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Donor/recipient sex mismatch and survival after heart transplantation: only an issue in male recipients? An analysis of the Spanish Heart Transplantation Registry

Manuel Martinez-Selles,[1] Luis Almenar,[2] Maria J. Paniagua-Martin,[3] Javier Segovia,[4] Juan F. Delgado,[5] Jose M. Arizón,[6] Ana Ayesta,[7] Ernesto Lage,[8] Vicens Brossa,[9] Nicolás Manito,[10] Félix Pérez-Villa,[11] Beatriz Diaz-Molina,[12] Gregorio Rábago,[13] Teresa Blasco-Peiró,[14] Luis De La Fuente Galán,[15] Domingo Pascual-Figal,[16] and Francisco Gonzalez-Vilchez[17] on behalf of the Spanish Registry of Heart Transplantation[†]

1 Hospital Universitario Gregorio Marañón, Universidad Europea de Madrid, Madrid, Spain
2 Hospital Clinic i Politecnic, La Fe, Valencia, Spain
3 Centro Hospitalario de A Coruña, A Coruña, Spain
4 Hospital Universitario Puerta de Hierro, Majadahonda, Madrid, Spain
5 Hospital Universitario Doce de Octubre, Madrid, Spain
6 Hospital Universitario Reina Sofía, Córdoba, Spain
7 Hospital General Universitario Gregorio Marañón, Madrid, Spain
8 Hospital Universitario Virgen del Rocío, Sevilla, Spain
9 Hospital Santa Creu i Sant Pau, Barcelona, Spain
10 Hospital Universitary Bellvitge, L'Hospitalet de Llobregat, Barcelona, Spain
11 Hospital Clinic, Barcelona, Spain
12 Hospital Universitario Central de Asturias, Oviedo, Spain
13 Clínica Universitaria de Navarra, Pamplona, Spain
14 Hospital Universitario Miguel Servet, Zaragoza, Spain
15 Hospital Clínico, Valladolid, Spain
16 Hospital Virgen de la Arrixaca, Murcia, Spain
17 Hospital Universitario Marqués de Valdecilla, Santander, Spain

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Correspondence
Manuel Martínez-Sellés MD, PhD, Department of Cardiology, Hospital General Universitario Gregorio Marañón and Universidad Europea de Madrid. Doctor Esquerdo 46, 28007 Madrid, Spain.
Tel.: 34915868286;
fax: 34915868276;
e-mail: mmselles@secardiologia.es

Conflicts of interest
The authors declare that they have no conflict of interests.

[†]Collaborators of the Spanish Registry of Heart Transplantation: Luis Martínez-Dolz Ignacio Sánchez-Lázaro, Mónica Cebrián, Elena Marqués, María J. Paniagua, Raquel Marzoa-Rivas, Eduardo Barge Caballero, Maria G. Crespo-Leiro, Manuel Gómez-Bueno, Miguel

Summary

The results of studies on the association between sex mismatch and survival after heart transplantation are conflicting. Data from the Spanish Heart Transplantation Registry. From 4625 recipients, 3707 (80%) were men. The donor was female in 943 male recipients (25%) and male in 481 female recipients (52%). Recipients of male hearts had a higher body mass index (25.9 ± 4.1 vs. 24.3 ± 3.7; $P < 0.01$), and male donors were younger than female donors (33.4 ± 12.7 vs. 38.2 ± 12.3; $P < 0.01$). No further relevant differences related to donor sex were detected. In the univariate analysis, mismatch was associated with mortality in men (hazard ratio [HR], 1.18; 95% confidence interval [CI], 1.06–1.32; $P = 0.003$) but not in women (HR, 0.91; 95% CI 0.74–1.12; $P = 0.4$). A significant interaction was detected between sex mismatch and recipient gender ($P = 0.02$). In the multivariate analysis, sex mismatch was associated with long-term mortality (HR, 1.14; 95% CI 1.01–1.29; $P = 0.04$), and there was a tendency toward significance for the interaction between sex mismatch and recipient gender ($P = 0.08$). In male recipients, mismatch increased mortality mainly during the first month and in patients with pulmonary gradient >13 mmHg. Sex mismatch seems to be associated with mortality after heart transplantation in men but not in women.

Angel Gómez Sánchez, Pilar Escribano Subías, Maria José Ruiz Cano, Marta Paradina, Amador López-Granados, Adolfo Villa, Jesús Palomo, Juan Fernandez-Yañez, Iago Sousa, Pablo Diez, José M. Sobrino Márquez, Eulalia Roig, Sonia Mirabet, Joseph Roca-Elías, José Gonzalez-Costelo, Joel Salazar-Mendiguchía, Montserrat Cardona, Jose L. Lambert, Cristian Delgado, Marisa Sanz-Julvé, Amada Recio Platero, Iris Garrido-Bravo, Jose A. Vázquez de Prada, Manuel Cobo, Miguel Llano.

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Introduction

Orthotopic heart transplantation is the treatment of choice for selected patients with terminal heart disease. However, despite improvements in immunosuppressive treatment and allograft selection, patient survival is still suboptimal, and donor and recipient gender could play an important role in postoperative outcomes. The results of studies analyzing the influence of associations between donor and recipient sex on survival after heart transplantation are contradictory. Initial studies identified female donor as an independent predictor of recipient death after heart transplantation [1–4]. More recent reports and data from international registries have highlighted the importance of gender in donor/recipient sex mismatch and show reduced survival only in male recipients with female allografts [5–9]. However, an analysis of the International Society for Heart and Lung Transplantation (ISHLT) registry suggested that the association between donor/recipient sex mismatch and reduced survival was also valid for female recipients [10]. A larger and more recent analysis of the same registry [11] showed that reduced survival is exclusive to male recipients with female allografts. Our aim was to clarify the influence of recipient sex on prognosis in cases of donor/recipient sex mismatch in heart transplantation.

Patients and methods

We used data from the Spanish Heart Transplantation Registry [12]. A total of 4953 heart transplants were performed in Spain in patients ≥16 years between January 1, 1995 and December 31, 2012. We excluded combined transplants (n = 123) and patients for whom donor age or sex was unknown (n = 205); therefore, the analysis was performed in 4625 patients, with follow-up until March 3, 2013. We divided patients into two groups depending on the sex of the donor and the recipient, as follows: no mismatch (male donor–male recipient or female donor–female recipient) and mismatch (male donor–female recipient or female donor–male recipient). The study complies with the tenets of the Declarations of Helsinki and Istanbul and was approved by the Ethics Committee of the Hospital Universitario Gregorio Marañón, Madrid, Spain.

Statistical analysis

Quantitative variables are reported as mean ± standard deviation (SD), while qualitative variables are reported as number and percentage. Continuous variables were compared using the t-test, while categorical variables were compared using the chi-square test or Fisher's exact test when the chi-square test was not appropriate. Cox regression modeling, including potential confounders, was performed to assess the association between sex mismatch and prognosis. The relevant clinical characteristics of the donor and recipient were analyzed as potential confounders, as were all variables with a significant hazard ratio ($P < 0.1$). We considered all-cause mortality as the only outcome. The hazard ratio of sex mismatch was estimated unadjusted and adjusted. Kaplan–Meier survival curves were constructed and compared using the log-rank test. All statistical analyses were performed using SPSS v. 16 (SPSS Inc., Chicago, IL, USA).

Results

A total of 4625 recipients were included in the study, 3707 (80%) were men and 918 were women (20%). The donor was female in 943 male recipients (25%) and male in 481 female recipients (52%). Differences according to donor sex are shown in Table 1. Recipients of male hearts had a higher body mass index (25.9 ± 4.1 vs. 24.3 ± 3.7), and

male donors were younger than female donors (33.4 ± 12.7 vs. 38.2 ± 12.3). No further relevant differences related to donor gender were identified.

Univariate hazard ratios (HR) for mortality during follow-up (mean 75.4 months) according to donor sex are shown in Table 2. Mismatch was associated with mortality in men (HR, 1.18; 95% CI, 1.06–1.32; $P = 0.003$) but not in women (HR, 0.91; 95% CI, 0.74–1.12; $P = 0.4$). The HRs for sex mismatch adjusted for different variables are presented in Table 3; sex mismatch in male recipients was always significantly associated with mortality, except when that association was adjusted for the donor's age, and, even in that case, a strong tendency existed ($P = 0.07$). In female recipients, sex mismatch was not associated with mortality but with better survival, although the trend was nonsignificant. Figure 1 presents survival curves with and without sex mismatch; the difference was only significant in the case of male recipients ($P = 0.005$ in male recipients and $P = 0.40$ in female recipients). In male recipients, the difference was only seen in patients with pulmonary gradient >13 mmHg (Fig. 2), and during the first month (Fig. 3). The rates of primary graft dysfunction are depicted in Fig. 4 and were higher in the case of female donors. Table 3 shows the different effects of sex mismatch in mortality according to the gender of the recipient. In the univariate analysis, sex mismatch was associated with increased mortality in male recipients (HR 1.16); however, as the interaction between sex mismatch and recipient

Table 1. Differences according to donor sex in (a) male recipients (b) female recipients.

	Male donor			Female donor			
	n	Mean	SD	*n*	Mean	SD	*P* value
(a)							
Recipient age	2764	53.4	10.7	943	53.3	11.1	0.570
Recipient body mass index	2705	26.2	3.9	918	24.5	3.4	<0.001
Ischemia time (minutes)	2682	192.9	62.5	926	190.0	63.2	0.221
Pulmonary gradient (mmHg)	2313	8.5	5.0	795	8.3	6.0	0.457
Donor weight/recipient weight	2612	1.1	0.3	894	1.0	0.2	0.325
Donor age	2764	33.6	12.5	943	38.7	12.1	<0.001
1995–2004	1735	62.8%		571	60.6%		0.225
2005–2012	1029	37.2%		372	39.5%		
Recipient characteristics							
Ischemic etiology	1038	37.7%		325	34.7%		0.100
Diabetes	453	16.9%		127	13.9%		0.029
Peripheral arterial disease	196	7.3%		74	8.1%		0.443
Cancer	64	2.4%		33	3.6%		0.053
Kidney failure	498	18.6%		137	15.2%		0.018
Liver failure	631	24.6%		227	25.7%		0.515
Previous cardiac surgery	729	27.0%		245	26.6%		0.818
Emergency transplantation	724	26.5%		234	25.0%		0.358
(b)							
Recipient age	481	50.4	12.6	437	51.1	12.4	0.500
Recipient body mass index	467	25.3	4.7	430	24.0	4.2	<0.001
Ischemia time (minutes)	473	189.3	61.8	418	196.4	62.9	0.233
Pulmonary gradient (mmHg)	394	8.4	5.2	359	7.3	3.8	0.198
Donor weight/recipient weight	454	1.2	0.2	416	1.1	0.2	0.368
Donor age	481	33.0	13.1	437	37.2	12.8	<0.001
1995–2004	281	58.4%		219	50.1%		0.012
2005–2012	200	41.6%		218	49.9%		
Recipient characteristics							
Ischemic etiology	75	15.7%		72	16.6%		0.701
Diabetes	50	10.6%		58	13.7%		0.164
Peripheral arterial disease	10	2.1%		10	2.4%		0.835
Cancer	33	7.0%		29	6.9%		0.947
Kidney failure	55	12.0%		58	13.9%		0.410
Liver failure	106	24.0%		99	24.4%		0.875
Previous cardiac surgery	123	26.1%		115	26.9%		0.767
Emergency transplantation	150	31.7%		108	24.9%		0.024

Table 2. Univariate hazard ratio (HR) for mortality in (a) male recipients (b) female recipients.

	HR	95% CI		*P* value
(a)				
Transplant period	1.02	0.91	1.16	0.717
Age	1.02	1.02	1.03	<0.001
Body mass index	1.01	1.00	1.03	0.054
Ischemic etiology	1.07	0.97	1.18	0.186
Diabetes	1.24	1.09	1.41	0.001
Peripheral arterial disease	1.36	1.15	1.61	<0.001
Cancer	1.50	1.13	1.97	0.004
Kidney failure	1.42	1.25	1.61	<0.001
Liver failure	1.10	0.98	1.23	0.123
Previous cardiac surgery	1.33	1.19	1.48	<0.001
Emergency transplantation	1.16	1.04	1.30	0.010
Ischemia time (minutes)	1.00	1.00	1.00	0.070
Donor age	1.01	1.01	1.02	<0.001
Sex mismatch	1.18	1.06	1.32	0.003
(b)				
Transplant period	1.06	0.84	1.34	0.634
Age	1.01	1.00	1.02	0.054
Body mass index	1.03	1.01	1.06	0.005
Ischemic etiology	1.21	0.93	1.59	0.161
Diabetes	1.56	1.17	2.09	0.003
Peripheral arterial disease	1.74	0.95	3.18	0.070
Cancer	1.50	1.01	2.23	0.043
Kidney failure	1.70	1.27	2.27	<0.001
Liver failure	1.27	0.98	1.63	0.067
Previous cardiac surgery	1.29	1.02	1.64	0.034
Emergency transplantation	1.37	1.09	1.73	0.006
Ischemia time (minutes)	1.00	1.00	1.00	0.210
Donor age	1.01	1.00	1.02	0.058
Sex mismatch	0.91	0.74	1.12	0.400

Table 3. Adjusted hazard ratio (HR) for sex mismatch in (a) male recipients (b) female recipients (c) Nonadjusted and adjusted hazard ratio (HR) for sex mismatch, gender of the recipient, and the interaction sex mismatch–gender of the recipient.

	HR	95% CI		*P* value
(a)				
Adjusted by				
Body mass index	1.20	1.07	1.34	0.002
Diabetes	1.19	1.06	1.33	0.002
Cancer	1.18	1.06	1.32	0.003
Kidney failure	1.19	1.06	1.30	0.002
Donor age	1.11	0.99	1.24	0.072
Age	1.17	1.05	1.30	0.005
Peripheral arterial disease	1.16	1.03	1.29	0.011
Previous cardiac surgery	1.16	1.04	1.30	0.007
Emergency transplantation	1.18	1.06	1.32	0.003
Ischemia time	1.18	1.06	1.32	0.004
(b)				
Adjusted by				
Body mass index	0.88	0.71	1.09	0.235
Diabetes	0.93	0.75	1.16	0.527
Cancer	0.91	0.74	1.13	0.408
Kidney failure	0.89	0.71	1.10	0.268
Donor age	0.94	0.76	1.17	0.591
Age	0.93	0.75	1.15	0.485
Peripheral arterial disease	0.94	0.76	1.17	0.577
Previous cardiac surgery	0.93	0.75	1.15	0.517
Emergency transplantation	0.90	0.73	1.12	0.354
Ischemia time	0.89	0.71	1.09	0.321
(c)				
Nonadjusted				
Sex mismatch	1.16	1.04	1.30	0.01
Gender of the recipient	1.03	0.87	1.21	0.73
Interaction	0.76	0.60	0.96	0.02
Adjusted				
Sex mismatch	1.14	1.01	1.29	0.04
Gender of the recipient	1.07	0.90	1.29	0.45
Interaction	0.79	0.61	1.03	0.08

gender was significant ($P = 0.006$), the presence of sex mismatch was associated with lower mortality in female recipients (HR 0.88). In multivariate analysis, there was a tendency toward significance for the interaction between sex mismatch and recipient gender ($P = 0.08$).

Discussion

After analyzing the database that includes all adult heart transplantations in Spain (4625 patients), we found that gender mismatch was associated with mortality in men but not in women. As Figs 1 and 2 suggest, the combination female donor/male recipient carries a higher risk for early mortality. In female recipients, sex mismatch was not associated with mortality, and even had a nonsignificant trend, with better survival. Our data support the existence of an interaction between sex mismatch and recipient gender, although the multivariate analysis only revealed a tendency for the significance of this interaction ($P = 0.08$).

Multicentre studies, mainly those based on national and international outcome registries, have unanimously confirmed the role of gender mismatch in mortality after heart transplantation (Table 4). The studies that used the largest databases (Collaborative Transplant Study [CTS], United Network for Organ Sharing [UNOS], and ISHLT) all show that lower survival is observed only for males receiving organs from female donors. Using the CTS database, Zeier *et al.* [7] examined 25 432 cardiac transplants and found that female donors had significantly lower actuarial survival than male recipients, whereas no difference according to donor gender was detected in female recipients. Based on 18 240 patients from the UNOS data, Weiss *et al.* [8] also found that men receiving organs from same sex donors have significantly improved short- and long-term survival, whereas no survival advantage was seen for women receiving organs from women. The ISHLT is the largest existing heart transplant data repository. A previous

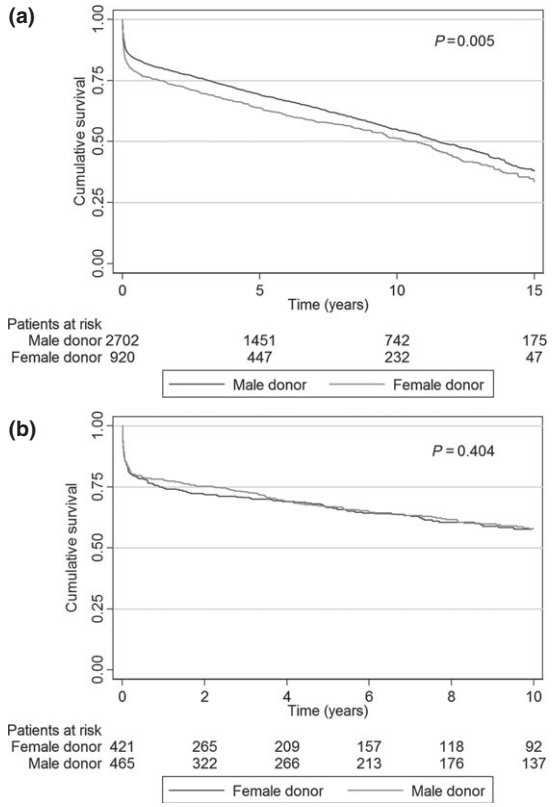

Figure 1 Survival curves with and without sex mismatch in male (a) and female (b) recipients.

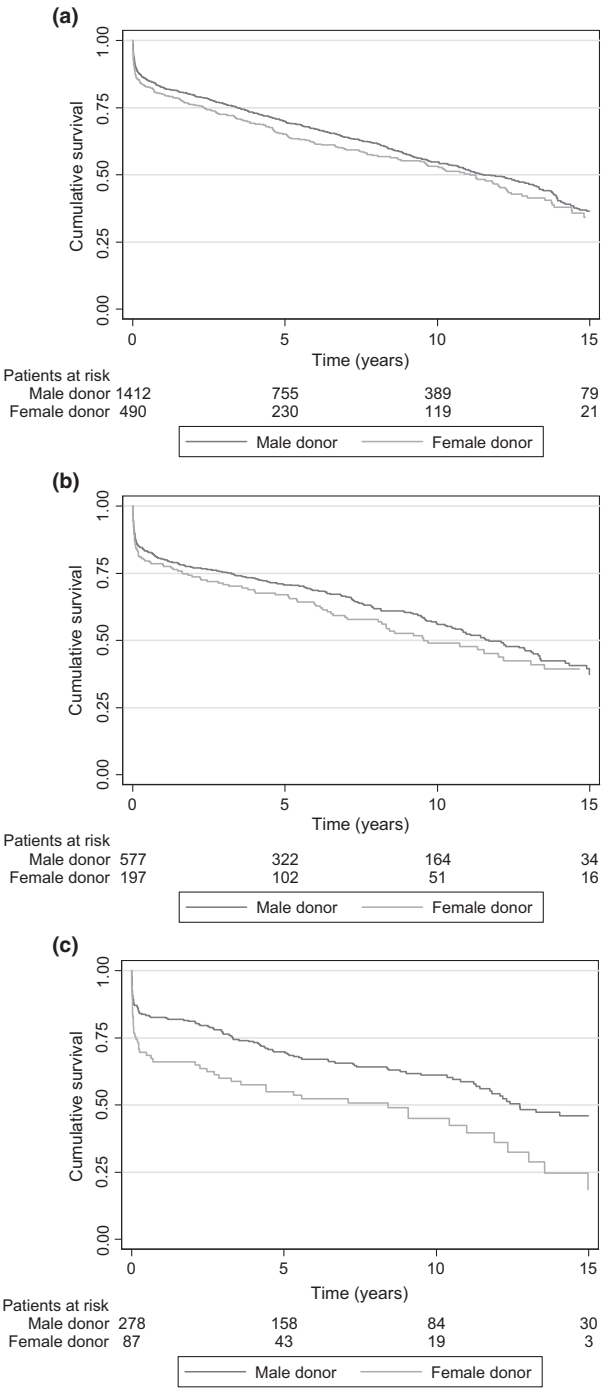

Figure 2 Survival curves for male recipients with and without sex mismatch according to pulmonary gradient (a) Pulmonary gradient <10 mmHg (n = 2.354), P = 0.14. (b) Pulmonary gradient 10–13 mmHg (n = 916), P = 0.48. (c) Pulmonary gradient >13 mmHg (n = 437), P = 0.0005.

study of this database suggested that the association between donor/recipient sex mismatch and reduced survival was also valid for female recipients [10]. However, in the most recent and extensive analysis, Kaczmarek *et al.* [11] (67 855 patients) confirmed that male recipients of female allografts had the worst survival rates and that survival rates for the remaining combinations were similar. In fact, the ISHLT database shows that female donor hearts are associated with higher early mortality in male recipients and that short-term results for male donor hearts are better in female recipients. These findings are consistent with the possible interaction between sex mismatch and recipient gender.

The reasons for the influence of gender on survival or why it affects only male recipients are unknown. Potential mechanisms by which donor/recipient gender mismatch might affect survival after transplantation include hormonal and genetic differences, antigen development and other immunologic factors, and size. Mismatch has been associated with organ failure [25,27], and results for acute rejection and cardiac allograft vasculopathy in sex-mismatched patients are controversial, mainly owing to the large amount of missing results and differences in diagnostic criteria [28]. In our series, the predominant mortality in males with mismatched donors appears to occur at the time of transplant (Figs 1 and 2) and we found

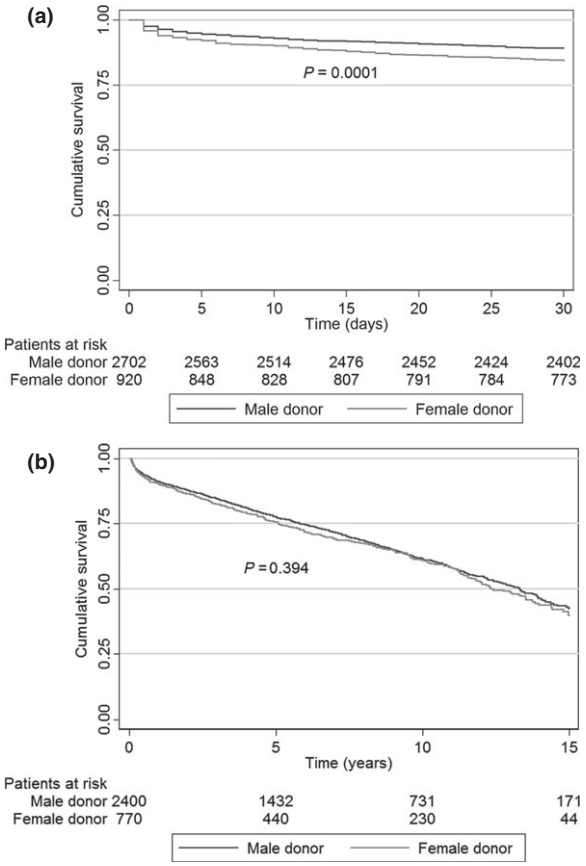

Figure 3 Survival curves for male recipients with and without sex mismatch during the first month (a) and, for those who survive the first month, long term (b).

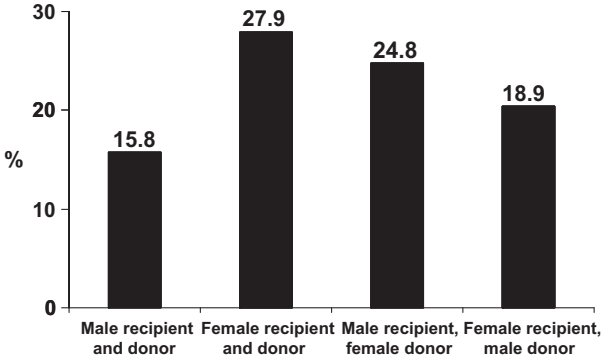

Figure 4 Rates of primary graft dysfunction. *P* value for the comparison of the four groups <0.001.

that male recipients with sex mismatch presented primary graft dysfunction more frequently than female recipients with sex mismatch (24.8% vs. 18.9%, Fig. 3). Also, previous studies have suggested a role for gender mismatch in cardiac allograft vasculopathy, with male recipients of female allografts having a higher degree of vascular intimal hyperplasia after heart transplantation [29]. However, findings on the role of donor sex are contradictory, with increased frequencies of coronary vasculopathy among recipients of female allografts [30] or among recipients of male allografts [31–33]. Donor and recipient gender could influence the pathogenesis of cardiac allograft vasculopathy, although this is probably not the only explanation for the influence of gender mismatch on mortality and why it

Table 4. Previous data regarding influence of sex mismatch on prognosis after heart transplantation (only the last report of each group/registry is shown).

First author	Publication year	*N*	
Single-centre studies			
No influence of sex mismatch in survival			
De Santo [13]	2001	99	
Tsao [14]	2008	240	
Mastrobouni [15]	2012	245	
Keogh [16]	1991	313	
Jalowiec [17]	2012	347	
Yamani [18]	2005	361	
Izquierdo [19]	2007	464	
Correia [20]	2014	200	
Sex mismatch associated with worse survival			
Kirsh [20]	1998	234	No data regarding gender of the recipient
Schelecta [21]	1999	609	Worse survival mainly in male recipients
Sex mismatch associated with worse survival only in male recipients			
Prendergast [6]	1998	174	
Welp [9]	2009	236	
Kittleson [22]	2011	857	
Al-Khaldi [5]	2006	869	Only if age >45 years
Eiffert [23]	2012	1000	
Aliabadi [24]	2011	1079	Mismatch in male recipient with lowest survival
Multicentre studies			
No influence of sex mismatch in survival			
–			
Sex mismatch associated with worse survival			
Maltais [25]	2013	*N* = 2785	No data on recipients gender
Sex mismatch associated with worse survival only in male recipients			
Bryan [1]	1996	*N* = 279	Worse survival with female donors in all
Stehlik [26]	2010	*N* = 7321	Especially if weight difference
Weiss [8]	2009	*N* = 18 240	
Zeier [7]	2002	*N* = 25 432	
Kaczmarek [11]	2013	*N* = 67 855	

specifically affects male recipients. In patients with heart failure, survival is better in women than in men [34], and biological reasons for the better response of female hearts [35] may also explain why women adapt better to a mismatched heart. During pregnancy, specific fetal and maternal factors explain why the mother does not reject the fetus. Moreover, persisting fetal male cells in the maternal heart (microchimerism) have been reported [36] and could explain why women can tolerate a mismatched heart better than men. In addition, the "undersizing" effect has been suggested as a possible explanation [28], as female hearts are smaller than male hearts even after correction for weight and height [37-39]. On the other hand, the "oversizing" effect could improve short-term survival of male donor hearts in female recipients, especially in the presence of elevated pulmonary pressures and risk of right heart failure [28]. In our series, the relation of sex mismatch with increased mortality was mainly seen in male recipients with pulmonary gradient >13 mmHg.

Our data suggest that, at least in the case of male recipients, gender matching should be included in the criteria for donor heart allocation. Therefore, donor hearts should be promoted whenever possible in gender-matched recipients. Transplant management in the case of gender mismatch is a problematic issue. First, there are fewer male donors than needed for a perfect gender match. Of the 3707 male recipients in our study, 3245 received a heart from a male donor. Therefore, it seems reasonable to suppose that some male recipients will have to receive female hearts. Second, and most importantly, the shortage of organs, particularly in the case emergency transplantations, makes this selection difficult, as candidates are better served by receiving gender-mismatched hearts than by receiving none at all. In fact, the matching process must already account for recipient suitability and waiting list status, donor and recipient blood type, and the presence of preformed anti-human leukocyte antigen antibodies in the recipient. Accepting or declining an allograft for a particular patient is a difficult decision and, although gender-matched heart transplantation might be ideal, it does not seem to be suitable in practice.

Although we studied 4625 patients, the size of our database is smaller than the three databases referred to above. The Cardiac Transplant Research Database is the fourth in size [26], and ours is the fifth. Our sample size may have prevented us from showing a significant interaction between sex mismatch and recipient gender. However, the main strength of our study is that the Spanish Heart Transplantation Registry includes all heart transplantations performed in Spain [12]. Moreover, it uses detailed, standardized, and prospective data entry in a single database, with uniform definitions and a periodical data quality check. Finally, the meticulous follow-up applied in the Spanish Heart Transplantation Registry makes it possible to study factors associated with long-term survival. The four larger registries mentioned above are based on voluntary reporting, have a high frequency of incomplete follow-up and missing data, permit errors in data entry, and have no quality check [7,8,10,11,26]. Therefore, we think that the database used in the present study could be more bias-free while providing results for a large number of patients.

In conclusion, gender mismatch is associated with mortality in men after heart transplantation but not in women. The combination female donor–male recipient should be evaluated with caution owing to the increased risk for early mortality, particularly in patients with pulmonary gradient >13 mmHg.

Authorship

MMS: conception, research design, performance of the research, data acquisition and analysis, and writing of the paper. All the other authors: performance of the research, data acquisition and analysis, and writing of the paper.

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