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Sex Matters, But to What Clinical Avail?

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Despite substantial advances in mechanical circulatory support, cardiac transplantation remains the “gold standard” treatment option for eligible patients with American Heart Association/American College of Cardiology class D end-stage heart failure. Transplant survival rates have progressively improved at all time points, with 55% of recipients now surviving 10 years after transplantation, despite an increase in donor and recipient age and comorbidity and greater recipient urgency. Survival has improved with every 5- to 10-year era, but most of the mortality aversion is in the first 6 to 12 months.^{1,2}

In this issue of *Circulation: Heart Failure*, Weiss and colleagues³ from The Johns Hopkins University, evaluated United Network for Organ Sharing data on all first US adult heart transplantations from 1998 to 2007 (n=18,240). The authors show that female recipients had marginally ($P=0.06$) worse 5-year survival than male recipients (absolute increase risk of 3.6%; 11% higher risk-adjusted mortality). However, the overall better survival in male recipients was present only in male recipients of a male donor; by using multivariable Cox modeling, they found that male recipients of a female donor (FD/MR) were 15% more likely to die than male recipients of a male donor (MD/MR). Moreover, after the addition of propensity adjustment for the likelihood of receiving a same-sex donor, the FD/MR group was 20% more likely to die than those male recipients who received a same-sex donor. The survivals of donor/recipient sex-matched female (FD/FR) and male (MD/MR) recipients were statistically indistinguishable after multivariable adjustment (with and without propensity adjustment), but when considered together, donor-recipient sex mismatches (FD/MR and MD/FR) were 14% ($P<0.001$) more likely to have died at 5 years than the sex-matched group (MD/MR and FD/FR). However, among female recipients alone, the multivariable propensity-adjusted analysis revealed no increase in the risk of death (hazard ratio, 1.24; 95% confidence interval [CI], 0.92–1.35; $P=0.31$). The authors conclude that matching donor and recipient sex provides a survival advantage for men but not for women.

This study raises three questions. Are the results and conclusions valid? Why might this happen? Are the findings actionable?

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Despite the small number of recipients at any single transplant center, the field of heart transplantation has been blessed by the foresight of those who developed and sustained national and international outcome registries. The United Network for Organ Sharing (UNOS) stores data collected by federal mandate on all US heart transplant recipients. During the past 25 years, these data have been analyzed by UNOS and more recently by Arbor Research as the Scientific Registry of Transplant Recipients. Non-US members of the International Society of Heart and Lung Transplant (ISHLT) contribute data to the combined UNOS/ISHLT Registry. Two voluntary registries, the Collaborative Transplant Study (CTS; mainly non-US) and the Cardiac Transplant Research Database (US only), have collected more detailed information. Together, these provide a wealth of outcome data on the majority of the world's heart transplant recipients.

As demonstrated in this analysis and several others, survival is inferior for female US adult heart transplant recipients, with differences both early (91.1% versus 92.5% for males at 3 months) and late (72.8% versus 75.0% for males at 5 years) after transplantation.² In the 2008 report from the Registry of the International Society for Heart and Lung Transplantation, female recipient status is no longer a multivariable risk factor for 1-year mortality (it was in earlier reports) but remains a risk factor for 10-year mortality (conditional on survival to 3 years), with female recipients approximately 20% more likely to die than male recipients of male donors.¹

Others have also examined the impact of donor and recipient sex matching on outcome, and conclusions, while seemingly contradictory, may actually be similar within the constraints of study power. A 2002 analysis of data from 25,432 heart transplant (4159 female and 21,273 male) recipients from the CTS provides interesting parallels to the present study.⁴ In the CTS study, the authors concluded that female donation had a negative impact on the actuarial survival of male recipients (FD/MR=46.2±1.0 years versus MD/MR=48.0±0.6; $P<0.0001$), but male donation had no negative impact on the actuarial survival of female recipients (MD/FR=49.9±1.7 versus FD/FR=51.8±1.7 years; $P=0.96$). Noting that the difference in 10-year survival between donor/recipient sex-mismatched pairs in this study was 1.8 years for male recipients and 1.9 years for female recipients and that female recipients made up approximately 20% of the sample, one is tempted to suspect a type II error (lack of statistical power) in this analysis of female donor/recipient sex mismatch. In separate multivariable Cox models for male and female recipients, the hazard ratio for death during 10 years was 1.13 (95% CI, 1.08–1.19; $P<0.0001$) for sex-mismatched male recipients (ie, FD/MR versus MD/MR). Unfortunately, the authors did not state the point estimate for the corresponding hazard ratio for female recipients (ie, MD/FR versus FD/FR), only that it was not statistically significant.

In a much smaller ($n=174$) study by Prendergast and colleagues,⁵ gender-mismatched transplants (FD/MR or MD/FR) were associated with increased rejections ($P=0.04$) and worse 1-year survival (67%) compared with gender-matched transplants (85%; $P=0.003$). MD/FR had more rejections than FD/FR and, although not statistically significant, a trend toward reduced 1-year survival was noted (MD/FR=71% versus FD/FR=89%; $P=0.16$). In contrast, FD/MR transplants had lower 1-year survival (65%) than MD/MR (84%; $P=0.007$).⁵ Similarly, Al-Khalidi et al⁶ studied 869 consecutive cardiac transplants and demonstrated that male recipients of a female donor had higher 1-year mortality (24%) than sex-matched male donors (13%; $P=0.009$), with female donors in general increasing the odds of recipient death 2-fold.⁶ In the present study by Weiss and colleagues,³ there was significantly impaired survival for sex-mismatched male recipients (FD/MR versus MD/MR: hazard ratio, 1.14; 95% CI, 1.01–1.28; $P=0.04$) but no statistically significant survival difference for sex-mismatched female recipients (MD/FR versus FD/FR: hazard ratio, 1.24; 95% CI, 0.92–1.35; $P=0.31$). The magnitude of increased hazard was actually larger in sex-mismatched female recipients, again

raising the question of a type II error and the possibility that donor/recipient sex mismatch acts adversely in *both* men and women.

Why Sex May Impact on Outcomes

Several possibilities may explain why “sex matters” in transplant. It is likely that biological factors and sex-associated (but not necessarily sex-dependent) factors influence cardiac transplant outcomes. Female sex is associated with smaller recipient height, smaller donor body mass index, higher pretransplant allosensitization, and of course, previous pregnancy, all of which have been identified with multivariable analyses as risk factors for mortality in the ISHLT Registry.¹ Weiss and colleagues³ adjusted for these factors in their analysis, suggesting that other biological factors specific to female sex may be at play.

Immunologic differences between men and women are obvious candidates. Female heart transplant recipients are at higher risk of rejection and of hemodynamically significant rejection and require greater immunosuppression.^{7,8} Studies of the influence of recipient sex on posttransplant outcomes in cardiac and other organ transplants suggest a plausible explanation for biological consequences that are directly related to subject sex. A retrospective, single center study of 520 consecutive cardiac allograft recipients demonstrated that female recipients had increased pretransplant immunoreactivity (as manifested by higher prevalences of HLA-B8 and DR3 haplotypes and antinuclear antibodies) and significantly shorter durations to first rejection, more rejection episodes, and earlier production of anti-HLA antibodies posttransplant.⁹ A study using the Australian Bone Marrow Donor Registry demonstrated that female T cells are more reactive than male T cells in their response to self-antigens and mismatched antigens, potentially explaining the worse outcomes in female transplant recipients.¹⁰

Young women and women receiving oral contraceptives have higher immunoglobulin M levels, suggesting a role for estrogen in immunoglobulin production.¹¹ Hormonal differences may influence pathophysiological mechanisms operational in chronic allograft vasculopathy, a leading cause of posttransplant mortality. At the Berlin Heart Center, allografts (n=873) from premenopausal female to male transplants more frequently developed endothelial disease and stenotic microvasculopathy than premenopausal female to female transplants, raising the question of hormonal influences on transplant immunoreactivity.¹²

The influence of the Y chromosome on posttransplant outcome also warrants further investigation. Studies in renal and allogenic stem cell transplantation repeatedly demonstrate worse outcomes in sex-mismatched transplants, with higher rates of rejection in MD/FR renal and stem cell transplants and increased incidence of graft versus host disease and mortality in FD/MR stem cell transplants.^{13–17} The development of antibodies against the Y chromosome of male donors in female renal transplant recipients may partially explain these findings. In 26 female recipients of male kidneys, Tan et al¹⁸ demonstrated the development of H-Y antibodies in 46%, the presence of which were strongly correlated with the development of acute rejection ($P<0.001$) and plasma cell infiltrate within biopsy specimens. Similarly, in female recipients of male donor stem cell transplants, the risk of rejection was 2-fold higher than sex-matched grafts and the risk of death was increased 44% (both $P=0.01$). Conversely, the risk of graft versus host disease increased 44% in male recipients of female donor stem cells ($P=0.03$).¹⁸ In stem cell grafts, major histocompatibility complex class II-restricted CD4+ T cells specific to H-Y have been identified. Thus, it is possible that the development of H-Y antibodies partially explains the poorer outcomes in female cardiac transplant recipients of male donor organs.¹⁹

The present analysis also suggests that the increased risk of female donation to male recipients is explained by a greater frequency of urgent (ie, UNOS status 1) transplants, as there was a marked increased risk in these recipients (with the period of risk appearing to be in the first weeks after transplant) with no increased risk in less ill (UNOS status 2) recipients (see Figure 5A and 5B).³ This was also seen in a single center study from Spain, in which 30-day mortality was increased in male recipients of female donors but only for urgent heart transplants. In this study, FD/MR patients were twice as likely to receive an urgent transplant as were MD/MR patients.²⁰

Receiving a heart from a female donor may be particularly hazardous in the urgent transplant setting, in which patients often enter surgery with more significant end-organ dysfunction and higher pulmonary pressures. Receipt from a female donor (independent of recipient status) is a risk factor for low cardiac output in the early postoperative period and is associated with greater postoperative intra-aortic balloon pump utilization.²¹ The authors of the present study, using a data set from the same UNOS Registry, showed that a high male recipient pulmonary vascular resistance (>4 Wood units) was associated with worse survival following transplant of female versus male donor hearts.²² Whereas donor/recipient size mismatch (by body mass index or body surface area, each evaluated continuously) was not independently associated with 5-year outcome in the present analysis, it did significantly influence 5-year survival (conditional on 1-year survival) in the 2008 UNOS Registry analysis.¹ Therefore, as in kidney transplantation, in which “nephron underdosing” has been implicated as playing a role in worse outcomes for donor sex-mismatched male recipients,⁴ males receiving an undersized female heart may be disadvantaged and particularly so in the urgent transplant setting.

Implications on Donor Organ Allocation

If donor/recipient sex mismatch is a risk for poor posttransplant outcome, should cardiac organ allocation be amended? To address this question, one must consider the magnitude of increased posttransplant risk in the awaiting recipient and organ donor availability. The absolute and relative increased posttransplant mortality risks for FD/MR vs. MD/MR were 3.6% and 15%, respectively. Does this amount of increased risk justify delay of transplant in men to find a more suitable donor? Donor/recipient sex mismatch is one of many donor and recipient factors that influence survival, many of which exert effects of a magnitude as large or larger. An ischemic (versus nonischemic) heart failure etiology, a prior transfusion history, and receipt of a compatible but nonidentical ABO group heart are independently associated with 16%, 19%, and 25% higher risks of death in the first year posttransplant.¹ Recipients with a history of diabetes who survive the first year posttransplant still have a 39% greater probability of death by 5 years compared with recipients without diabetes before transplant.¹ Given the multiplicity of donor and recipient factors that influence posttransplant outcomes, a rational response to a single donor or recipient factor should be made in the context of the company it would be keeping.²³

Because approximately 70% of heart donors are male, females with heart failure would be particularly disadvantaged by avoidance of male donors. This would have been especially true in the early mechanical support era when utilization of left ventricular assist devices was limited in women by the relatively large devices then in use and may have adversely influenced the survival of female recipients in present analysis.

For males awaiting cardiac transplant, should we aim to select male donors? The finding by Weiss et al,³ that the excess risk is present *only* in the UNOS 1 patients, could lead to more rational use of female donors in potential UNOS 2 recipients. For male UNOS 1 recipients, a more selective approach, in the context of other donor and recipient risk factors as previously discussed, might seem reasonable, avoiding female donors in unstable recipients but using

them in more stable recipients (eg, stable patients chronically supported on a left ventricular assist device or on a single low-dose inotrope with low pulmonary vascular resistance and preserved renal function). Such a strategy might be evaluated retrospectively by delving somewhat deeper into existing multicenter registries. However, the fact that transplant centers are more likely to select a mismatched donor in an urgent (UNOS 1a) versus less urgent (UNOS 2) situation²⁰ suggests the potential pitfall of a retrospective study and the difficulty of proposing sex matching of donors and recipients: centers avoid the FD/MR situation whenever possible and accept sex-mismatch only when “forced” by the need to find the first available organ in patients at the highest risk of imminent death. As such, any strategy that prolongs waiting time in the least stable UNOS 1 patients must be weighed against the underlying mortality risk of withholding transplant. Given the heightened risk in unstable patients supported on intravenous inotropic agents, the additional risk of a sex-mismatched organ should be included in the calculus of whether and when to move to a left ventricular assist device.²⁴

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