*8th Annual Women's Heart & Vascular Symposium*

# Sex-Related Differences in Outcomes

## of Thoracic Organ Transplantation and Mechanical Circulatory Support

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In current practice, donors and recipients of solid-organ transplants are not matched by sex.[1] Although sparingly, authors have begun to report sex-specific differences in thoracic organ transplantation and mechanical circulatory support outcomes.

### Lung Transplantation

Lung transplant surgery is procedurally similar in men and women; nevertheless, investigators have identified disparate outcomes, usually in favor of female recipients. Loor and colleagues,[2] in examining a large single-institution experience with lung transplantation after lung allocation scores came into use, found 5-year survival rates of 58% in men and 71% in women. The worst 5-year survival rate, 43%, occurred in male recipients of lungs from female donors. Freedom from long-term graft dysfunction was 25% at 5 years for men, compared with 35% for women.[2]

Several theoretical reasons, including psychosocial, hormonal, physiologic, and immunologic differences, may explain why female recipients have better long-term outcomes. It is conceivable (although not well studied) that female recipients have more and stronger psychosocial support groups. Hormonal characteristics favor higher estrogen levels in women over those of testosterone in men. Elevated estrogen levels during pregnancy might provide protection against long-term rejection. Although the underlying mechanism is unclear, the demonstrated tolerance for alloantigens in women may contribute to improved outcomes after transplantation. Subtle sex-specific physiologic differences exist in cardiovascular status, circulation, blood pressure, vascular tone, and kidney function. Immunologic differences are also notable; more human leukocyte antigens are found in female kidneys than in male kidneys.[3] Female heart allografts did worse than those of males in an animal model, and this phenomenon was reversed by blocking estrogen receptors.[4] These findings suggest that hormonal differences affect both physiologic and immune response. The use of biomarkers may provide insight into differences in the circulating protein milieu between male and female lung recipients at baseline, and using ex vivo perfusion platforms will facilitate analysis of biomarkers in donors. Studies of differences in the molecular phenotype between males and females are needed to clarify factors that either cause or are associated with better outcomes for female patients after lung transplantation. This knowledge may enable us to modify practice or identify high-risk features.

### Heart Transplantation

Every year, approximately 3,000 patients who have end-stage heart disease undergo heart transplantation (HT) in the United States. The surgery is procedurally similar in men and women, but again, differences in outcomes have been identified. Unlike lung transplantation, in which women have a substantial advantage, sex-specific HT outcomes are less clear. Khush and colleagues[5] analyzed the International Society for Heart and Lung Transplantation registry to study the influence of donor–recipient sex mismatch on HT outcomes. They reviewed 60,584 procedures and found statistically significant differences between male and female recipients with respect to overall survival rates and death-censored allograft survival rates for female versus male donors. Male recipients of female donor hearts had a 10% higher mortality rate than did male recipients of male hearts. Female recipients of female hearts had a 10% lower mortality rate than did female recipients of male hearts. Of note, the female–female

combination is a minority of all HTs performed. The investigators observed that female-to-male HT steadily decreased during the last several years of their analysis because of the higher mortality rates, and that male-to-male was most prevalent. Overall long-term survival rates between males and females were similar; conversely, the survival rates in sex-mismatched recipients were significantly lower. The investigators also evaluated the formation of cardiac allograft vasculopathy (a leading cause of long-term graft dysfunction) in men and women, but found nothing significant.

Kaczmarek and associates[6] analyzed sex-specific short- and long-term outcomes in 67,855 HT patients. In this study, men fared better than did women. The male donor–male recipient group had a 1-year survival rate of 84%; in the male–female group, it was 79%. Among 1-year survivors, 5-year survival rates did not differ. These findings indicate that sex mismatch predominantly influences short-term outcome and highlights the importance of immediate postoperative care. Hsich and colleagues[7] evaluated sex differences in mortality rates in terms of United Network for Organ Sharing (UNOS) status among patients awaiting HT. The overall mortality rate of patients on the waiting list was 16%, and the hazard ratio for female status was 3:1. After risk adjustment, female status was still a significant hazard for death, especially for UNOS status 1 patients, who are the sickest ones on the list.

The New Heart study[8] was performed to investigate different sex-related electrocardiographic and clinical findings in heart recipients. Among the 238 men and 92 women patients, women had 14% of the rejection episodes and the men, 5%. Women also underwent more hospitalizations (59% vs 46%). Smetana and associates[9] studied the sensitivity to perioperative ischemia reperfusion injury in male and female donor myocardium. Female donor hearts had elevated baseline levels of necrotic cell death markers; however, levels of apoptotic cell death markers were equally elevated in both sexes one week after HT. This finding suggests sex-related differences in cell death mechanisms, particularly in the necrotic cell death pathway. Both pathways are regulated by key enzymes that would be expected to function similarly in either sex; however, perhaps expression levels of these enzymes differ between the sexes and lead to differences in graft performance.

### Mechanical Circulatory Support

The use of ventricular assist devices (VADs) has increased in patients with end-stage heart disease who need a bridge to HT or who need permanent circulatory support because they are not eligible for HT. Device placement involves suturing an inflow cannula into the left ventricular apex and an outflow cannula into the aorta. Sex-related differences have been noted. Yavar and colleagues[10] reported more bleeding complications in women than in men after implantation of a continuous-flow left VAD (LVAD); in women, nasopharyngeal and vaginal bleeding occurred most often. In addition, the cumulative survival rate at 3 years was approximately 40% for men versus 18% for women. Acharya and co-authors[11] found a 10.57% postoperative stroke rate in 7,112 Interagency Registry for Mechanically Assisted Circulatory Support (Intermacs) patients supported with continuous-flow LVADs. Women had a 50% increase in stroke risk after implantation, and female sex was an independent predictor; the authors proposed that endogenous estrogen affects coagulation status and predisposes women to strokes. Blumer and colleagues[12] performed a meta-analysis to evaluate sex-specific outcome disparities in continuous-flow LVAD recipients and reported a 90% increase in stroke risk for women. In addition, women were twice as likely to need a right VAD. Respective rates of bleeding, renal failure, infection, and death were similar.

Newer-generation LVADs were evaluated in a cohort from the Multicenter Study of MagLev Technology in Patients Undergoing MCS Therapy with HeartMate 3 (Momentum 3). Males and females had similar predicted 6-month probabilities of death, disabling stroke, and device reoperation, but age was more influential than sex as a contributing factor.[13] In 815 men and 151 women in the European Registry for Patients with Mechanical Circulatory Support,[14] the study investigators noted significant differences in right ventricular failure, postoperative arrhythmias, and major bleeding, all of which were more prevalent in women than in men.

## Conclusion

Outcomes for women who undergo thoracic organ transplantation differ from those in men. Women fare better with transplanted lungs, and men slightly better with hearts. Women fare worse after VAD implantation. Results can improve with risk factor modification and anticoagulation regimens. Donor–recipient sex mismatch may adversely affect outcomes after thoracic organ transplantation; however, this risk should be weighed against the current donor shortage and risk of death while awaiting a transplant. Further research into sex-specific regimens is warranted, as is prospective analysis of biological and immunologic characteristics of both sexes.

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