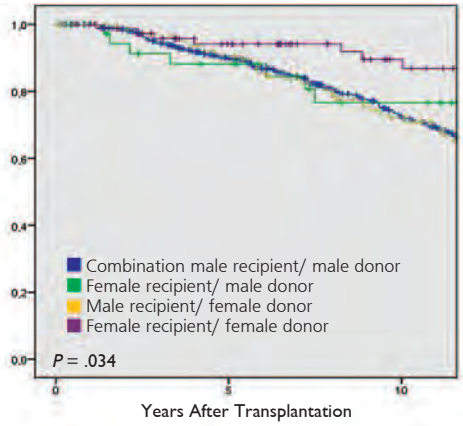
male recipients or subgroups of female donors and either male or female recipients (Figure 4). For heart transplant recipients who survived > 1 year after transplantation, long-term survival was significantly greater for the subgroup of female donor hearts and female recipients than the subgroups of male donors and either male or female recipients or subgroup of female donors and male recipients (Figure 5). There was no significant difference between the different

Figure 4. Survival Depending on Gender Combinations



Relation between cumulative survival and gender combinations of donor and recipient patients. Survival at 1 year for the 4 gender combination groups was male donors and male recipients, 76%; male donors and female recipients, 91%; female donors and male recipients, 74%; and female donors and female recipients, 71%. The group with male donors and female recipients had significantly less early graft failure compared with the other 3 combinations ($P = .045$).

Figure 5. Conditional Survival Depending on Gender Combinations (Without 1-Year Mortality)



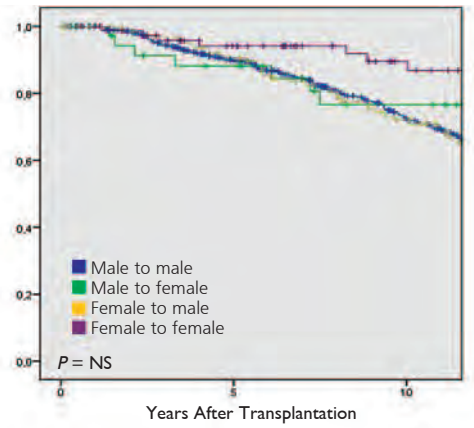
Relation between cumulative survival and gender of donor and recipient, for recipients who survived > 1 year after heart transplantation. Survival of recipients in the subgroup of female donors and female recipients was significantly greater at 10 years than in other gender combination groups: male donors and male recipients, 72%; male donors and female recipients, 77%; female donors and male recipients, 72%; and female donors and female recipients, 90% ($P = .034$).

subgroups of male or female donors or recipients in cardiac allograft vasculopathy (Figure 6).

Multivariate analysis was performed, because donor and recipient ages were gender-specific confounders (Table 2). The results of the Cox proportional hazard model for survival did not confirm most of the univariate results. The higher age of female donors was the most important confounder, and recipient age, diagnosis, and ischemic time were the predominant risk factors for early and late mortality. After correction for mortality ≤ 1 year after heart transplantation, the multivariate comparison of variables (such as donor age, recipient age, and ischemic time, that had been significant in univariate analysis [data not shown]), showed that the combination female donor and female recipient was a significant independent indicator for greater long-term survival (Table 3).

Evaluation of metabolic parameters in heart transplant recipients showed that mean serum creatinine at 1 year after heart transplantation was significantly lower in female than in male transplant recipients (Table 4). Male recipients had significantly lower total cholesterol at 1 year and lower high-density lipoprotein at 1 year, 5 years, and 15 years after heart transplantation than female recipients did (Table 4). There was no significant difference in frequency of complications between male and female recipients (Table 5).

Figure 6. Freedom from Cardiac Allograft Vasculopathy Depending on Gender Combination



Relation between absence of cardiac allograft vasculopathy and gender of donor and recipient. Absence of cardiac allograft vasculopathy at 5, 10, and 20 years after heart transplantation was similar for the subgroups of male donors and male recipients (82%, 67%, and 36%); male donors and female recipients (84%, 61%, and 18%); female donors and male recipients (80%, 66%, and 48%); and female donors and female recipients (88%, 77%, and 54%).

Table 3. Multivariate Analysis of Risk Factors for Survival After Heart Transplantation*

	Significance (P)	Hazard Ratio	95% Confidence Interval	
			Lower	Upper
Recipient age at HTx	.053	1.017	1	1.034
Donor age	.904	0.999	0.985	1.013
Ischemic time	.607	1.001	0.998	1.004
Female donor and female recipient†	.037	0.747	0.568	0.983

*Cox proportional hazard analysis
†Compared with the subgroup with female donors and male recipients or subgroups with male donors and either male or female recipients. Analysis limited to recipients who survived > 1 year after heart transplantation.
Abbreviations: HTx, heart transplantation

Table 4. Metabolic Parameters in Heart Transplant Recipients*

Metabolic parameter	Time after Transplant (y)	Male	Female	$P \leq$ †
Creatinine (μmol/L)	1	150.3 ± 61.9	132.6 ± 44.2	.01
Total cholesterol (mmol/L)	1	5.1 ± 1.1	5.5 ± 1.4	.007
LDL (mmol/L)	1	3.1 ± 1	3.2 ± 1.1	NS
HDL (mmol/L)	1	1.2 ± 0.4	1.6 ± 0.6	.0002
HDL (mmol/L)	5	1.2 ± 0.4	1.6 ± 0.5	.001
HDL (mmol/L)	10	1.4 ± 0.5	1.5 ± 0.5	NS
HDL (mmol/L)	15	1.4 ± 0.4	2 ± 1.1	.005

*Data reported as means ± SD.
Abbreviations: HDL, high-density lipoproteins; LDL, low-density lipoproteins
†NS, not significant ($P > .05$)

Table 5. Complications Associated with Heart Transplantation

Complications	Number (%) of patients Male	Female	$P \leq$*
Revision heart transplantation	36 (4)	4 (2)	NS
Assist device implantation before heart transplantation	52 (7)	10 (7)	NS
Acute rejection episodes (y/n)	240 (36)	47 (36)	NS
Cardiac allograft vasculopathy (y/n)	184 (27)	32 (25)	NS

*NS, not significant ($P > .05$)

Discussion

The present results show significant gender-specific differences in outcomes of heart transplantations, especially significantly improved long-term survival for female recipients who receive transplanted hearts from female donors (Table 3).

The frequency of female recipients was low compared with male recipients (Table 1), consistent with previous studies, possibly because females have a lower risk of end-stage heart failure, later age at which heart failure develops, and different referral patterns for heart transplantation in women.[1, 2] In a previous study, only 91 of 386 patients (24%) accepted for a heart transplantation were females, and females more frequently refused to undergo heart transplantation candidacy (self-refusal of female patients).[1] The older age of male than female transplant recipients (Table 1) was likely because of age- and gender-specific indications for transplantation including dilative and ischemic cardiomyopathy, which were more frequent in male than female recipients (Table 1).

The smaller height and weight values of female than male donors and recipients (Table 1) are consistent with previous studies. In samples of healthy subjects, female hearts typically have smaller absolute left ventricular mass (males, 155 g; females, 103 g), systolic and diastolic volumes, and linear dimensions than male hearts.[10] These findings must be taken into account, especially when a female donor is chosen for a male recipient. Even if donor and recipient height and weight are equal, the female donor heart is considerably smaller.

The present data confirm that outcomes after heart transplantation may be gender-specific and therefore, influenced mainly by donor gender and recipient gender. Female donor hearts were associated with higher early mortality (lower survival at 1 year after surgery) in male recipients than male donor hearts were (Figure 4). This could be attributed to "undersizing," with consecutive primary graft failure predominantly caused by the failing right ventricle. Male donor hearts were associated with greater survival at 1 year in female recipients (Figure 4), possibly because of "oversizing," with the recipient receiving a larger heart larger that can cope with secondary pulmonary hypertension.[10] In long-term follow-up, corrected for early mortality, survival was greater with female than with male donor hearts (Figure 3), possibly because of lower risk of subclinical atherosclerosis in female than male donors.

The present results are consistent with previous findings of greater early mortality (lower early survival) with female donor hearts transplanted to male recipients (Figure 4).[11] However, in the previous study, female donor hearts were used more often for urgent heart transplantations to male recipients, and the greater early mortality might have been attributable to the higher risk profile of the recipients[11]; this effect was not identified in the present study.

Another study of 869 heart transplantations showed a negative effect of female donor gender on the survival of male recipients, but only for recipients older than 45 years.[12] In another study in which mortality was not significantly higher with female donor hearts, female donor gender was a risk factor for lower cardiac output and more frequent intra-aortic balloon pump insertions after heart transplantation.[13] Furthermore, a review of data from > 18 000 heart transplantations from multiple centers showed that female recipients, irrespective of donor gender, had 3.6% lower survival than male recipients 5 years after heart transplantation; males who received organs from male donors had the greatest cumulative survival at 5 years (75%), but males receiving female hearts had a 15% increase in the risk of adjusted cumulative mortality.[3]

Cardiac allograft vasculopathy is a major cause of mortality after heart transplantation. Gender-specific differences in kinetics of immunosuppressive drugs may contribute to chronic rejection and cardiac allograft vasculopathy.[14] Previous data suggested that female donor hearts may be associated with a lower risk for developing cardiac allograft vasculopathy within 5 years after heart transplantation,[6] and hearts from male donors aged > 35 years are at greater risk of developing cardiac allograft vasculopathy, probably because of pre-existing coronary lesions.[6] However, stenotic microvasculopathy detected in myocardial biopsies has been observed equally with male (38%) and female (39%) donor hearts.[15] Allografts from premenopausal female donors to male recipients more frequently develop endothelial disease and stenotic microvasculopathy. However, these data were not associated with different long-term outcomes.[15, 16] Although gender may have an effect on cardiac allograft vasculopathy,[1, 17] no significant effect of donor and recipient gender on cardiac allograft vasculopathy was noted in the present study (Figure 6).

The greater mean serum creatinine observed in male than female recipients (Table 4) may have been caused by several factors such as less immunosuppressant agents related to the body weight, hormonal influences, and better abilities of women to regenerate. Previous studies have shown that female recipients typically have worse preoperative renal function as an indicator of severity of heart failure than male recipients. Owing to the younger age of female recipients in the present study (Tables 1 and 2), renal function of these females was better in comparison with other investigated groups.

Although patients received cholesterol-lowering medications after heart transplantation, total cholesterol levels frequently were elevated (in women more so than in men) because of adverse effects of immunosuppressive drugs (Table 4). Middle-aged women with healthy hearts typically have a higher mean HDL level by 0.3 mmol/L compared with healthy men. The female recipients in the present study had a younger mean age than male recipients (Table 1), and female premenopausal hormonal status may have influenced lipid levels in the female recipients.

Complications in the present study were infrequent, including revision transplantation and use of assist devices before transplantation (Table 5). Although acute graft rejection episodes were frequent, the frequency of this complication was similar between male and female recipients (Table 5).

Limitations of the present study include the retrospective design and several confounders such as different age distribution and many others, which are difficult to measure such as compliance and hormonal differences.

In conclusion, the results of a heart transplantation may depend on the gender of donors and recipients. Male donor hearts had greater 1-year survival in female than male recipients (Figure 4). However, for recipients who survived beyond 1 year after transplantation, multivariate analysis showed that the combination of female donor and female recipient was a significant indicator of greater long-term survival than other donor-recipient combinations (Table 3).

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