Review Article

Adult heart transplant: indications and outcomes

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Abstract: Cardiac transplantation is the treatment of choice for many patients with end-stage heart failure (HF) who remain symptomatic despite optimal medical therapy. For carefully selected patients, heart transplantation offers markedly improved survival and quality of life. Risk stratification of the large group of patients with end-stage HF is essential for identifying patients who are most likely to benefit, particularly as the number of suitable donors is insufficient to meet demand. The indications for heart transplant and review components of the pre-transplant evaluation, including the role for exercise testing and risk scores such as the Heart Failure Survival Score (HFSS) and Seattle Heart Failure Model (SHFM) are summarized. Common contraindications are also discussed. Outcomes, including survival and common complications such as coronary allograft vasculopathy are reviewed.

Keywords: Heart transplant; indications; outcomes

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Introduction

Congestive heart failure (CHF) affects 23 million people worldwide including 7.5 million in North America. The prevalence of HF in the US population age 20 and older is 2.6% (1). Half of these patients have systolic dysfunction. Cardiac transplantation is the treatment of choice for many patients with end-stage HF who remain symptomatic despite optimal medical therapy (2). The annual mortality rate while on the waiting list in 2001 was 17%, which has declined continually over the last decade to 13.7% in 2009 (3), likely from improved medical therapy for end-stage CHF and increased use of implantable cardioverter-defibrillator and cardiac resynchronization therapy (3,4). Long-term outcomes after transplantation have improved with the advances made in transplant candidate selection, surgical techniques, immunosuppressive modalities, and postoperative care (5,6). The International Society for Heart and Lung Transplantation (ISHLT) registry has reported 89,000 heart transplants worldwide since 1983; there is broad agreement that underreporting is present and the actual number is higher (7). The total number of cardiac transplant likely exceeds 5,000 worldwide with current median survival rate as approximately 50% at 12 years (7). Nevertheless, there are far more eligible candidates than suitable donor organs. Risk stratification of the large group of patients with end-stage HF is essential for identifying patients who are most likely to benefit (8).

Patients with advanced HF are classified into two systems based on the severity; New York Heart Association Class which classifies patients by their functional status, from I (no limitation in activities) to IV (symptoms at rest). NYHA class III (symptoms with minimal exertion) and NYHA class II mild shortness of breath limiting ordinary activity (9). The other system was generated by joint American College of Cardiology and American Heart Association (ACC/AHA) classification uses four stages, from A (high risk of developing HF, i.e., family history of heart disease, hypertension, or diabetes) to D (advanced heart disease despite treatment) (9-11). Patients in stage D tend to require recurrent hospitalization despite cardiac resynchronization therapy and drug therapy, and they cannot be safely discharged without specialized interventions (12). The options for these patients are limited: either end-of-life care or extraordinary measures such as heart transplantation, long-term treatment with inotropic drugs, permanent mechanical

circulatory support, or experimental therapies (9). The estimated number of people in ACC/AHA stage D or NYHA class IV is 15,600 to 156,000 (7). Heart transplant in patients with inadequate response to medical therapy has been shown to extend survival and improve quality of life.

Who is considered for heart transplant?

In general, patients with advanced HF should be considered for heart transplantation if optimal medical therapy as recommended by the ACC/AHA guidelines and cardiac resynchronization therapy have failed to improve symptoms or halt progression of the underlying pathology (9,12-14). Furthermore, any reversible or surgically amenable cardiac conditions should be addressed before transplantation is considered. The latter is important to guarantee the candidacy for heart transplant and reserve organs for the more needed patients. Patients who are in advanced NYHA class IV need evaluation by advanced HF teams for optimal management of multi-organ failure (9,15). Patients with severe HF have a 1 to 2 year mortality rate approaching 50%, despite advanced medical treatment (7,16). The primary indications for heart transplantation for adult patients have been nonischemic cardiomyopathy (53%) and ischemic cardiomyopathy (38%). Other indications include: valvular heart disease (3%), retransplantation (3%) and others (<1%) (7,8,17).

Indications for heart transplantation

The ACC/AHA guidelines include the following indications for cardiac transplantation (11):

- Refractory cardiogenic shock requiring intra-aortic balloon pump counterpulsation or left ventricular assist device (LVAD);
- Cardiogenic shock requiring continuous intravenous inotropic therapy (i.e., dobutamine, milrinone, etc.);
- Peak VO_2 (VO_{2max}) less than 10 mL/kg per min;
- NYHA class of III or IV despite maximized medical and resynchronization therapy;
- Recurrent life-threatening left ventricular arrhythmias despite an implantable cardiac defibrillator, antiarrhythmic therapy, or catheter-based ablation;
- End-stage congenital HF with no evidence of pulmonary hypertension;
- Refractory angina without potential medical or surgical therapeutic options.

Similarly, the European Society of Cardiology describes a series of features that must be met before consideration for heart transplant which are more specific and include, functional, structural and symptoms parameters (18);

- Severe symptoms, with dyspnea at rest or with minimal exertion (NYHA class III or IV);
- Episodes of fluid retention (pulmonary or systemic congestion, peripheral edema) or of reduced cardiac output at rest (peripheral hypoperfusion);
- Objective evidence of severe cardiac dysfunction (at least one of the following): left ventricular ejection fraction less than 30%, pseudonormal or restrictive mitral inflow pattern on Doppler echocardiography, high left and/or right ventricular filling pressure severely impaired functional capacity demonstrated by one of the following: inability to exercise, 6-minute walk test distance less than 300 m (or less in women or patients who are age 75 and older), or peak oxygen intake less than 12 to 14 mL/kg/min;
- One or more hospitalizations for HF in the past 6 months.

Pre-transplantation evaluation

Many of the criteria defining eligibility for heart transplant are somewhat subjective, and focused primarily on resting hemodynamic data and NYHA classification. However, a substantial percentage of patients with severe resting hemodynamic abnormalities may survive for extended periods. Furthermore, NYHA classification as a measure of functional capacity is a subjective and frequently inaccurate index, which can vary from day to day depending on evanescent factors. Tools to improve risk stratification of HF patients are critical to ensure that only patients with a high probability of benefit are subjected to the risks of heart transplant. In patients with HF, several methods are typically employed to objectively estimate adverse prognosis with medical therapy alone.

Exercise capacity as assessed by peak VO_2 (VO_{2max})

Exercise capacity as assessed by VO_{2max} is a dynamic objective variable that assesses cardiac reserve and peripheral adaptations to a reduced cardiac output much more accurately than NYHA classification. It is generally considered the gold standard for establishing a severity of functional cardiac impairment that merits active consideration for transplant. Patients with preserved exercise capacity (peak exercise VO_2 of more than 14 mL/min/kg) despite severe resting

hemodynamic impairment, have survival and functional capacity equal to those afforded by cardiac transplantation (19,20). Moreover, patients with compensated CHF and a peak oxygen consumption of less than 14 mL/kg/min or <50% predicted are considered sufficiently impaired for transplantation (9,11,21). This approach suggests that cardiac transplantation can be safely deferred in ambulatory patients with severe left ventricular dysfunction and a peak oxygen consumption of greater than 14 mL/kg/min. Beta blocker therapy has improved survival rates in patients with systolic HF including patients with very low VO_{2max} to as low as 10 mL/kg per min. The prognostic power of VO_{2max} was initially validated prior to the widespread use of beta blockers, but several studies have demonstrated the continued usefulness of VO_2 in the modern drug era with beta blocker use (5,21). With the current evidence-based HF therapy including beta-blockers, spironolactone, angiotensin converting enzyme inhibitors and devices (i.e., implantable cardioverter-defibrillator and cardiac resynchronization therapy), a VO_{2max} ≤10 mL/kg/min rather than the traditional cutoff value ≤14 mL/min/kg may be more useful for risk stratification in the device era (20). More recent work has suggested that ventilatory efficiency (VE/VCO_2) may be a more powerful prognostic factor than VO_{2max} (22,23). Ventilatory efficiency also appears to be more effective in risk stratification for patients with inadequate peak respiratory exchange ratios (RERs), which are used to confirm that anaerobic threshold has been achieved (24). Finally, ventilatory efficiency has been shown to maintain prognostic value regardless of body mass index, another potential confounding factor that can limit interpretation of VO_{2max} (25).

Cardiopulmonary exercise testing is a relatively specialized test, and is not routinely available outside of transplant centers. It would also be expensive and impractical to screen all HF patients with full exercise testing. Exercise testing also provides a single perspective of performance and prognosis. To meet this need, several risk scores have been developed to help clinicians identify HF patients whose severity of illness is sufficient to merit consideration for transplant. The two best known and most widely used for the advanced HF population are the Heart Failure Survival Score (HFSS) and the Seattle Heart Failure Model (SHFM).

Heart Failure Survival Score (HFSS)

This score was derived from a multivariable analysis of 268 ambulatory patients referred for consideration of cardiac transplantation from 1986 to 1991 and validated in 199 similar patients from 1993 to 1995 (26). The predictors of survival in the HFSS include:

- Presence or absence of coronary artery disease;
- Resting heart rate;
- Left ventricular ejection fraction;
- Mean arterial blood pressure;
- Presence or absence of an intraventricular conduction delay on ECG;
- Serum sodium;
- VO_{2max}.

Scores are categorized into low-risk (score ≥8.1), medium-risk (score ≥7.2 and <8.1), and high-risk (<7.2). Patients in medium and high-risk groups (1-year survival of 72% and 43%, respectively) are most likely to die or require urgent transplant in the following year; they should be considered for cardiac transplantation if no contraindications are present. Transplantation can be safely deferred in patients in the low-risk group (1-year survival 93%). HFSS has been reported to outperform peak oxygen consumption for heart transplant selection in the current era of ventricular assist device therapy (20).

The Seattle Heart Failure Model (SHFM)

The SHFM gives an estimate of prognosis for ambulatory patients with advanced HF (27). This model is based on age, sex, NYHA class, weight, ejection fraction, blood pressure, medications, a few laboratory values, and other clinical information. Furthermore, the model has incorporated the impact of newer HF therapies on survival, including ICDs and CRT. The model provides an accurate estimate of 1-, 2-, and 3-year survival with the use of clinical, pharmacologic, device, and laboratory characteristics. It is available on the internet (http://depts.washington.edu/shfm, accessed on 24 March 2014), and applications for handheld electronic devices. It also allows evaluation of the estimated effect of interventions on an individual patient's prognosis. The model also was able to provide information about the likely mode of death among ambulatory HF patients (28). SHFM was developed in an ambulatory HF population and there has been concern that it may overestimate survival in the advanced HF population (29,30). Nevertheless, it remains a useful method for estimating survival in HF patients.

Finally, the Index for Mortality Prediction After Cardiac Transplantation (IMPACT) score was recently noted to predict short- and long-term mortality after heart transplant (31).

Efforts to combine evaluation of risk of mortality from HF with prediction of outcome after transplant may offer opportunities to further improve the net outcomes after transplant through the development of a "cardiac allocation score" (32).

Heart transplant contraindications

Once the question of whether or not an individual is "sick enough" to merit consideration for transplant has been addressed, the next question that must be asked is whether or not the patient is "too sick" for transplant. Improving cardiac status only to die of hepatic failure would not be considered a judicious use of a truly scarce resource. The following circumstances are typically felt to be absolute contraindications to heart transplantation (9,11,33):

(I) Advanced irreversible renal failure with Cr >2 or creatinine clearance <30-50 mL/min without plans for concurrent renal transplant;
(II) Advanced irreversible liver disease;
(III) Advanced irreversible pulmonary parenchymal disease or (FEV_1 <1 L/min);
(IV) Advanced irreversible pulmonary artery hypertension (pulmonary artery systolic pressure >60 mmHg, pulmonary vascular resistance >4-5 wood units despite vasodilators) due to risk of acute right ventricular failure soon after transplant from insufficient accommodation of the donor heart to high pulmonary vascular resistance pressures;
(V) History of solid organ or hematologic malignancy within the last 5 years due to probability of recurrence.

The following are generally considered relative contraindications for heart transplant due to the reversibility of the disease or due to lack of direct impact on the transplanted organ (33).

(I) Severe peripheral vascular disease;
(II) Severe cerebrovascular disease;
(III) Severe osteoporosis;
(IV) Severe obesity (BMI >35 kg/m^2) or cachexia;
(V) Acute pulmonary embolism;
(VI) Active infection (excluding LVAD-related infections);
(VII) Advanced age (>70 years old);
(VIII) Psychological instability (e.g., PTSD);
(IX) Active or recent (within 6 months) substance abuse (alcohol, cocaine, opioids, tobacco products, etc.);
(X) Diabetes mellitus with end organ damage;
(XI) Lack of social support or sufficient resources to permit ongoing access to immunosuppressive medication and frequent medical follow-up.

Allosensitization to human leukocyte antigen (HLA) antibodies can pose a particular problem, and may also preclude transplant eligibility. Further details on this topic are beyond the scope of this work, but have been recently reviewed elsewhere (34,35).

The United Network of Organ Sharing (UNOS) and heart transplant listing

Based on their medical condition, UNOS assigns all transplant candidates a status (3,36). The highest status, 1A, goes to patients who are seriously ill, in the hospital, on high doses of inotropic drugs (specific dosages are defined) and mechanical circulatory support such as an LVAD, and expected to live less than 1 month without a transplant. Status 1B patients are stable on lower-dose inotropic therapy or on mechanical support, and can be in the hospital or at home. Status 2 patients are stable and ambulatory and are not on inotropic drugs. Priority is given to patient with status 1A and those who have been waiting the longest. The national median waiting time by UNOS status at listing from 2003 to 2004 data is as follows: 49 days for status 1A, 77 days for status 1B, and 308 for status 2 patients. However, this heavily influenced by several factors. For example, patients with blood type O wait significantly longer than patients with other blood types such as blood type AB. Blood type O patients who are on status 2 can wait years for a suitable donor organ, and for all practical purposes, are listed in name only without realistic chance of transplant without change in priority as a result of deterioration in medical status. Due to the scarcity of donor organs and growing transplant waiting lists, it is crucial that cardiac transplant program adequately screen and properly select potential transplant recipients. Effective use of this limited resource is essential; to avoid "wasting" organs that become available for suboptimal recipients. The IMPACT score (31) was recently developed and validated from UNOS data to help estimate survival after cardiac transplant.

Management of patients on the waiting list

There has been significant development and ongoing research in to improve the management of HF patients

who are considered for transplant. These areas are focused around the continued improvement in outcomes with LVAD technologies for the management of patients on the transplant waiting list, or as an alternative to transplantation in patients who are not candidates for transplantation.

Mechanical circulatory support

Mechanical circulatory support is indicated for patients who are listed for transplant to keep them alive and functioning as well as possible while they are waiting (bridge to transplant). For others it is destination therapy since these patients are not candidates for a transplant, but a device may improve and prolong the rest of their life (37-39). However, there are approximately twofold more patients with advanced HF waiting for heart transplantation than available donors. Despite parallel advances in ventricular assist device therapy, approximately 8% of these patients die awaiting a suitable allograft (3,39). The role of mechanical circulatory support in patients eligible for transplant has increased tremendously over the last two decades. Data from the International Society of Heart and Lung Transplantation notes that 28% of transplant recipients between 2006 and 2012 had a ventricular assist device, a marked increase from 12% in 1992-2000 (40). Survival on the transplant waiting list was also recently demonstrated to be superior to survival on inotropes or intra-aortic balloon pump (41), suggesting that clinicians are increasingly using LVAD as a therapy that maximizes chance of survival for many candidates. Markedly improved survival following LVAD over the past decade has also increased enthusiasm for this option as a bridge to transplant. Finally, current UNOS organ allocation policy for candidates supported with LVAD may also be playing a role in the increased utilization (42).

Despite the improvements in outcomes after LVAD, the question of whether this confers increased risk after transplant has been critical. For example, the additional sternotomy alone might be expected to have an adverse impact on post-transplant outcomes. Fortunately, excellent short- and long-term post-cardiac transplant survival following LVAD in the current era has been reported (40,43), and duration of LVAD support does not appear to confer additional risk (44). UNOS data has also demonstrated similar post-transplant survival after LVAD, despite noting increased use of older donors in this population (45). Donneyong *et al.* also reported the results of a retrospective, propensity-matched analysis of UNOS data, in which use of HeartMate II prior to transplant was not associated with a statistically significant difference in 30 day or 1 year post-transplant mortality (46). Of note, an association was found between HeartMate II use prior to transplant and 64% lower risk of mortality among patients who survived beyond the first year after transplantation. However, another analysis of UNOS data found that adjusted 1-year post-transplantation mortality was higher among patients with LVADs compared to patients with inotropes (41), suggesting that the true impact of need for LVAD prior to transplant on outcome may require additional analysis.

Inotropic therapy

Inotropic drugs, which include intravenous dobutamine and milrinone, are used to help maintain end-organ function (9,47,48). This intervention can be used as a bridge until a patient can obtain a heart transplant or LVAD. Inotropic therapy is typically used for palliation and has been shown to increase the risk of mortality, which is about 50% at 6 months and nearly 100% at 1 year (9,47). A patient who requires inotrope infusion should be considered for hospice if they are not a candidate for a transplant or an assist device.

Heart transplant outcomes

Detailed information on heart transplant outcomes is published in an annual report by the International Society of Heart and Lung Transplant (40) and the reader is referred to this outstanding resource for additional information beyond the brief summary provided in this work.

Survival after heart transplantation is now excellent (33). The 1-year survival rate is about 90%, the 5-year rate is about 70%, but only about 20% survive 20 years or longer (12,16,49). Quality of life after heart transplantation is also generally excellent (15) and patients are frequently able to return to work, regardless of their profession (3,5,50). The leading cause of death after heart transplantation is malignancy, followed by coronary artery vasculopathy (CAV), then by graft failure. Some patients develop left ventricular dysfunction and HF of unknown cause. Others develop antibody-mediated rejection; in recent years this has been more promptly recognized, but treatment remains a challenge (1,6,34). Acute rejection, which used to be one of the main causes of death, now has a low incidence because of modern drug therapies.

Complications

The major causes of late morbidity and mortality are infections, chronic kidney disease, cardiac allograft vasculopathy (CAV), and malignancy (7). Adverse effects of immunosuppressive drugs continue to be problematic as well. These include infection, malignancy, osteoporosis, chronic kidney toxicity, hypertension, and neuropathy.

Coronary artery vasculopathy (CAV)

CAV was the largest problem when heart transplantation began and continues to be a major concern and focus of research (7,8). The precise molecular mechanism for the development of vasculopathy is not known. Both immune and nonimmune mechanisms have been implicated in the progression of vasculopathy. Coronary vasculopathy develops in 30% to 40% of heart transplant recipients within 5 years, and much over the years has not reduced the incidence. However, probably fewer than 5% of these patients die or even need bypass surgery or stenting, and the problem is managed the same as native atherosclerosis (17,51).

Infectious complications

Infection is common in organ transplant recipients. The types of infections expected in cardiac transplant recipients vary, depending on the time from transplantation. This is because the intensity of immunosuppression administered varies directly with the propensity for rejection, and the propensity to reject decreases over time. Bacteria and viruses account for more than 80% of infections after transplantation. The most common bacterial infections early after transplantation are nosocomial, caused by infected intravascular catheters or lines, or gram-negative pneumonias.

Renal dysfunction

Immunosuppressive therapy with calcineurin inhibitors has improved both graft function and survival in heart transplantation. However, calcineurin inhibitor-induced-induced nephrotoxicity still remains a serious clinical challenge. Chronic calcineurin inhibitor nephrotoxicity is characterized by a decrease in glomerular filtration rate (GFR), afferent arteriolopathy, and striped tubulointerstitial fibrosis. The greatest decline in GFR with cyclosporine occurs in the first 3 to 6 months (7). About 10% of heart transplant recipients develop stage four-kidney disease (with a GFR <30 mL/min) and need kidney transplantation or renal replacement therapy because of the use of calcineurin inhibitors for immunosuppression (52). Close monitoring of tacrolimus and cyclosporine blood levels is critically important to limit progressive decline in renal function, because there is no known treatment for preventing or reversing nephrotoxicity. At the time of transplantation, initiation of tacrolimus or cyclosporine is delayed postoperatively in patients at high risk for nephrotoxicity, and induction therapy (such as antithymocyte globulin or an IL-2 receptor antagonist such as basiliximab) may be used to permit delay or minimization of nephrotoxic calcineurin inhibitors.

Malignancy

Following heart transplantation, malignancy is identified in 3% to 18% of the recipients, with an estimated risk of 1% to 2% per year. It ranks second to coronary vasculopathy as a major cause of mortality, accounting for 10% to 23% of all deaths following heart transplantation (7,8). Cutaneous malignancy is the most common type, seen in up to 17% of patients, with a predominance of squamous cell carcinoma. Post-transplantation lymphoproliferative disorder (PTLD) is a frequently fatal complication, occurring in 1.7% to 6% of cardiac transplant recipients. The peak occurrence of PTLD is 3 to 4 months after transplantation. A strong association of PTLD with Epstein-Barr virus has been observed in several series. The use of OKT3, which may favorably affect the rejection rate, has been shown to increase the risk of lymphoma more than eightfold. This association remains contentious and has been challenged. OKT3 is rarely used in current clinical practice.

Conclusions

Heart transplantation is continuing to evolve with exciting new advancements in the preoperative, perioperative, and postoperative management of heart transplantation patients. Improvements in immunology and organ preservation are likely to further improve care. For carefully selected patients, heart transplantation offers markedly improved survival and quality of life. Novel immunosuppressive regimens and better understanding of immunobiology are keys to combat the ongoing issues of cardiac allograft rejection. In the years to come, limitations in donor organ availability and preservation,

along with immunosuppression, will be important areas for improvement. Newer, more technologically advanced mechanical assist devices, stem cell transplantation, and improved medical therapy are research areas that are growing exponentially and should continue to be explored as alternatives to transplantation in patients with HF. The future holds promise for many patients suffering from severe HF.

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