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ORIGINAL ARTICLE

Gender mismatch between donor and recipient is a factor of morbidity but does not condition survival after cardiac transplantation

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Summary

We intended to evaluate the influence of sex mismatch between donor and recipient, which is still under much debate, on survival and comorbidities after cardiac transplantation. From November 2003 to December 2013, a total of 258 patients were transplanted in our center. From these, 200 receptors were male (77.5%) and constituted our study population, further divided into those who received the heart from a female donor (Group A) – 44 patients (22%) and those who received it from a male donor (Group B) – 156 (78%). Median follow-up was 4.2 ± 3.0 years (1–10 years). The two groups were quite comparable with each other, except for body mass index, systolic pulmonary artery pressure, and transpulmonary gradient, which were significantly lower in Group A. A low donor/recipient weigh ratio (<0.8) was avoided whenever possible. Hospital mortality was not different in the two groups. During follow-up, global survival was similar, as was survival free from acute cellular rejection and cardiac allograft vasculopathy. However, patients in Group A had decreased survival free from serious infections and malignant tumors. Allocation of female donors to male receptors can be done safely, at least in receptors without pulmonary hypertension and when an adequate donor/recipient weigh ratio is ensured.

Introduction

Heart transplantation remains the treatment of choice for symptomatic terminal heart failure [1]. However, the long-term results are still far from ideal, essentially characterized by the morbidity and mortality caused by acute cellular rejection and vascular graft disease, on the one hand, and episodes of infection and neoplasia, on the other [2], and influenced by many factors related to the characteristics of both the recipient and donor.

Among these, the impact of the gender mismatch between donor and recipient on patient survival and in each of those morbidities is still under debate, with disparate results in different studies. While some consider the simple fact of the donor being female as a risk factor for survival [3], others found no difference in long-term mortality whatever the sex of the donor or receptor [4]. Recently, Kush *et al.* [5] indicated sex mismatch between donor and recipient, regardless of the sex of the recipient, as a cause of increased long-term mortality. However, the negative impact of the mismatch female donor to male recipient seems more consensual.

Beyond pure survival analysis, few studies have been devoted to the research of the influence of gender disparity between donor and recipient on other morbidities such as acute cellular rejection, vascular graft disease, infections, and neoplasms. In this study, we intended to evaluate the influence of gender disparity in male recipients, not only

on survival but also on the incidence of those important morbidities.

Patients and methods

From November 2003 to December 2013, a total of 258 patients were transplanted in our center. Of these, 200 male recipients (77.5%) were selected for this study and were divided into two groups: Group A – recipients receiving an organ from a female donor, that is, with gender mismatch – 44 patients (22%); and Group B – recipients from a male donor, that is, with matching gender – 156 patients (78%).

All transplantations, including the respective organ recovery, were performed by the same surgical team. The technique used was the bi-caval anastomosis with modifications previously described with the aim of reducing the duration of ischemia [6]. After transplantation, the immediate and early postoperative period, the regular clinical follow-up and treatment of various complications in the medium and long term were also carried out at the center by members of the surgical team, which includes an Internal Medicine specialist specifically dedicated to this activity. Only exceptionally have we resorted to the assistance of centers nearest to the residence of the patients. This is the current case with four patients currently residing abroad, from whom we also got the tracking data.

We had access to a pretransplant cross-match in all cases, and have only transplanted patients in whom this was negative. Analysis of the panel-reactive antibody (PRA), which is usually only known after transplantation and conditioned the immunosuppression regimen, was also performed in the majority of cases.

All patients received induction immunosuppression with the antagonist of interleukin-2 receptor (basiliximab – 20 mg intravenously), methylprednisolone (500 mg iv), and mycophenolate (1 g oral), immediately before and/or during the intervention. In the majority of patients (97.7% vs. 96.2%; $P = 1.000$), follow-up immunosuppression was initiated with cyclosporine, dose-adjusted to serum levels, mycophenolate mofetil (500–1000 mg tid, initiated before surgery) and prednisone in decreasing doses from 0.8 mg/kg initially to 10 mg/day after around 5 weeks, 7.5 mg/day after 6 months and 5 mg/day after 1 year. Tacrolimus instead of cyclosporine was reserved for younger patients, or those already doing this drug for a kidney transplantation (2.3% vs. 3.2%; $P = 1.000$) [7].

Early mortality was defined as death occurring during the hospitalization of surgery or within 30 days and late mortality as that which occurred after this period. Endomyocardial biopsies were performed routinely by protocol or when considered medically necessary. Acute cellular rejection was diagnosed and treated if grade ≥2R of the classification of the International Society for Heart and Lung Transplantation (ISHLT) [8]. Each patient underwent coronary angiography annually, with graft vascular disease diagnosed using the criteria also defined by ISHLT [9]. For the calculation of the freedom-survival curves, the definition of malignancies included malignant neoplasms of the skin, blood, breast, gastrointestinal, prostate, or other. The definition of infections included serious infectious complications, regardless of origin, which obliged to hospital admission for intravenous antibiotics.

The pre-and postoperative clinical data, as well as information for analysis of survival and incidence of adverse long-term events were prospectively collected in a database constructed in conjunction with our national society of transplantation (Sociedade Portuguesa de Transplantação – SPT), which aims at collating all transplantation activity country-wide. For this work, the data from this single center were extracted.

Statistical analysis

Continuous variables are presented as mean ± standard deviation and compared between groups using the Student's *t*-test for normally distributed variables and Mann–Whitney *U*-test for variables with non-normal distribution. The normality of variables was evaluated by the Kolmogorov–Smirmov and Shapiro–Wilk tests. Categorical variables are expressed as frequencies and percentages and comparison was made using the chi-square test or, when appropriate, Fisher's exact test. Overall survival and group survival, as well as event-free survivals, were assessed by the Kaplan–Meier method, and statistical significance was analyzed using the log-rank test. Values of $P < 0.05$ (two-tailed) were considered statistically significant. Data were analyzed using the IBM Corp. program (Released 2011, IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp).

Results

Table 1 documents the main demographic and preoperative clinical characteristics of both groups of recipients. The mean age of Group A was slightly higher (55.8 vs. 53.1 years) but without statistical significance ($P = 0.196$). This group includes one patient (2.3%) under the age of 18, while in Group B there were 4 (2.6%; $P = 1.000$). The body mass index was significantly lower in patients with gender mismatch, and sPAP and transpulmonary gradient were significantly lower, resulting from a deliberate move to avoid the use of female donors in recipients with some degree of pulmonary hypertension. Regarding the presence of other comorbidities, both groups proved fairly homogeneous, with comparable incidence of diabetes, hypertension, dyslipidemia, peripheral vascular disease, or carotid

Table 1. Preoperative data of heart transplant recipients in the two groups.

Recipient	Group A (w/sex mismatch) (% or mean ± SD)	Group B (w/o sex mismatch) (% or mean ± SD)	*P*
n	44 (22)	156 (78)	
Recipient age (years)	55.8 ± 11.3	53.1 ± 12.3	0.196
BMI mean (kg/m^2)	22.9 ± 2.3	24.4 ± 3.5	**0.001**
Diabetes	45 (28.8)	9 (20.5)	0.268
Essential hypertension	17 (38.6)	60 (38.5)	0.983
Dyslipidemia	21 (47.7)	84 (53.8)	0.473
Prior cardiac surgery	14 (31.8)	46 (29.5)	0.766
Prior CABG	6 (13.6)	30 (19.2)	0.394
Ischemic cardiomyopathy	18 (40.9)	70 (44.9)	0.640
Dilated cardiomyopathy	11 (25.0)	43 (27.6)	0.735
Peripheral vascular disease	19 (43.2)	60 (38.5)	0.572
Carotid stenosis	3 (6.8)	9 (5.8)	0.729
Cardiac index (l/min/m^2)	1.95 ± 0.56	1.99 ± 0.48	0.672
Systolic pulmonary artery pressure	44.6 ± 14.5	51.0 ± 15.2	**0.017**
Trans-pulmonary gradient (mmHg)	8.32 ± 3.47	10.45 ± 4.99	**0.002**
Pulmonary vascular resistance (UW)	3.07 ± 2.80	3.35 ± 1.91	0.469
VO_2 max (ml/kg/min)	13.8 ± 2.6	13.4 ± 2.9	0.436
Bilirubin (mg/dl)	1.4 ± 0.9	1.3 ± 0.9	0.692
Glomerular filtration rate (ml/min)	57.4 ± 23.3	63.1 ± 23.2	0.171
Creatinine level (mg/dl)	1.7 ± 1.0	1.5 ± 0.7	0.271
Wait-list time (days)	39.8 ± 41.6	46.3 ± 44.6	0.388
Follow-up (years)	4.35 ± 3.34	4.21 ± 2.95	0.793
High urgency classification	14 (31.8)	45 (28.8)	0.703

BMI, body mass index; CABG, coronary artery bypass grafting; VO_2 max, maximal oxygen consumption.
P values in bold are those considered significative.

artery disease. Also in the etiology of the underlying heart disease, the prevalence of ischemic and dilated causes was similar, as was the history of previous cardiac surgery. Two patients (1.3%) in Group B and none in Group A ($P = 1.000$) had previously been transplanted to other organs (kidney and liver).

Donors in Group A were older than in Group B (Table 2). We also found significant differences in the cause of death of the donor. Hemorrhagic cerebral accidents were more frequent in female donors, while the cranio-cerebral injuries were more frequent in males.

Intraoperatively, a mitral valvuloplasty for previously known mitral disease, which has been the subject of a previous publication [10], was performed in nine patients and was more prevalent in the hearts from female donors. The data in Table 3 shows that although the time of ischemia, time to extubation, and the need for mechanical assistance were similar, prolonged use of inotropic drugs (>48 h) was more frequently required in Group A. Concurrent renal transplantation was performed in one patient (2.3%) in Group A and in three (1.9%) in Group B ($P = 1.000$). The

Table 2. Characteristics of the donors.

Donor	Group A (female donor) (% or mean ± SD)	Group B (male donor) (% or mean ± SD)	*P*
n	44 (22)	156 (78)	
Age (years)	37.9 ± 9.1	34.3 ± 11.5	**0.032**
PRA (%)	0.2 ± 1.2	1.1 ± 4.2	0.302
Ratio weight donor/recipient	1.05 ± 0.21	1.15 ± 0.29	**0.030**
Ratio weight donor/recipient <0.8	1 (2.3)	5 (3.2)	1.000
Ratio weight donor/recipient >1.2	8 (18.2)	48 (31.2)	0.092
Inotropic dependence >1 week	3 (6.8)	8 (5.1)	0.709
Ventilator assistance >1 week	6 (13.6)	20 (12.8)	0.887
Cause of death			
Ischemic cerebral accident	0 (0)	3 (1.9)	1.000
Hemorrhagic cerebral accident	25 (56.8)	41 (26.3)	**<0.001**
Brain trauma	12 (27.3)	102 (65.4)	**<0.001**

PRA, panel-reactive antibodies.
P values in bold are those considered significative.

Table 3. Operative and postoperative data.

Surgery	Group A (w/sex mismatch) (% or mean ± SD)	Group B (w/o sex mismatch) (% or mean ± SD)	*P*
Total ischemic time (min)	96.9 ± 33.2	87.9 ± 37.7	0.127
CPB time mean (min)	96.8 ± 29.4	97.3 ± 28.8	0.923
Mitral valvuloplasty	6 (13.6)	3 (1.9)	**0.004**
Time to extubation (h)	18.4 ± 9.0	20.6 ± 26.8	0.587
Inotropic requirement	10 (22.7)	16 (10.3)	**0.030**
Mechanical assistance	1 (2.3)	6 (3.8)	1.000
Hemorrhage	6 (13.6)	7 (4.5)	**0.041**
Length of hospital stay (days)	21.5 ± 28.7	14.8 ± 10.8	0.144
Hospital mortality	1 (2.3)	8 (5.1)	0.687
Immunosuppression			
Cyclosporine *ab initio*	43 (97.7)	150 (96.2)	1.000
Calcineurin inhibitor change	7 (15.9)	17 (10.9)	0.366
MMF to everolimus change	6 (13.6)	33 (21.2)	0.266
MMF to sirolimus change	1 (2.3)	2 (1.3)	0.527

CPB, cardiopulmonary bypass; MMF, mycophenolate mofetil.
P values in bold are those considered significative.

Table 4. Global mortality and causes of death.

Mortality	Group A (w/sex mismatch) (%)	Group B (w/o sex mismatch) (%)	*P*
Global mortality	12 (27.3)	34 (21.8)	0.446
Cause of death			
Cardiac	2 (4.5)	6 (3.8)	1.000
Vascular	3 (6.8)	7 (4.5)	0.461
Ischemic cerebral accident	1 (2.3)	2 (1.3)	0.527
Hemorrhagic cerebral accident	1 (2.3)	2 (1.3)	0.527
Acute mesenteric ischemia	1 (2.3)	1 (0.6)	0.392
Pulmonary hypertension	0 (0.0)	2 (1.3)	1.000
Malignant tumor	0 (0.0)	8 (5.1)	0.204
Neuropsychiatric	0 (0.0)	2 (1.3)	1.000
Infectious	4 (9.1)	8 (5.1)	0.303

hospital stay was, on average, longer in the group with mismatch, but without statistical significance. Finally, the mortality rate was lower in Group A (2.3% vs. 5.1%), although this difference did not reach statistical significance ($P = 0.687$). The incidence of acute cellular rejection grade 1R during the first 3 months post-transplantation was marginally but not significantly higher in Group A (40.9% vs. 31.4%; $P = 0.238$).

There was a need to change the calcineurin inhibitor in 15.9% vs. 10.9% ($P = 0.366$), mainly due to renal, infectious or neoplastic complications, humoral and/or cellular rejection, convulsions, and allograft vasculopathy. The need to change from mycophenolate mofetil to everolimus (13.6% vs. 21.2%; $P = 0.266$) and sirolimus (2.3% vs. 1.3%; $P = 0.527$) was related to the development of graft vascular disease.

For a mean follow-up period of more than 4 years and a maximum of 10 in both groups (Table 1), with regard to the long-term adverse events, we found an overlapping incidence of humoral rejection between groups A and B (2.3% vs. 2.6%, $P = 1.000$). The incidence of new onset diabetes after transplantation (NODAT) was slightly higher, but with no statistical significance, in the group without mismatch (11.4% vs. 15.4%; $P = 0.503$). There was worsening renal function, requiring permanent dialysis or kidney transplantation during follow-up, in three cases in Group A (6.8%) and four in Group B (2.6%, $P = 0.181$).

The overall mortality of Group A and B was 27.3% and 21.8% ($P = 0.446$), respectively. There were no marked differences in the incidence of major causes of death (cardiac, infectious, vascular, neoplastic, and neuropsychiatric; Table 4). Overall survival at 1, 5, and 8 years was 86.1 ± 5.3%, 71.0 ± 7.6%, and 66.6 ± 8.3%, respectively,

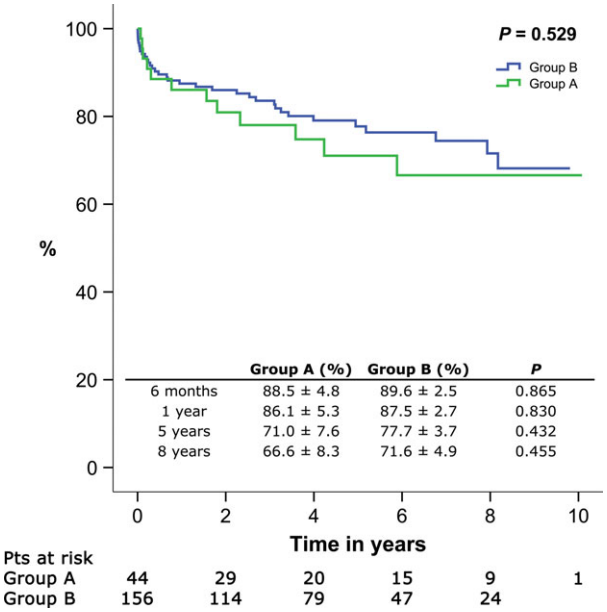

Figure 1 Overall survival in groups A and B.

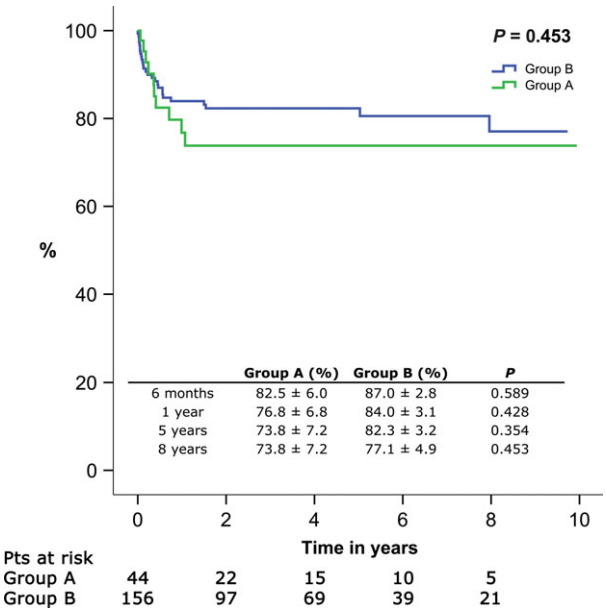

Figure 2 Survival free from acute cellular rejection grade ≥2R in groups A and B.

in Group A and 87.5 ± 2.7%, 77.7 ± 3.7%, and 71.6 ± 4.9% for Group B. There was, therefore, no significant difference in survival between the two groups ($P = 0.529$; Fig. 1).

During the first year of follow-up, acute cellular rejection grade 2R or 3R occurred in nine cases (20.5%) in recipients with gender mismatch and in 23 (14.7%) in the group without mismatch ($P = 0.361$). Survival free from this type

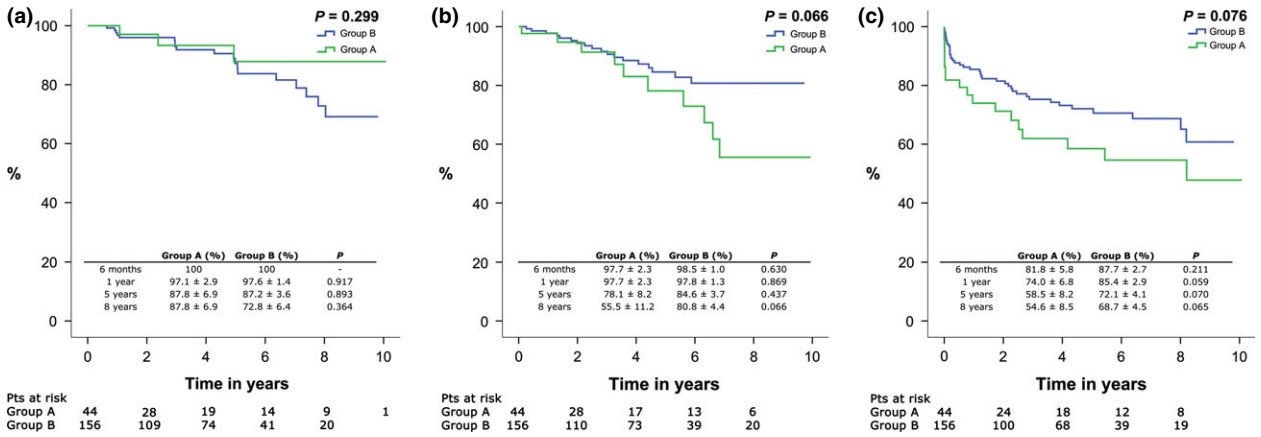

Figure 3 (a) Survival free from cardiac allograft vasculopathy; (b) survival free from malignancy; and (c) survival free from serious infections.

of rejection at 1, 5, and 8 years was 76.8 ± 6.8%, 73.8 ± 7.2%, and 73.8 ± 7.2%, respectively, in Group A and 84.0 ± 3.1%, 82.3 ± 3.2%, and 77.1 ± 4.9% for Group B. As one would expect and can be seen in Fig. 2, the incidence of cellular rejection was most pronounced in the first 2 years. Although survival free from acute cellular rejection was slightly better in Group B, the difference did not reach statistical significance ($P = 0.453$).

Survival free from graft vascular disease at 1, 5, and 8 years was 97.1 ± 2.9%, 87.8 ± 6.9%, and 87.8 ± 6.9%, respectively, in Group A and 97.6 ± 1.4%, 87.2 ± 3.6%, and 72.8 ± 6.4% for Group B ($P = 0.299$). In this case, the survival curve (Fig. 3a) is very similar during the first 5 years, and from then onwards the group with gender mismatch seems to have a better disease-free survival of the graft.

Malignancy-free survival at 1, 5, and 8 years was, respectively, 97.7 ± 2.3%, 78.1 ± 8.2%, and 55.5 ± 11.2% in Group A and 97.8 ± 1.3%, 84.6 ± 3.7%, and 80.8 ± 4.4% in Group B. Although survival overlaps in the first 4 years (Fig. 3b), thereafter the survival falls in Group A, the difference being at the limit of statistical significance ($P = 0.066$).

Survival free from serious infections at 1, 5, and 8 years was, respectively, 74.0 ± 6.8%, 58.5 ± 8.2%, and 54.6 ± 8.5% in Group A and 85.4 ± 2.9%, 72.1 ± 4.1%, and 68.7 ± 4.5% for Group B. Hence, there is a decrease in survival free from serious infections in the sex mismatched group, in the threshold of statistical significance ($P = 0.076$; Fig. 3c).

Discussion

The results of cardiac transplantation are influenced by multiple donor factors [2]. The mismatch of sex as an adverse factor has not been consensual. Initially, female donors were thought to be responsible for decreased survival, irrespective of the recipient gender [3]. However, the fact that the majority of recipients are male could hide the mismatch of gender as a risk factor. Indeed, while some groups have found no differences in late mortality [4,11,12], others have identified female donors as a risk factor only to male recipients [13–15]. Weiss *et al.* [16] using the registry of the United Network for Organ Sharing (UNOS) containing data on 18 240 patients, pointed in this direction. However, more recently, Khush *et al.* [5] analyzed the registry of the ISHLT with 60 584 recipients and concluded that sex mismatch reduces survival in both male and female recipients. Although these large multicenter experiences have a clear statistical advantage, they have the disadvantage of different approaches to the selection of both donors and recipients. Here, we believe, lies an advantage of our study.

In our country, we are blessed by a legal presumed donor consent, which allowed us to have short wait-list times, low average donor age, and, related to a relatively small geographic area, low ischemic times. The quality of the donors partially explains the good overall results. But even in this good ground, we believe that if a difference exists in the behavior of the female donors on male receptors, it should be apparent.

Even if some results in the literature indicate that the sex mismatch may result in decreased survival, the progressive reduction of donor availability legitimizes its use, especially in confront with the mortality of patients in the waiting list. Hence, we have never rejected an, otherwise suitable, female donor. We intended to study only the effect of the female donor to male recipient, which appears to be the mismatch with most important consequences. We believe that our series also has the advantage of being recent, contrasting with the results of other series of patients with important historical components, which may no longer be translated to real life.

One of the possible reasons that have been identified for worse outcomes of female donors to male recipients is the disparity in the size of the heart itself, usually smaller in the female gender. In this series, the two groups of recipients, with and without mismatch, were quite homogeneous, including for the immunosuppressive regimen, but for two significant differences: BMI and transpulmonary gradient/sPAP. This results from the fact that we tended to choose smaller male recipients, with less pulmonary hypertension, to receive hearts from female donors.

Due to denervation, the transplanted heart usually shows chronotropic incompetence and diastolic dysfunction. As such, the increase in cardiac output depends primarily on the increase in stroke volume at the expense of increased filling pressures [17,18]. Small hearts have lower reserves and greater difficulty to adapt to the new situation. If we add to these conditions an increase in right ventricular afterload, cardiac output may be compromised. Recently, Reed *et al.* [18] have shown, through the analysis of 31 634 patients of the UNOS registry, that the difference in mortality in male recipients with sex mismatch disappeared when adjusted to the predicted size of the heart.

Our results are in line with these. We registered only a few cases of donor/recipient weight ratio <0.8. These facts partially explain the good behavior of our transplanted patients with gender mismatch, overlapping those of the group with male donors. Overall survival after 8 years was very similar between the two groups (66.6 ± 8.3% vs. 71.6 ± 4.9%; $P = 0.529$) and slightly better than those of the more recent (2002–2005 and 2006–2011) records of the ISHLT [2]. Yet, in Group A, prolonged inotropic support (>48 h) was required two times more frequently than in Group B, revealing some degree of perioperative dysfunction.

On a different note, the increased mortality in patients with gender mismatch has been touted by some to be the consequence of an increase in the number of acute cellular rejection episodes [12,13]. However, the larger multicentric series did not find an association between sex mismatch and the incidence of acute rejection [5,18], but these large registries have the limitations of lack of homogeneity caused by significant differences in the definition and registration from center to center. In the present study, acute cellular rejection was always defined according to the ISHLT 2005 classification [8]. In our experience, the incidence of acute rejection grade ≥2R in the first year was 20.5% and 14.7%, respectively, for groups A and B. These values are similar to or lower than those internationally reported [2]. The incidence of milder degrees of rejection (1R), not undergoing treatment, was also marginally higher in Group A (40.9% vs. 31.4% in the first 3 months). Although these differences did not reach statistical significance, it is doubtful whether this would have happened if the series were larger. The same goes for survival free from acute rejection.

An increased incidence of vascular graft disease in male recipients with gender mismatch has been documented in some works [19,20]. Among possible reasons for this are the hemodynamic stress in smaller caliber coronary arteries [21] and the increased immune response in the female donor heart [19]. Our series does not confirm these findings. Indeed, survival free from graft vascular disease appears better in the recipients from female donors, although statistical significance was not reached. This finding has been described before [5,22] and among the speculative reasons given is the higher prevalence of coronary artery disease in male donors, which could progress as vascular disease of the graft [23].

By contrast, the group with gender mismatch had a lower survival free from malignancy, another late-appearing factor of morbidity, in the threshold of statistical significance. Although only malignant cases are considered, the spectrum includes rapidly progressive variants and more indolent forms. Reasons for these results, as the need for more aggressive immunosuppression in female donors, and hormonal and/or immune factors, are also speculative. Although the present study does not allow us to infer about the cause, to the best of our knowledge, this is the first time that the association between gender mismatch and differences in the incidence of cancer is reported.

Finally, survival free from severe infection requiring hospitalization for intravenous therapy was lower in Group A, also in the threshold of statistical significance. Looking at the literature on the subject, we found series that, despite reporting significant differences in the incidence of acute cellular rejection associated to sex mismatch, showed similar incidence of infections [12]. Analyzing the curve of Fig. 3c, we find that the difference is mainly in the first months post-transplant. Still, we believe that this might be associated with a higher, yet nonsignificant, incidence of acute rejection episodes grade 1R in the first 3 months, besides grade 2R and 3R occurrences. If the relationship between treatment with high-dose corticosteroids in the latter and a higher incidence of infection seems likely, in the case of grade 1R episodes, it may be associated with a trend to higher levels of immunosuppression deliberately used in mismatch cases, which may be important to correct.

Study limitations

This study presents the obvious advantage of originating from a single center, with uniform use of selection criteria for donors and recipients, and surgical and medical therapeutic approaches, and standardized follow-up. And, unlike large multicenter series, the fact that our data are

collected from a single institution allowed us not to have significant missing data on most variables. However, the relatively small numbers do not allow us to perform a statistical matching analysis that could make the results more powerful. But we have tried to interpret the results in view of these limitations throughout the text. Finally, other reasons for differences in mortality in patients with donor sex mismatch which have been identified or suggested, such as genetic, hormonal, or immunologic factors [24,25], have not been studied in this work.

Conclusions

The allocation of hearts from female donors to male recipients can be safely done, at least in the case of recipients without pulmonary hypertension and when a standard weight ratio between donor and recipient is ensured. During follow-up, there was no significant association of gender mismatch with global survival and survival free from acute cellular rejection and graft vascular disease, although these patients showed a greater tendency to suffer from infections and malignancies.

Authorship

PC: wrote the paper and analyzed data. DP: wrote the paper and performed research. MB: follow-up and collected data. MA: designed study and reviewed the paper.

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References

1. McMurray JJV, Adamopoulos S, Anker SD, *et al.* ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur. Heart* 2012; **33**: 1787.
2. Lund LH, Edwards LB, Kucheryavaya AY, *et al.* The Registry of the International Society for Heart and Lung Transplantation: thirtieth official adult heart transplant report–2013; focus theme: age. *J Heart Lung Transplant* 2013; **32**: 951.
3. McCarthy JF, McCarthy PM, Massad MG, *et al.* Risk factors for death after heart transplantation: does a single-center experience correlate with multicenter registries? *Ann Thorac Surg* 1998; **65**: 1574.
4. Tsao CI, Chen RJ, Chou NK, *et al.* The influence of gender on survival after heart transplantation. *Transplant Proc* 2008; **40**: 2634.
5. Khush KK, Kubo JT, Desai M. Influence of donor and recipient sex mismatch on heart transplant outcomes: analysis of the International Society for Heart and Lung Transplantation Registry. *J Heart Lung Transplant* 2012; **31**: 459.
6. Antunes MJ, Prieto D, Sola E, *et al.* Cardiac transplantation: five years' activity. *Rev Port Cardiol* 2010; **29**: 731.
7. Costanzo MR, Dipchand A, Starling R, *et al.* The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. *J Heart Lung Transplant* 2010; **29**: 914.
8. Stewart S, Winters GL, Fishbein MC, *et al.* Revision of the 1990 working formulation for the standardization of nomenclature in the diagnosis of heart rejection. *J Heart Lung Transplant* 2005; **24**: 1710.
9. Mehra MR, Crespo-Leiro MG, Dipchand A, *et al.* International Society for Heart and Lung Transplantation working formulation of a standardized nomenclature for cardiac allograft vasculopathy-2010. *J Heart Lung Transplant* 2010; **29**: 717.
10. Prieto D, Antunes P, Antunes MJ. Donor mitral valve repair in cardiac transplantation. *Transplant Proc* 2009; **41**: 932.
11. De Santo LS, Marra C, De Feo M, Amarelli C, Romano G, Cotrufo M. The impact of gender on heart transplantation outcomes: a single center experience. *Ital Heart J* 2002; **3**: 419.
12. Jalowiec A, Grady KL, White-Williams C. First-year clinical outcomes in gender-mismatched heart transplant recipients. *J Cardiovasc Nurs* 2013; **27**: 519.
13. Prendergast TW, Furukawa S, Beyer AJ, Browne BJ, Eisen HJ, Jeevanandam V. The role of gender in heart transplantation. *Ann Thorac Surg* 1998; **65**: 88.
14. Al-Khaldi A, Oyer PE, Robbins RC. Outcome analysis of donor gender in heart transplantation. *J Heart Lung Transplant* 2006; **25**: 461.
15. Zeier M, Döhler B, Opelz G, Ritz E. The effect of donor gender on graft survival. *J Am Soc Nephrol* 2002; **13**: 2570.
16. Weiss ES, Allen JG, Patel ND, *et al.* The impact of donor–recipient sex matching on survival after orthotopic heart transplantation: analysis of 18 000 transplants in the modern era. *Circ Heart Fail* 2009; **2**: 401.
17. Mather PJ, Jeevanandam V, Eisen HJ, *et al.* Functional and morphologic adaptation of undersized donor hearts after heart transplantation. *J Am Coll Cardiol* 1995; **26**: 737.
18. Reed RM, Netzer G, Hunsicker L, *et al.* Cardiac size and sex-matching in heart transplantation: size matters in matters of sex and the heart. *JACC Heart Fail* 2014; **2**: 73.
19. Erinc K, Yamani MH, Starling RC, *et al.* The influence of donor gender on allograft vasculopathy: evidence from intravascular ultrasound. *Transplant Proc* 2004; **36**: 3129.
20. Mehra MR, Stapleton DD, Ventura HO, *et al.* Influence of donor and recipient gender on cardiac allograft vasculopathy. An intravascular ultrasound study. *Circulation* 1994; **90**: II78.
21. Sharples LD, Caine N, Mullins P, *et al.* Risk factor analysis for the major hazards following heart transplantation–

rejection, infection, and coronary occlusive disease. *Transplantation* 1991; **52**: 244.
22. Kittleson MM, Shemin R, Patel JK, *et al.* Donor–recipient sex mismatch portends poor 10-year outcomes in a single-center experience. *J Heart Lung Transplant* 2011; **30**: 1018.
23. Li H, Tanaka K, Anzai H, *et al.* Influence of pre-existing donor atherosclerosis on the development of cardiac allograft vasculopathy and outcomes in heart transplant recipients. *J Am Coll Cardiol* 2006; **47**: 2470.
24. Olivetti G, Giordano G, Corradi D, *et al.* Gender differences and aging: effects on the human heart. *J Am Coll Cardiol* 1995; **26**: 1068.
25. Panajotopoulos N, Ianhez LE, Neumann J, Sabbaga E, Kalil J. Immunological tolerance in human transplantation. The possible existence of a maternal effect. *Transplantation* 1990; **50**: 443.