Advances in the understanding and management of heart transplantation

Dhssraj Singh and David O. Taylor*

Address: Department of Cardiovascular Medicine, Heart and Vascular Institute, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, Ohio 44195, USA

* Corresponding author: David O. Taylor (taylord2@ccf.org)

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Abstract

Cardiac transplantation represents one of the great triumphs in modern medicine and remains the cornerstone in the treatment of advanced heart failure. In this review, we contextualize pivotal developments in our understanding and management of cardiac transplant immunology, histopathology, rejection surveillance, drug development and surgery. We also discuss current limitations in their application and the impact of the left ventricular assist devices in bridging this gap.

Introduction

As we approach 2017, the 50th anniversary of the first heart transplant, cardiac transplantation remains the gold standard in the treatment of end-stage heart failure and represents one of the great triumphs of modern medicine. In this review, we historically contextualize the major developments in the field by closely dissecting the challenges faced during its growth period, as well as discussing current and future developments.

The beginning

While research into the feasibility of heart transplantation and transplant immunology had started many decades earlier, the world's first cardiac transplantation was performed by Dr. Christiaan Barnard on Louis Washkansky on 3 December 1967 in Cape Town, South Africa [1]. Although Mr. Washkansky succumbed 18 days later to Pseudomonas pneumonia, Dr. Barnard's next transplant patient went on to live for 20 months. Optimism sparked by the feasibility of this new experimental technique led to marked enthusiasm and rapid development of numerous programs worldwide. Within a year of the first cardiac transplant, 102 heart transplants were performed in 50 institutions in 17 countries. Initial unbridled enthusiasm was quickly curtailed by the sobering realities of poor outcomes: 8-day mortality was 60 percent and mean survival after cardiac transplantation was only 29 days. Within 1 year, all but 3 of the 50 early-adopting institutions shut down their heart transplant programs. One year survival rates in the early days were hampered by allograft rejection. The initial immunosuppression regimen consisted of local irradiation, azathioprine, prednisone and actinomycin C, and later evolved to consist of corticosteroids and azathioprine, with use of the latter causing significant bone marrow suppression, skin eruptions, nausea and vomiting. In the first 3 years of experience with cardiac transplantation, 1 year survival was 40-50 percent [2].

Development in the understanding of transplant immunology

An important breakthrough in the field came in the form of the development of transvenous myocardial biopsy in 1973 [3]. This provided the impetus for the pioneering work in the field of cardiac pathology by Margaret Billingham in understanding and classifying allograft rejection [4]. Prior to this, the diagnosis of acute allograft rejection was made clinically, where a wrong diagnosis led to the misguided escalation of immunosuppression, causing significant harm. Endomyocardial biopsy quickly became, and remains, the gold standard in diagnosing rejection episodes as it allows for clinical signs and symptoms of rejection to be corroborated by

histopathological evidence. Serial endomyocardial biopsies were then incorporated into transplant surveillance protocols and this proved pivotal in improving the accuracy of the diagnosis, as well as deepening our understanding of mechanisms, gradation and timing of allograft rejection [5,6].

Allograft rejection can be divided largely into four categories: (a) hyperacute rejection – occurring minutes to hours after transplantation, and mediated by pre-formed antibodies to ABO blood group, human leukocyte antigen (HLA), or endothelial antigens; (b) acute cellular rejection – occurring any time after transplantation, although frequently 3–6 months after, and mediated by cellular immune mechanisms; (c) acute antibody- (formerly called "humorally-") mediated rejection – occurring days to weeks post transplantation and caused by cell lysis secondary to antibody formation against donor HLA or endothelial antigens; and (d) chronic rejection – occurring months to years post transplantation and manifesting as coronary allograft vasculopathy and/or interstitial fibrosis.

In 1983, there was another landmark breakthrough in the field of transplant cardiology with the approval of the calcineurin inhibitor (CNI) cyclosporin A for clinical use [7]. One year survival after heart transplantation with the use of cyclosporin A increased from 63 to 85 percent [8]. The use of cyclosporin A in the US led to a déjà vu of the late 1960s cardiac transplant boom and there was rapid revival and mushrooming of transplant programs nationwide. By the late 1980s, there were approximately 150 active cardiac transplant programs in the US and a rapid increase in the annual volume of heart transplants, from less than 500 in 1983 to close to 2360 in 1995 [9].

In the early 1990s, another CNI (tacrolimus, formerly known as FK506) was introduced as an alternative to cyclosporine [10]. The use of tacrolimus has been shown to result in a lower side effect profile than cyclosporine with less hypertension, hyperlipidemia [11], gingival hyperplasia and hirsutism [12]. Later in that decade, mycophenolate mofetil was found to be superior to azathioprine in reducing 1 year mortality in heart transplant recipients [13].

A transplant maintenance immunosuppression regimen in the modern era is largely comprised of steroids tapered over the first year, a CNI and mycophenalate mofetil. The goal of maintenance immunosuppression is to minimize allograft rejection and allograft vasculopathy. Three different agents are used to target different components of the immune system and to minimize the doses and subsequent side effects of these agents. In patients with renal insufficiency, basiliximab

(monoclonal antibody against B cells) or anti-thymocyte globulin (ATG) can be used in place of the nephrotoxic CNI as an initial agent to induce immunosuppression and safely delay the introduction of the CNI until the renal function has recovered post-operatively.

Advances in surgical technique
In 1960, Richard Lower and Norman Shumway developed the bi-atrial incision technique on animal models as a viable surgical technique for orthotopic heart transplantation [14]. Heterotopic heart transplantation as a surgical technique was then introduced by Christiaan Barnard in 1974 [1]. The donor heart would be used as a native left ventricular bypass conduit and inserted in the right lower side of the chest. This was particularly useful when allograft rejection was more prevalent, as the native heart provided backup to allograft dysfunction from rejection, and became less common with advances in immunosuppression therapy. It is now rarely used and only considered in patients with pulmonary hypertension where there is concern for right ventricular failure in donor hearts. In 1991, the bicaval technique of orthotopic transplantation was introduced, advantages of which include preservation of the geometry of both atria and the right ventricle, and less atrio-ventricular valve regurgitation and sinus node dysfunction [15,16].

Allograft rejection surveillance
Standard post-transplant surveillance protocols require frequent invasive endomyocardial biopsies to be performed, particularly in the first 6-12 months. In patients at low risk of rejection, gene expression profiling has emerged as a useful rejection surveillance modality. This technology is based on the premise that a unique set of genes are activated via different pathways during episodes of rejection, including for the activation of T and natural killer cells, hematopoesis and alloimmune recognition. Measuring expression of these genes therefore provides surrogate indicators of allograft rejection. This was investigated in the IMAGE trial where 602 heart transplant patients who were at low risk of rejection were randomized to either standard endomyocardial biopsy surveillance or rejection monitoring using gene expression profiling (AlloMAP) 6 months to 5 years post transplantation. This study showed that, among patients who are at low risk for rejection, gene-expression profiling monitoring was not associated with an increased risk of serious adverse outcomes and resulted in significantly fewer biopsies [17]. While its uptake is not uniform among transplant centers, it remains an option in patients at otherwise low risk of rejection in whom endomyocardial biopsy is especially problematic. Preliminary reports have shown that the use of AlloMAP may be comparable to endomyocardial biopsy within

6 months of transplantation, although final data are still pending [18].

Advances in donor organ preservation

Currently, hearts explanted from donors are stored in a container filled with a cold potassium-based crystalloid solution that is transported within an ice chest. The duration the heart is stored in hypothermic conditions and is referred to as ischemic or "cold" time. This has proven to be an inexpensive, cost-effective and viable method of transporting donor hearts to recipients. However, limitations exist: there is a relationship between cold time and primary graft dysfunction and an ischemic time of >4 hours is associated with significantly reduced survival [19]. Due to the limitations of the current methods, donor organ preservation techniques have become an area of intense research, as the benefits of improving organ preservation could expand the number and reach of donor hearts as well as possibly reduce the incidence of primary graft dysfunction. The PROCEED-II trial is a prospective multicenter randomized controlled trial that revealed the Organ Care System (OCS) technology of storing donor hearts in a portable normothermic blood perfusion system as non-inferior compared to the traditional hypothermic bath [20].

The face of cardiac transplantation in the current era

To date, more than 100,000 adult cardiac transplantations have been performed worldwide [21]. The number of transplants performed annually peaked in 1993 and declined between 1999 and 2004 before subsequently plateauing between 2004 and 2012 [21]. Out of 297 transplant centers worldwide, 62 of these centers perform 50 percent of total transplants, suggesting a marked variation in transplant volume between centers. Higher transplant volume per center is an independent predictor for improved survival [22].

Although survival has improved post-cardiac transplantation performed in the 21st century, compared to those performed in the 1980s and 1990s, there has not been a significant change in survival between 2000 and 2006 and between 2006 and 2012 [21]. Actually, this lack of apparent improvement has taken place in the face of important evolution in transplant recipient demographics, including a wider range of recipient ages (younger and older), increasing numbers of congenital heart disease recipients, increased proportion of sensitized patients, increased proportion of patients with hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD) and on dialysis [21]—all of which, when considered individually, are independent risk factors for decreased survival [23]. Thus, the

lack of apparent survival improvement in the last 12 years has actually occurred in the setting of transplanting high-risk patients, suggesting continued progress within the field.

Donor organ allocation is based on urgency as stratified on the United Network for Organ Sharing (UNOS) heart transplant list. An understanding of the listing criteria is important, as advances in the treatment of heart failure discussed below have significantly impacted the demographic of the transplant recipient in the current era. Patients are listed on different tiers: Status 1A, 1B, 2 or 7. Status 1A is of highest priority and subsequently decreases through 1B and 2 with status 7 being "inactive". The specific requirements to qualify for listing within designated tiers are listed in Table 1. When a donor heart becomes available, it is matched for size and ABO blood type in the order of where a patient is within the list.

The rising prevalence of end-stage heart failure has not been matched by the donor organ supply. Among the initiatives to bridge this gap include the advent, innovation and subsequent commercialization of durable left ventricular assist devices (LVADs) which currently can be used as a bridge to transplantation and as permanent or destination therapy. The receipt of LVAD for bridge to transplantation places the patient on status 1B, with the potential to be on status 1A for 30 days on a discretionary basis or if certain complications arise from LVAD therapy. With the continued increase in the number of patients receiving durable LVADs, the vast majority of patients that are being transplanted are on status 1A or 1B and it has become increasingly difficult for patients to be transplanted when placed on status 2.

Furthermore, LVADs as rescue therapy have proven to be a feasible option for decompensated advanced heart failure patients in intensive care units. The profile of these patients may include pulmonary hypertension or cardiogenic shock with high inotropic or temporary circulatory support requirement, for which a donor heart may be contraindicated or not immediately available – in these patients, the use of LVADs may be life-saving [24]. In contrast to the first-generation pulsatile flow devices, patients who are bridged with the newer generation continuous flow devices are not at major risk of mortality after heart transplant [21].

The use of higher risk donor profile

In attempts to expand the donor heart pool, higher volume centers with more risk tolerance have continued to push the envelope by considering organs that are traditionally deemed suboptimal or high risk. Trends from the International Society for Heart and Lung Transplantation

Table 1. United Network for Organ Sharing (UNOS) status codes

Status 1A	Candidates are admitted to the hospital and have at least one of the following devices or therapies in place:
	1. Mechanical circulatory support for acute hemodynamic decompensation (i.e. ventricular assist device [=<30 days duration], total artificial heart, intra-aortic balloon pump, extracorporeal membrane oxygenator).
	2. Mechanical circulatory support >=30 days with device-related complications (admission to the hospital is not required).
	3. Mechanical ventilation.
	4. Infusion of single high-dose inotrope (i.e. dobutamine >= 7.5 mcg/kg/min, milrinone >= 0.5 mcg/kg/min, dopamine 7.5 mcg/kg/min, or epinephrine 0.02 mcg/kg/min) or multiple inotropes, plus continuous hemodynamic monitoring (valid for 7 days).
	5. Patients who do not meet criteria specified above may be listed as 1A if admitted with a life expectancy <7 days (valid for 7 days and requires recertification every 7 days for review by UNOS Regional Review Board).
Status 1B	Candidates listed as status 1B have at least one of the following devices or therapies in place:
	1. Ventricular assist device implanted >30 days duration.
	2. Continuous inotrope infusion.
Status 2	Candidates who do not meet the criteria for status 1A or 1B are listed as status 2.
Status 7	Candidates who are considered temporarily unsuitable to receive a transplant and are inactive on the waiting list.

(ISHLT) registry have shown that there has been an increase in the average age of the donor hearts being used for cardiac transplantation [25]. Centers have also reported the successful use of organs with pre-existing coronary artery disease [26,27] and longer ischemic times [28].

Extended criteria and higher risk recipients
Despite the undisputed benefits of its technology, LVAD patients are subject to significant morbidity and mortality related to their devices. Complications may stem from the need for therapeutic anticoagulation, the introduction of a foreign body, and the physiological effects of continuous flow rather than pulsatile arterial blood. These complications include significant bleeding (including gastrointestinal bleeding and hemorrhagic stroke from arterio-venous malformations or anticoagulation), infection, device-related thrombosis and ischemic strokes, and lead to rehospitalizations, morbidity and mortality [29]. In carefully selected patients within limited transplant centers, consideration has been given to transplant patients with extended criteria [30–32] as opposed to LVAD as destination therapy, with the thought that heart transplantation may still provide a superior quality of life compared to LVADs [33]. This reasoning is not without controversy and is balanced by the fact that transplant centers are closely scrutinized through their quality outcomes and are subject to inquiry and regulatory penalties in the event of consistently poor outcomes.

With improvement in antiviral therapy and outcomes of HIV positive patients, a limited number of centers have also considered cardiac transplantation of HIV positive patients [34]. The increasing risk exposure of a participating transplant program with an internal extended criteria list needs to be balanced against its institutional outcomes data.

Summary
Cardiac transplantation remains the cornerstone in the treatment of advanced heart failure, particularly given the major strides in the understanding and treatment of allograft rejection over the last 5 decades. The major limiting factor in offering this treatment modality universally remains donor availability. Breakthroughs in technology that can potentially expand the donor pool will be important as the field continues to progress into the future.

Abbreviations
CNI, calcineurin inhibitor; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; IMAGE, Invasive Monitoring Attenuation through Gene Expression; ISHLT, International Society for Heart and Lung Transplantation; LVAD, left ventricular assist device; OCS, Organ Care Systems; PROCEED-II, Prospective Multi-Center Safety and Effectiveness Evaluation of the Organ Care System Device for Cardiac Use II; UNOS, United Network for Organ Sharing.

Disclosures
The authors declare that they have no disclosures.

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