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The Journal of Heart and Lung Transplantation

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Advances in heart transplantation: The year in review

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KEYWORDS:
heart transplant;
immunosuppression;
allograft rejection;
survival;
vasculopathy

Although the world of advanced heart failure has intensely focused its spotlight on mechanical circulatory support, the field of heart transplantation has continued to evolve. We highlight the latest clinical and laboratory research that have affected the field of adult heart transplantation. Major scientific and clinical advances in the field of heart transplantation have focused on expanding the donor pool, refining the use of immunosuppression, and monitoring the effects of therapy.
J Heart Lung Transplant 2011;30:241–6

Although the world of advanced heart failure has intensely focused its spotlight on mechanical circulatory support, the field of heart transplantation has continued to evolve. In 2010, the International Society of Heart and Lung Transplantation (ISHLT) published the first comprehensive guideline covering the care of patients after transplantation. This involved the amalgamation of nearly 40 years of scientific and clinical experience.[1] The ISHLT also published guidelines to standardize nomenclature for cardiac allograft vasculopathy.[2] In this review, we highlight the latest clinical and laboratory research that have affected the field of adult heart transplantation.

Organ procurement and allocation

Limited organ availability continues to further patient attrition on the heart transplant waiting list. Scientists have worked to better understand procurement-related allograft injury and potential mechanisms to improve organ recovery and survivability. Bulcao et al[3] found that donor hearts exhibiting systolic dysfunction have increased interleukin-6 expression, JAK2-STAT3 signaling, and activity of inducible nitric oxide synthase. They proposed that this pathway, which is known to cause myocardial dysfunction, could be a therapeutic target to improve donor heart function.[3]

Yang and Yu[4] studied the effect of adding pinacidil, an adenosine triphosphate–sensitive potassium channel *opener,* to a hyperpolarizing cardioplegic agent in rats. They found that potassium channel modulation improved energy stores and decreased myocardial damage.[4] Nakao et al[5] showed, in an animal model, that after standard and extended periods of cold ischemia, donor and recipient treatment with inhaled hydrogen and carbon monoxide ameliorated the degree of ischemia-reperfusion injury. The proposed mechanism was through an anti-inflammatory and anti-oxidant effect, as the researchers were able to show reduced expression of inflammatory markers, decreased markers of necrosis, decreased apoptosis, and improved myocardial function in the transplanted allograft.[5] These studies identified potential opportunities to augment organ protection during procurement and will require validation in humans.

Deceased cardiac donors have been a major source of kidneys for transplantation. Increasing numbers of lung transplants have also been done with such organs, but there has been very little experience with hearts from these donors. Recent studies have evaluated methods to resuscitate non-beating donor hearts after a cardiocirculatory arrest. Repse et al[6] examined a novel approach to incorporating pre-reperfusion cardioplegia and warm storage in a donor animal after cardiopulmonary arrest. They showed transient although not sustained improvement with this technique over cold storage in this non-brain death model.[6] Hirota et al[7] showed that infusion of tissue plasminogen activator after cardiopulmonary arrest provided similar allograft functional recovery as pre-treatment with heparin.

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1053-2498/$ -see front matter
doi:10.1016/j.healun.2010.10.013

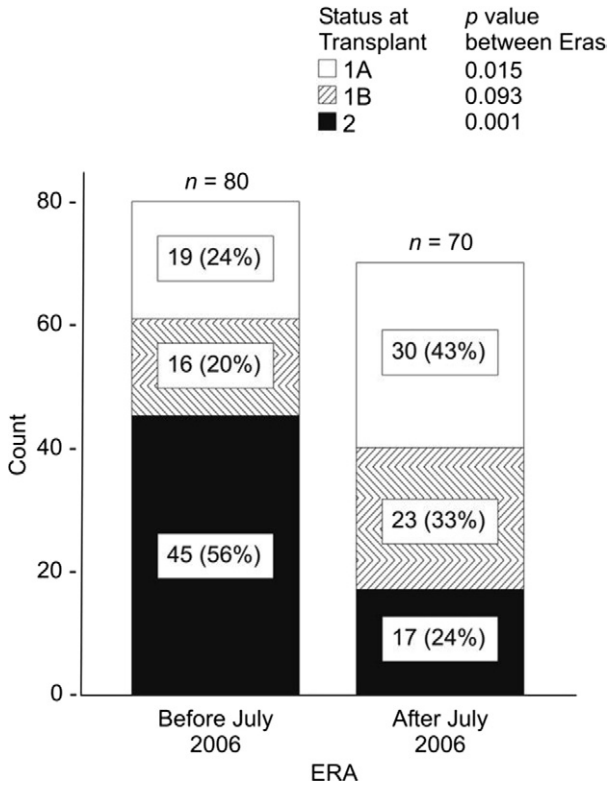

Figure 1 Bar graph shows the distribution of heart transplants by listing status comparing the eras before and after the United Network for Organ Sharing allocation policy change. Reprinted from *The Journal of Heart and Lung Transplantation* with permission from Elsevier.[8]

Clinicians also continued to re-evaluate the effect of organ allocation algorithms on clinical outcomes and efficient organ utilization. Nativi et al[8] examined the effect of the 2006 United Network for Organ Sharing (UNOS) changes to the organ allocation algorithm for heart transplantation, which allowed regional sharing of organs with the intention of allocating organs to more critically ill patients, thereby decreasing wait-list mortality. Their single-center analysis showed the protocol increased the proportion of status 1A or 1B patients receiving heart transplants, with the consequence of increased waiting time for the other patients and ischemic time for the allograft (Figure 1).[8] Komodo et al[9] analyzed the effect of the Eurotransplant donor heart allocation system on patients with mechanical assist devices. In Germany, at least 80% of all heart transplants occur in patients who are on the "urgent" list; the guidelines allow urgent listing of patients with mechanical circulatory support (MCS) only after specific complications arise. The authors present retrospective data from their center showing that those requiring MCS have a comparable mortality rate with patients listed for transplantation not requiring an assist device. Although the study did not exclusively evaluate contemporary continuous-flow devices, the authors suggest that the listing criteria in Germany be modified to give some priority to patients with assist devices.[9]

Outcomes

Stehlik et al[10] reviewed more than 7,000 patients in the Cardiac Transplant Research Database and identified interactions between donor characteristics that conferred increased risk to allograft survival; for example, donor hypertension in male but not female donors increased risk. Higher recipient-donor weight differentials also affected survival adversely only if the donor was female or older.[10] These findings highlight the complex and challenging nature of donor organ selection and allocation and may serve as an impetus to refine the way we accept donor organs and match donor to recipient. These data also argue against more centralized allocation systems.

Singh et al[11] report on the negative effects of poor socioeconomic status and non-white race on allograft rejection and survival after heart transplantation. Their study reiterates the importance of having adequate access to medical and social resources after heart transplant but also brings to the forefront the growing concern about race-specific differences in immune and inflammatory responses to organ transplant.

Shuhaiber et al[12] examined the Scientific Registry of Transplant Recipients and confirmed that in the modern era, centers performing very low volumes of heart transplantation continue to have poorer survival rates.

Other investigations on survival after heart transplantation focused on higher-risk sub-groups. Wu et al[13] reviewed outcomes in the Cardiac Transplant Research Database for patients with muscular dystrophy. Survival was similar in patients with a variety of muscular dystrophies compared with age-matched controls. These data may suggest that heart transplantation is safe in patients with muscular dystrophy and cardiomyopathy, but the authors cautioned that they did not quantify functional capacity, skeletal muscle atrophy, and respiratory capacity of this study cohort and that the results are prone to selection bias.

Uriel et al[14] provided a single-center case series reviewing the outcomes of heart transplant in lymphoma patients who had received mediastinal radiation. They reported higher post-operative mortality (3 of 9 patients) and a high rate of secondary malignancies (5 of 6 patients) in patients surviving to hospital discharge.[14] The results assert the prevailing observations that heart transplantation is a high-risk endeavor in this population.

Karamlou et al[15] examined the UNOS database to evaluate the outcomes of adults with congenital heart disease (ACHD) undergoing heart transplantation. Mortality was higher after transplant in ACHD patients due to early post-operative death, and there have been no improvements in recent eras. In addition to acknowledging the contribution of previously identified risk factors, including increased ischemic time, prior cardiac surgeries, and bleeding risk, the authors identified less frequent use of induction immunosuppression and higher rates of steroid withdrawal in ACHD patients that may or may not be clinically relevant.[15]