Review Article

Latest Developments in Heart Transplantation: A Review

Andrew Jabbour MBBS, PhD, FRACP, FCSANZ[1,2,3]; and Peter Macdonald, MD, PhD, FRACP, FCSANZ[1,2,3]

[1]Heart and Lung Transplant Unit, St. Vincent's Hospital, Darlinghurst, Australia; [2]Cardiac Physiology and Transplantation Laboratory, Victor Chang Cardiac Research Institute, Darlinghurst, Australia; and the [3]Faculty of Medicine, University of New South Wales, Kensington, Australia

ABSTRACT

Purpose: Heart transplantation (HT) remains the treatment of choice for advanced heart failure despite improvements in medical therapy and mechanical circulatory support. Significant developments have occurred in the field of HT over the past year, in particular the successful transplantation of donor hearts after circulatory determination of death. The purpose of this article was to review developments in HT published in 2014 and 2015.

Methods: Selected articles found using a MEDLINE search of the key term *heart transplant* were reviewed.

Findings: The year has seen improvements in the attenuation of ischemia and reperfusion injury, patient selection, immunosuppression, imaging of the transplanted heart, and donor organ preservation that hold promise for increasing the number of transplantations and improving outcomes in HT recipients. Advances in the detection and attenuation of cardiac rejection and allograft vasculopathy are highlighted.

Implications: A number of significant advances over the past year hold promise for tangible improvements in outcomes in the field of HT. (*Clin Ther*. 2015;37:2234–2241) Crown Copyright © 2015 Published by Elsevier HS Journals, Inc. All rights reserved.

Key words: aging, donation after circulatory death, heart transplantation, immunosuppression, ischemia-reperfusion injury, rejection.

INTRODUCTION

Increasingly stringent traffic laws and improvements in vehicle and workplace safety have reduced accident-related deaths and, hence, the rate of donor organs from young adults. With this phenomenon, combined with an aging population, the average age of organ donors increased from 20 years in 1983 to 32 years in 2011. Medical comorbidities, such as diabetes mellitus and hypertension, in donors are more common, potentially affecting the quality of donor organs. Comorbidities in recipients have also increased, with 46% affected by prior cardiac surgery; 45%, hypertension; 25%, diabetes mellitus; 7%, prior malignancy; and 33%, significantly exposed to alloantigens that induce immunologic memory cells that predispose to subsequent cardiac rejection. Close to 40% of all adult recipients are bridged to HT with a mechanical assist device, increasing the complexity of transplant surgery.[1] It is in this changing and increasingly complex environment that we welcome the recent advances in HT.

MATERIALS AND METHODS

Selected articles found using a MEDLINE search of the key word *heart transplant* were reviewed.

RESULTS

Donation after Circulatory Death

This article reviews developments in HT published in 2014 and 2015. Twenty three original manuscripts found

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using a MEDLINE search were reviewed and are described below. Articles were subjectively chosen by the authors for their scientific merit and potential impact on clinical practice. Although donation after circulatory death (DCD) has been used for kidney, liver, and lung transplantation, until recently it was not used for HT. Earlier this year, Dhital et al[2] reported a case series of HTs from DCDs. Three recipients received HTs from DCDs aged <40 years and with a maximum warm ischemic time (WIT) of 30 minutes. Hearts were retrieved with organ-preserving supplemented cardioplegia and transferred to an ex vivo perfusion system (Organ Care System; Transmedics, Inc, Andover, Massachusetts) for preservation, resuscitation, and transportation to the recipient's hospital. Although 2 patients needed temporary mechanical support, all 3 recipients had normal cardiac function within a week of transplantation and were alive and well at 77, 91, and 176 days after transplantation. The findings from that study suggest that within strict limitations and with the use of a portable ex vivo organ perfusion platform, distantly procured orthotopic HT (OHT) from DCDs is feasible.

To allow for the translation of DCD HT to humans, Iyer et al. initially reported that pharmacologic postconditioning increased the tolerance of DCD hearts to warm ischemia in a porcine model of asphyxia. They evaluated the viability of DCD hearts subjected to WITs of 20 to 40 minutes before flushing with Celsior (C) solution. The potential benefits of supplementing C with erythropoietin, glyceryl trinitrate, and zoniporide (Cs) were then assessed. Hearts flushed with C/Cs were assessed for functional, biochemical, and metabolic recovery on an ex vivo working-heart apparatus. Hearts exposed to 20-minute WIT were reported to have full recovery of functional and metabolic profiles compared with control hearts (no WIT). The investigators concluded that Cs could extend the limit of WIT tolerability to 30 minutes.[3] The Cs solution was then trialed in a study that utilized a porcine OHT model.[4] DCD hearts were preserved with either normothermic ex vivo perfusion (NEVP) using a clinically approved device, or with standard cold storage for 4 hours. OHT into recipient animals was subsequently undertaken. Five of 6 hearts preserved with NEVP were reported to have favorable lactate profiles during NEVP, and all 5 could be weaned off cardiopulmonary bypass after transplantation compared with 0 of 3 hearts preserved with cold storage ($P < 0.05$ [Fisher exact test]). DCD hearts flushed with Cs solution and preserved with NEVP were reported to have viability before and after transplantation. That study formed the basis for the aforementioned first-in-human study of DCD HT using NEVP.

Donor Age

Prolonged HT waiting time is associated with high mortality. To increase the donor pool, the utilization of hearts from donors aged ≥50 years has become more common. Roig et al[5] retrospectively analyzed 2102 consecutive HTs at 8 hospitals in Spain from 1998 to 2010. Acute and overall mortality were compared in patients who received grafts from donors aged ≥50 years versus those who received grafts from younger donors. Cardiovascular risk factors were more prevalent in the patients who received hearts from the older donors, but there were no differences in acute mortality or acute rejection episodes between the 2 groups. Overall mortality was greater in the recipients of hearts from donors aged ≥50 years than in the recipients of hearts from the younger group (unadjusted risk ratio = 1.40; 95% CI, 1.18–1.67; $P = 0.001$); however, after adjustment for donor cause of death, donor smoking history, recipient age, induction therapy, and cyclosporine therapy, the differences lost statistical significance. The group of recipients of hearts from the older group had a greater prevalence of cardiac allograft vasculopathy (CAV) at 5 years (risk ratio = 1.67; 95% CI, 1.22–2.27; $P = 0.001$). The investigators concluded that the careful selection of recipients and close monitoring for CAV are especially warranted in patients who receive hearts from older donors.

In an elegant preclinical study, Oberhuber et al[6] characterized the effects of donor age on solid-organ transplantation using a murine model of HT. They observed reduced graft survival when utilizing older hearts; however, chimeric young or old organs that were repopulated with young passenger leukocytes were reported to have comparable survival times. The transplantation of older organs triggered more potent alloimmune responses via intragraft $CD11c^+$ dendritic cells that augmented $CD4^+$ and $CD8^+$ T-cell proliferation and proinflammatory cytokine production, especially interleukin (IL)-17A. Notably, the depletion of donor $CD11c^+$ dendritic cells