Selection of Cardiac Transplantation Candidates in 2010

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Heart failure is a progressive disease that now affects >5 million patients in the United States. Recent estimates suggest that between 5% and 10% of all patients with heart failure (HF) have advanced, or stage D, disease, which is associated with a very high mortality and very poor quality of life.[1] In the most advanced phase of HF, heart transplantation (HT) has been the only means of improving the quality of life and survival in these patients. With the advances in immunosuppression therapy, 1-year survival after cardiac transplantation approaches 90%, with 50% of patients surviving >11 years.[2] With the improving results of cardiac transplantation, more patients are referred for transplantation evaluation. Moreover, patients with comorbidities who in the past would not be suitable transplantation candidates are now often considered for transplantation.[3]

Unfortunately, this life-saving therapy is available to only a fraction of those who need it because of the constant shortage of available donors. Over the last 2 decades, only 2200 patients underwent HT annually in the United States. This has resulted in increasing number of patients awaiting transplants with longer waiting times. Efforts to modify the US heart allocation scheme to prioritize organ allocation to those candidates who are the least likely to survive was first introduced by the US United Network of Organ Sharing (UNOS) in 1989 as a high-priority UNOS status 1 listing. In 1999, this evolved into a 2-tiered system with UNOS status 1A and 1B.[4] These changes resulted in a shorter waiting time and a significant improvement in survival on the HT waiting lists.[5] Median time to cardiac transplantation has declined from 359 days in 1999 to 113 days in 2007. With the decline in waiting time, the absolute mortality rate for status 1A has declined from 21.7% in 1999 to 8.6% in 2007. Similar but less dramatic declines have been observed in status 1B patients from 10.3% to 6.2% and in status 2 from 6.6% to 3.4%.[5] These declines also coincided with a major shift in the severity of illness of the average candidate listed for HT. The number of ambulatory patients listed as status 2 for HT has decreased from 5000 to only 1000 de novo listings from the late 1990s to early 2000s.[5] The majority of listings in 2009 were of the sickest HF patients who either were inotrope dependent or required circulatory support such as intraaortic balloon pumps or surgical implantation of mechanical circulatory support (MCS) device as bridge to transplantation (BTT).[6] However, high-urgency HT candidates remained at a substantial risk of death. The rising proportion of extremely ill patients listed for HT renders the evaluation for MCS as BTT an important part of HT evaluation.

According to the UNOS registry data, nearly 9000 HT candidates underwent MCS device implantation as BTT since the new allocation system was introduced in 1999.[5] This constitutes more than one third of all listed adult HT candidates in the United States during this time period and 75% of those initially listed as UNOS status 1. The widespread application of MCS devices as BTT coincided with major advances in this field. Introduction of new, more durable, safer pumps[7,8] with simplified surgeries has resulted in a significant improvement in device outcomes.[9] Here, we review important developments pertaining to the optimal timing for cardiac replacement therapy with HT and the use of MCS devices as BTT, as well as the new challenges that have developed in the recent years in candidate selection for HT.

Selection Criteria for Cardiac Transplantation

When a patient with advanced HF is referred to a transplant center, the initial evaluation requires an assessment of the severity of HF, the identification of any potentially reversible factors, and an assessment of the adequacy of current medical therapy. In a patient with ischemic or valvular heart disease, this involves assessment of myocardial viability and/or severity of valvular disease to determine whether there are percutaneous or surgical options. Arrhythmias should be addressed and treated. In patients with atrial fibrillation, rate control, and/or restoration of sinus rhythm should be addressed. Similarly, treatment of ventricular arrhythmias with device implantation with or without antiarrhythmic therapy or ablation should be considered. In patients with prolonged QRS, use of biventricular pacing should be considered. Toxic agents such as persistent alcohol intake, illicit drug use, or salt-retaining drugs such as nonsteroidal agents need to be discontinued. Medical therapy should be optimized with uptitration of vasodilators, diuretics, and use of biventricular pacing as indicated. If possible, a few months of maximal medical therapy is administered to assess therapeutic response. If no reversible causes are identified and therapy is thought to be at an optimal level with the presence of class IIIB/IV symptoms, then the transplant evaluation process begins. However, if on referral the patient is in cardiogenic shock or on parenteral inotropic agents and cannot be tapered

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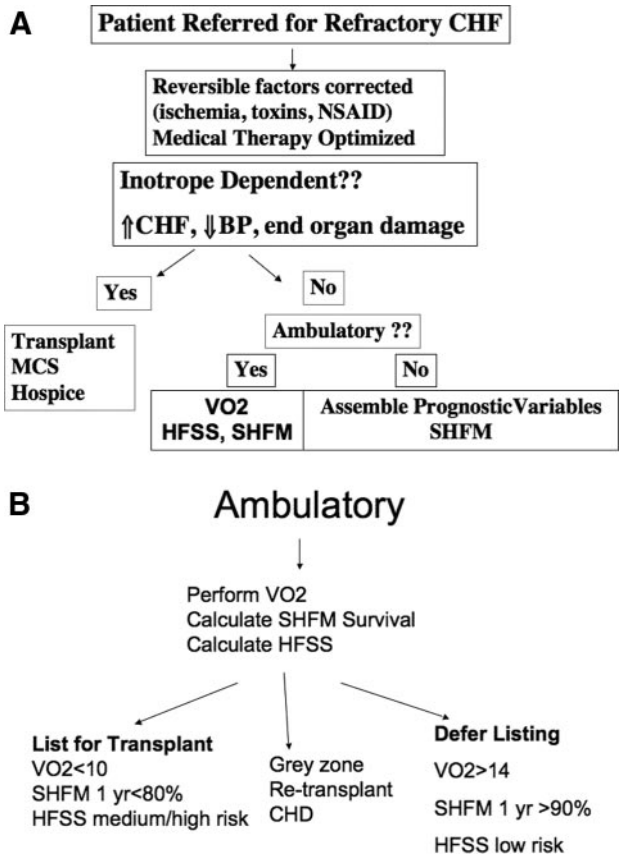

Figure 1. A and B, Algorithm for selecting patients with advanced HF for HT. CHF indicates congestive HF; NSAID, nonsteroidal antiinflammatory drug; BP, blood pressure; SHFM, Seattle Heart Failure Model; and CHD, congestive heart disease.

because of hypotension, end-organ dysfunction, or symptoms, then the options for this patient are limited to cardiac transplantation, mechanical device support, or palliative care (Figure 1A and B). Evaluation of patients who are not inotrope dependent requires the collection of key prognostic factors to estimate patient prognosis and need for transplant listing. This article focuses on the severity of HF as the most common indication for HT because <5% of cardiac transplants are performed for other indications such as intractable arrhythmia and severe angina (Table 1).

Screening for transplantation involves an extensive evaluation to exclude significant comorbidities that can increase either the short-term perioperative risk or long-term survival. Contraindications to transplantation continue to evolve, with centers expanding criteria for acceptance. The traditional contraindications to transplantation are listed in Table 2. In the present era, the criteria for candidacy have continually expanded, and areas that are evolving are discussed later in this review. Table 3 shows how these exclusion factors have evolved over the past 10 years.

Table 1. Indications for HT

Cardiogenic shock requiring either continuous intravenous inotropic support or MCS with an intraaortic balloon pump counterpulsation device or MCS
Persistent NYHA class IV congestive HF symptoms refractory to maximal medical therapy (LVEF <20%; peak $\dot{V}o_2$ <12 mL · kg^{-1} · min^{-1})
Intractable or severe anginal symptoms in patients with coronary artery disease not amenable to percutaneous or surgical revascularization
Intractable life-threatening arrhythmias unresponsive to medical therapy, catheter ablation, and/or implantation of intracardiac defibrillator

NYHA indicates New York Heart Association.

Table 2. Contraindications to HT

Absolute contraindications
Systemic illness with a life expectancy <2 y despite HT, including
Active or recent solid organ or blood malignancy within 5 y (eg. leukemia, low-grade neoplasms of prostate with persistently elevated prostate-specific antigen)
AIDS with frequent opportunistic infections
Systemic lupus erythematosus, sarcoid, or amyloidosis that has multisystem involvement and is still active
Irreversible renal or hepatic dysfunction in patients considered for only HT
Significant obstructive pulmonary disease (FEV_1 <1 L/min)
Fixed pulmonary hypertension
Pulmonary artery systolic pressure >60 mm Hg
Mean transpulmonary gradient >15 mm Hg
Pulmonary vascular resistance >6 Wood units
Relative contraindications
Age >72 y
Any active infection (with exception of device-related infection in VAD recipients)
Active peptic ulcer disease
Severe diabetes mellitus with end-organ damage (neuropathy, nephropathy, or retinopathy)
Severe peripheral vascular or cerebrovascular disease
Peripheral vascular disease not amenable to surgical or percutaneous therapy
Symptomatic carotid stenosis
Ankle brachial index <0.7
Uncorrected abdominal aortic aneurysm >6 cm
Morbid obesity (body mass index >35 kg/m^2) or cachexia (body mass index <18 kg/m^2)
Creatinine >2.5 mg/dL or creatinine clearance <25 mL/min*
Bilirubin >2.5 mg/dL, serum transaminases >3×, INR >1.5 off warfarin
Severe pulmonary dysfunction with FEV_1 <40% normal
Recent pulmonary infarction within 6 to 8 wk
Difficult-to-control hypertension
Irreversible neurological or neuromuscular disorder
Active mental illness or psychosocial instability
Drug, tobacco, or alcohol abuse within 6 mo
Heparin-induced thrombocytopenia within 100 d

INR indicates international normalized ratio.

*May be suitable for HT if inotropic support and hemodynamic management produce a creatinine <2 mg/dL and creatinine clearance >50 mL/min. Transplantation may also be advisable as combined heart-kidney transplantation.

Interagency Registry for Mechanical Assist Devices Levels of HF Severity

In 2006, the NIH-funded Interagency Registry for Mechanical Assist Devices (INTERMACS)[10] was created. It compiles detailed information on the severity of illness at the time of

Table 3. Change in Listing Characteristics From 1999 to 2009

	1999	2009
Age, y	<65	<72
PVR, Wood units	Fixed >6; trial of IV inotropes	Fixed >6; trial inotropes, sildenafil, mechanical assist device
Diabetes mellitus	Minimal end-organ involvement, insulin use	Moderate end-organ involvement, combined transplants
Malignancy	Remote	Bridge with mechanical assist device if malignancy within 2 y; in some low-grade malignancies, proceed after appropriate treatment
PVD	Severe	No change
Infections	Defer	Proceed in setting of device infection
Senitized patient	Pretreat with immunosuppression	Additional option of rituximab
$\dot{V}o_2$, mL · kg^{-1} · min^{-1}	<14	<12
Priority status, % at transplantation		2007
1A	34	50
1B	36	36
2	26	14

PVR indicates pulmonary vascular resistance.

device placement. The 7 INTERMACS levels proposed to classify the different degrees of clinical severity of advanced HF[11] are listed in Table 4. We use these INTERMACS levels to discuss the benefits of cardiac transplantation at various levels of advanced HF. The observed survival benefit of HT in inotrope-dependent candidates (INTERMACS levels 1 to 3) and those supported with MCS devices, who are listed as high-urgency UNOS status 1A and 1B, and those who are not

Table 4. INTERMACS Levels of Limitation at the Time of Implantation and the Time Frame of Need for Consideration of MCS

INTERMACS Profile Level	Status	Time Frame
1	Critical cardiogenic shock	Hours
2	Progressive decline	Days to week
3	Stable but inotrope dependent	Weeks
4	Recurrent advanced HF	Weeks to few months if baseline restored
5	Exertion intolerant	Weeks to months
6	Exertion limited	Months, if nutrition and activity maintained
7	Advanced NYHA class III	

NYHA indicates New York Heart Association. Adapted with permission from Stevenson et al.[11] Copyright © 2009, Elsevier.

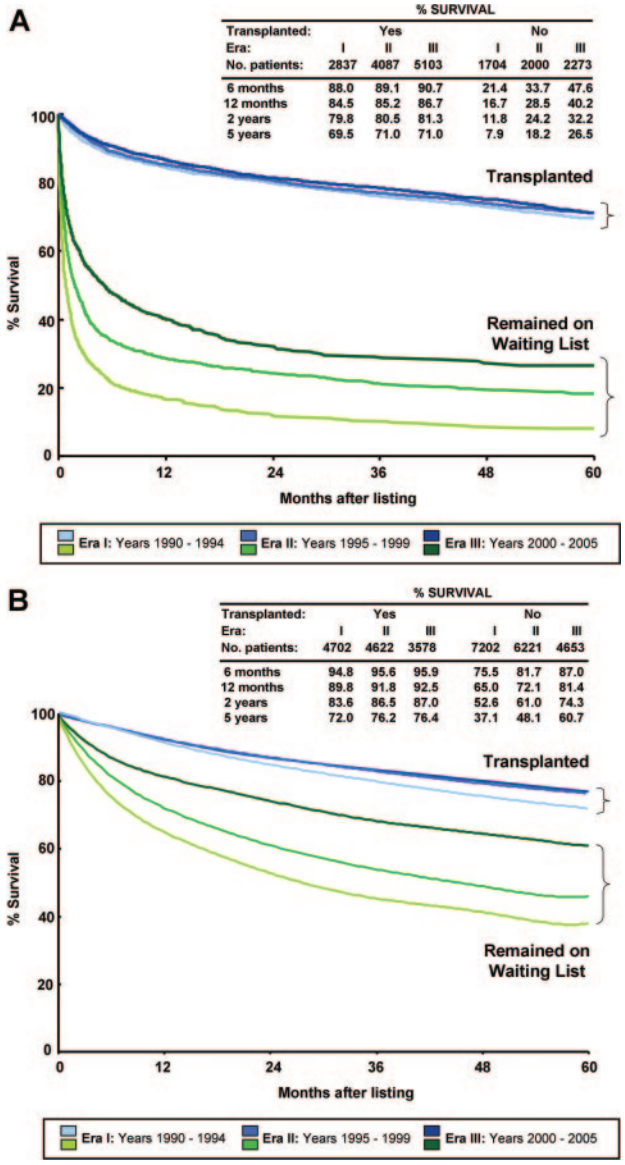

Figure 2. The actuarial survival of UNOS status 1 (A) and status 2 candidates (B) for HT who did and did not undergo HT depicted by the eras of listing, US Scientific Registry for Transplant Recipients, 1990 to 2005 (n=48 982). Survival is calculated from the day of listing for HT until death on the waiting list and is censored at time of transplantation, removal from the waiting list as a result of worsening or improvement of condition, or the day of last observation on June 1, 2006. Adapted with permission from Lietz and Miller.[6] Copyright © 2007, Elsevier.

inotrope dependent (INTERMACS levels 4 to 7) is illustrated in Figure 2A and 2B, respectively.

Cardiogenic Shock and Patients Declining on Inotropes (INTERMACS Level 1 and 2)

The most severely ill patients considered for HT are those presenting with cardiogenic shock (INTERMACS level 1) and worsening of symptoms in inotrope-dependent patients (INTERMACS level 2). Given the acuity of these patients, the transplant evaluation needs to be completed expeditiously, and frequently, waiting until a donor heart becomes available is not an option. Patients in INTERMACS level 1

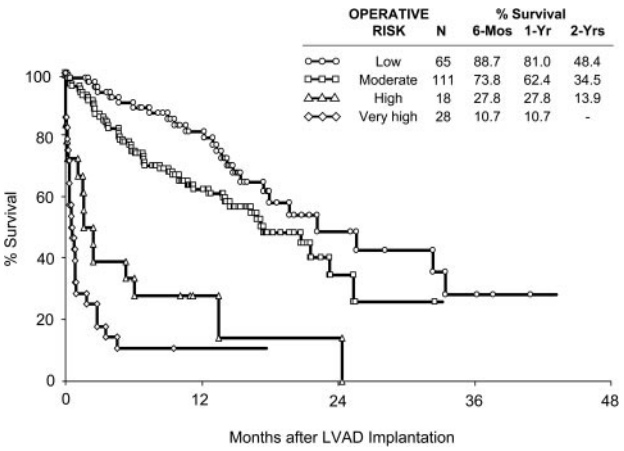

Figure 3. Survival after LVAD implantation as destination therapy (DT) by the candidate operative risk. Adapted with permission from Lietz K et al.[16] Copyright © 2007, American Heart Association, Inc.

who have not previously been evaluated and listed for HT present the greatest challenge to HT cardiologists. Most often, this situation is encountered in patients with postcardiotomy shock, acute myocardial infarction, or myocarditis. A number of logistical and ethical problems, including altered mental state or major end-organ failure, may severely jeopardize or render device implant futile. Brief assessment of HT candidacy and medical and social history and the final decision to proceed with rescue implantation of MCS must occur rapidly. Occasionally, short-term support with percutaneous or implantable devices as bridge to decision can be used in these uncertain cases[12] to allow time for recovery and better assessment of device and HT candidacy. This is particularly true in patients with fulminant myocarditis. Many case reports outline the use of percutaneous or long-term mechanical devices to bridge these patients to recovery after failing high-dose inotropic therapy and intraaortic balloon pumps. Device support ranges from several days to weeks.[13]

Although the operative risk of device implantation in these very ill patients is higher than in more stable HF patients,[14,15] these patients make up the vast majority of MCS implant recipients. Lietz et al[16] developed a scoring system to grade the futility of left ventricular assist device (LVAD) surgery in 222 patients who underwent placement of a destination LVAD. Patient characteristics that identified high risk included a platelet count $\leq$148 000/μL (7 points), albumin of $\leq$3.3 g/dL (5 points), international normalized ratio $>$1.1 (4 points), mean pulmonary artery pressure $<$25 mm Hg, aspartate aminotransferase $>$45 U/mL (3 points), hematocrit $<$34% (2 points), blood urea nitrogen $>$51 U/dL (2 points), inability to tolerate intravenous inotropes (2 points), and use of vasodilator therapy (nitroprusside, nitroglycerin, nesiritide, or hydralazine; 4 points). Patients with a score $>$16 had a 1-year survival of $<$28% and were called futile implants, as shown in Figure 3. How well this score can be extrapolated to the BTT population, which now is supported predominantly by newer-generation nonpulsatile devices, is under active investigation.

Given the increased perioperative mortality in the sickest patients, the practice of delaying placement of MCS in patients to spare them additional sternotomies has been challenged in recent years. Although new clinical algorithms have been proposed to guide the earlier timing of MCS in high-urgency HT candidates,[14] there are no standardized guidelines for elective device placement. With recent reports suggesting that MCS placement may be associated with decreased survival after cardiac transplantation, early device placement continues to generate much debate, and there is considerable variation in the threshold for MCS placement among transplant centers.[17]

Stable Inotrope-Dependent Patient (INTERMACS Level 3)

HF patients who require long-term infusion of intravenous inotropes to maintain end-organ function are classified as INTERMACS level 3. Several studies have demonstrated extremely low survival in this population. Notable data were derived from the medical arm of the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) study in which 44 of the 61 medically treated patients were inotrope dependent with a 1-year survival of only 23%.[18] Single-center and multicenter trials also demonstrated very high mortality in this group.[19–21] Thus, demonstration of parenteral inotrope dependence is a clear indication of the need to proceed to cardiac transplantation in the absence of contraindications.

It is important to note the differences in the management of stable inotrope-dependent patients in the United States and Europe. In the United States, patients who can be maintained on a single inotropic agent are frequently discharged home as status 1B. In Europe, discharge home on long-term inotropic support is not approved in most countries, and use of the oral calcium sensitizer levosimendan serves as an alternative to outpatient inotrope infusion.[22] Calcium sensitizers have not been approved in the United States for this indication.

MCS therapy has been shown to provide excellent survival benefit at this stage of HF, as demonstrated in the retrospective UNOS analysis of HT recipients,[5] the posthoc analysis of the REMATCH trial,[23] and the HeartMate II Destination therapy trial.[24] Although the criteria for timing MCS implantation in inotrope-dependent HT candidates have not been formally established, device placement should be strongly considered in candidates who reached this stage of HF and have an anticipated long wait time for HT such as those with high levels of anti-HLA antibodies, large body size, or ABO blood type O.

Additional questions that need to be addressed in regard to device placement are technical insertion considerations (ie, the presence of aortic insufficiency, prosthetic heart valves, congenital defects, restrictive diseases, the degree of right ventricular failure, and thus need for biventricular support). Predictors of right ventricular failure with MCS have been an area of active research. Evidence of severe right HF on physical examination and echocardiographic and hemodynamic indexes of right heart dysfunction such as elevated right atrial pressure, low pulmonary artery pressures, or low right ventricular stroke work index have all been used to predict need for biventricular support.[25–27] Investigators at the University of Michigan[28] have developed a right ventricular

Table 5. Factors Determining Placement of MCS as BTT

Severity of CHF
INTERMACS levels I-IV
Seattle Heart Failure Model with 1-y mortality >25%
HF survival score, high-risk group
Feasibility of LVAD placement
Cardiac anatomy (aortic insufficiency, congenital heart disease, restrictive cardiomyopathy, prosthetic valves)
Perioperative risk for LVAD placement
Lietz et al score
Coagulopathic, RA pressures, infection
Need for BiVAD
RVSWI
University of Michigan RVAD Score
Estimated wait-list time for transplant
Blood type
Sensitization
Weight

CHF indicates congestive HF; RA, right atrial; BiVAD, biventricular device support; RVSWI, right ventricular stroke work index; and RVAD, RV assist device.

Table 6. Univariate Predictors of Survival

Demographic: age, cause of HF, gender, race
Functional parameters: New York Heart Association class, peak Vo_2
Physical signs: increased HR, chronic hypotension, reduced body mass index
Ventricular function: LVEF, ventricular volumes, mitral regurgitation
Hemodynamic parameters: increased PCW, decreased CI
Laboratory parameters: serum sodium, elevated serum creatinine, low albumen
Neurohormones: norepinephrine, elevated BNP
ECG parameters: widened QRS, prolonged QTc, abnormal SAECG, T-wave alternans, decreased heart rate variability, past history of cardiac arrhythmias
Comorbidities: diabetes mellitus, obesity, renal insufficiency
Genetic polymorphisms: β1, β2, ACE
Medical therapy: inotrope dependent, inability to tolerate β-blockers or ACE inhibitors

HR indicates heart rate; LVEF, left ventricular ejection fraction; PCW, pulmonary capillary wedge pressure; CI, cardiac index; BNP, brain natriuretic peptide; SAECG, signal-averaged ECG; and ACE, angiotensin-converting enzyme.

risk score, which includes the need for vasopressor medications (4 points), presence of liver function abnormalities (2 points for aspartate aminotransferase >80; 2.5 points for total bilirubin >2), and renal dysfunction (serum creatinine >2.3 mg/dL) as the key elements in identifying patients in need of biventricular support. Patients with a score ≥4 have a 2.8 likelihood ratio of developing significant right HF. Investigators at the University of Pennsylvania[29] developed a risk score based on retrospective review of 266 patients who underwent LVAD insertion from 1998 to 2005. Parameters including hemodynamic measurements (cardiac index <2.2 $L \cdot min^{-1} \cdot m^{-2}$, right ventricular stroke work index <0.25 $mm\,Hg \cdot L^{-1} \cdot m^{-2}$), severe right ventricular dysfunction as defined by the cardiologist caring for the patient, serum creatinine ≥1.9 mg/dL, previous cardiac surgery, and chronic hypotension were markers for the need for biventricular support. However, this scoring system is derived from a retrospective analysis using a variety of devices and relied on the individual cardiologist assessment to determine the severity of right ventricular dysfunction. The University of Michigan analysis was prospective but has not been validated. Further study is needed to determine the best echocardiographic and clinical parameters to predict right HF.

Table 5 outlines a clinical approach to determine the need for bridging MCS therapy. Although mechanical device support provides an excellent method to sustain patients to transplant, there may also be negative consequences. Blood transfusions at the time of device placement, along with acute and chronic bleeding episodes, have resulted in an increase in allosensitization, which then prolongs and complicates donor selection. Additionally, interactions between the bioimplanted material of such devices as the Heartmate XVE and the host result in monocyte and T-cell activation. Unopposed activation of Th2 cytokine producing C4D T cells results in B-cell hyperreactivity and allosensitization. Pretransplantation immunosuppression and/or high-dose intravenous immunoglobulin to decrease antibody formation may be needed to facilitate transplantation.[30]

Other concerns about the use of mechanical support devices include the risk of infection, stroke, and device failure, which may complicate or preclude transplant. Device infection is a complication that is treated by explantation of the device. Frequently, the infection is controlled with antibiotics, and explantation is done at the time of transplantation. Postoperative vasodilatory shock and/or sepsis may occur. In a newly transplanted patient requiring intense immunosuppression, this is a difficult postoperative dilemma that may be one of the underlying reasons why, in the annual International Society of Heart Lung Transplant Registry,[31] device support is a frequent predictor of adverse outcome after transplantation. Additionally, increased postoperative bleeding may be observed at transplantation because of the need for long-term anticoagulation with some devices, increased adhesions from device placement, and development of acquired coagulation abnormalities with the newer axial flow devices.[32]

Patients With Class IV HF Symptoms, Not Inotrope Dependent (INTERMACS 4 to 6)

The patients who do not require advanced measures of hemodynamic support with New York Heart Association class IIIB/IV symptoms (NTERMACS levels 4 to 6) are the most challenging group to define transplant candidacy. These ambulatory patients make up the largest number of referrals. Although many univariate predictors of survival have been identified in ambulatory HF patients (Table 6), application of cardiopulmonary stress testing has been an extremely valuable tool to guide the transplant selection process in ambulatory patients. Metabolic carts equipped with rapidly responding O_2 and CO_2 analyzers are generally available and have become increasingly portable and user friendly. Because Vo_2 equals cardiac output times the arterial-venous oxygen difference, peak $\dot{V}o_2$ provides an indirect noninvasive assessment of cardiac output response to exercise. Cardiopulmo-

nary stress testing was first used in candidate selection in the late 1980s.[33] Patients with a preserved exercise capacity defined as a peak $\dot{V}O_2$ >14 mL · kg^{-1} · min^{-1} had a 1-year survival of 94%, which was significantly better than the survival of patients with reduced exercise capacity (ie, $\dot{V}O_2$ ≤14 mL · kg^{-1} · min^{-1}) and comparable to that of newly transplanted patients. Analysis of the additional ventilatory data collected during cardiopulmonary testing has been performed to refine risk stratification. The ventilatory response to exercise has been demonstrated to yield strong prognostic data.[34] Timing of the anaerobic threshold, measurement of cardiac power now with the advent of noninvasive rebreathing technologies,[35] and percent predicted $\dot{V}O_2$[36] are parameters that have been examined. Although additional prognostic information can be gleaned from the exercise test, a wealth of additional clinical and laboratory data collected at the time of transplant evaluation needs to be considered. In the 1990s, we developed and prospectively validated a clinical index to predict survival derived from data collected at the time of transplantation evaluation.[37] Multivariable proportional-hazards modeling was used to develop the model from 80 clinical characteristics in 268 ambulatory patients with severe HF. The statistical model was subsequently validated in 199 patients. The smallest number of prognostic variables that accurately predicted 1-year survival was used to develop the Heart Failure Survival Score (HFSS). The most significant prognostic factors were cause of HF, ie, presence or absence of coronary artery disease, resting heart rate, mean arterial blood pressure, left ventricular ejection fraction, presence or absence of intraventricular conduction defect, peak $\dot{V}O_2$ (in mL · kg^{-1} · min^{-1}), and serum sodium. The HFSS is calculated as the absolute value of the sum of the products of the prognostic variables and their computed coefficients. Noncontinuous variables were graded as 1 if present or 0 if absent. Low-risk patients are identified as those with a score >8.1; medium- and high-risk patients have scores <8.1. Medium- and high-risk candidates are appropriate for listing for transplantation.

Since the development of this model, many advances have been made in the treatment of HF, requiring the revalidation of both peak $\dot{V}O_2$ and the HFSS as prognostic markers. We[38] and several other investigators have demonstrated the efficacy of these parameters in the β-blocker era.[39,40] The discrimination between the low-, medium-, and high-risk groups of the HFSS is retained with the survival shifted upward, consistent with improved survival in patients receiving β-blockers. As medical and device therapies have advanced during the last 15 years, the cutoff value to define transplant candidacy has been lowered from a peak $\dot{V}O_2$ <14 to <12 mL · kg^{-1} · min^{-1}.

Many prognostic variables are tested at one point in time, but the value of $\dot{V}O_2$ and HFSS at serial assessments has been tested and shown to be effective.[41] This is particularly important for transplantation candidates who typically must wait months to years for a suitable organ. HF is a dynamic state and thus requires periodic reevaluation of the continued need for transplantation. We reassess ejection fraction and exercise capacity within 3 months of the initial evaluation in those patients with major alterations in therapy and/or with symptomatic improvement. In the majority of patients, reevaluation is performed every 12 months.

In 2006, another prognostic model was reported. The Seattle Heart Failure model is a 21-variable model derived from data collected during the Prospective Randomized Amlodipine Survival Evaluation (PRAISE) study.[42] It was validated on subsequent clinical trial data. The patient population from which this model was developed is analogous in time to the cohort used to develop the HFSS. Five of the 7 parameters of the HFSS are included in this model. Only heart rate and peak $\dot{V}O_2$ are not components. Several assumptions were made in the development of this model. The impact of therapies is imputed from the results of clinical trials, so all patients entered into the model are presumed to be responders to β-blockers, angiotensin-converting enzyme inhibitors, and/or biventricular pacing. A conversion formula is used to convert the diuretic dose to equivalent milligrams daily of furosemide. This is important because a key driver for mortality is diuretic dose. Despite these shortcomings, the Seattle Heart Failure Model has performed well as an additional tool by which to risk stratify HF patients. Direct comparison of these 2 models shows relatively good concordance, although the Seattle Heart Failure Model tends to be overly optimistic and HFSS more pessimistic in estimating survival.

The decreased survival benefit of cardiac replacement in ambulatory HT candidates raises the question of whether early listing is justified in all status 2 candidates. The experiences in Europe[43] and the United States in adult[5,44] and pediatric[45] ambulatory status 2 candidates consistently demonstrate little survival benefit from early HT. Because it is imperative that HT is reserved for only those patients who derive the greatest survival advantage, clinical trials have been proposed to justify cardiac replacement therapy in this population.[46] Delay of candidate listing or diversion of organs from status 2 to status 1 candidates, however, remains an area of controversy because status 2 candidates constitute a truly very heterogeneous population at high risk of upgrade to status 1 or need for emergent MCS implantation in 40% of listed candidates.[47] Application of clinical models may help to identify those status 2 patients in greatest need of cardiac replacement therapy, ie, candidates defined as high risk by the HFSS or those with >20% 1-year mortality with the Seattle Heart Failure model (Figure 1B).

Contraindications to Cardiac Transplantation

Through the years of experience in HT, a series of absolute and relative exclusion criteria have been empirically derived, including various comorbidities (eg, significant renal insufficiency or pulmonary hypertension) and laboratory and psychosocial factors, which can significantly increase perioperative risk or decrease long-term survival after HT, as listed in Table 2. As the indications for HT continue to expand, increasing number of patients are screened for HT.

Upper Age Limit

One of the most controversial aspects of patient selection is the upper age limit for cardiac transplantation. In 1970s, HT was reserved for only patients <50 to 55 years of age. In the

early 1980s, these criteria were modified to include patients >55 years of age, but there is no absolute cutoff for HT by age.[3] Today, 50% of transplanted patients are between 50 and 64 years of age.[2] Currently, the age of 65 years is considered the general upper age limit, although single-center experience has reported excellent outcomes in patients >70 years of age who were carefully screened for transplantation. Nevertheless, a large registry database analysis indicates decreased long-term survival in older patients.[48–51] The International Society for Heart and Lung Transplantation registry demonstrates decreased survival at all time points for the 174 patients >70 years who have been transplanted. The Scientific Registry of Transplant Recipients database demonstrates the 10-year survival after transplantation for patients >65 years of age to be 44.4% versus 57.2% for those recipients 35 to 47 years of age. Single-center studies also demonstrate decreased long-term survival in older recipients with an increased incidence of malignancy and renal failure.[52] These data suggest that moderate comorbidities in the older recipients should be considered carefully and more critically when considering transplantation than similar comorbidities in a younger population because of the limited reserve of the elderly.

Patients >65 years of age have lower rates of rejection, which most likely represents physiological changes that occur with aging. Immune senescence is linked to a decline in the ability of the host's body to defend against foreign pathogens or carcinogens. It is not surprising, therefore, that older age is also associated with a greater morbidity and mortality from infectious diseases and cancer.[51,52] It has been suggested that a reduction in the levels of immunosuppression in elderly recipients may decrease the incidence of infection with the rate of rejection being unchanged. In addition, steroid-induced diabetes mellitus and osteoporosis are more likely to occur in older patients, which may warrant closer screening of these patients for comorbid conditions before transplantation.

Pulmonary Hypertension

Increased pulmonary vascular resistance has traditionally been associated with increased risk of early graft dysfunction.[53,54] A transpulmonary gradient >15 mm Hg or a fixed pulmonary vascular resistance >5 Wood units has been found to be associated with an increased 30-day mortality rate.[55] The International Society of Heart Lung Transplant database consistently demonstrates a linear relationship between pulmonary vascular resistance and mortality after cardiac transplantation.[56] However, modern therapies such as the use of selective pulmonary vasodilators and implantation of an LVAD have been able to successfully reduce pulmonary pressures in many candidates.[57,58] Therefore, patients with elevated pulmonary vascular resistance should undergo sequential therapy with prolonged continuous infusion of milrinone with or without pulmonary vasodilators, including sildenafil (4 to 8 weeks) with serial right heart catheterizations and uptitration of medications followed by mechanical device support if pulmonary hypertension is persistent. The algorithm used to address pulmonary hypertension is variable among transplant centers with no uniform consensus approach.

Diabetes Mellitus

Diabetes mellitus with end-organ damage was considered a contraindication to transplantation, but now, more and more transplantation candidates have associated diabetes mellitus. As many as 10% patients who undergo transplantation have diabetes mellitus, with 13% receiving insulin therapy. Single-center studies have reported that carefully selected diabetic patients on insulin or drug therapy can undergo successful cardiac transplantation with morbidity and mortality similar to those of nondiabetic subjects.[59] Other centers have reported an increased 5-year mortality in diabetic patients with more frequent posttransplantation complications.[60] Analysis of the UNOS database[61] confirmed comparable survival in patients with uncomplicated diabetes mellitus but not in those diabetics with significant renal insufficiency (creatinine >2.5 mg/dL, morbid obesity, peripheral vascular disease, or past history of stroke). In diabetics without significant renal dysfunction, the effect of calcineurin inhibitor on renal function was comparable to that of nondiabetics over time.[62] In diabetics with renal dysfunction, combined heart-renal transplant can be considered because the reported outcomes of combined heart-kidney transplantation are comparable to those of HT alone.[63]

Human Immunodeficiency Virus

In the era of highly active antiretroviral therapy, even HIV-positive patients with end-stage cardiomyopathy can be considered for transplantation because 10-year survival after HIV seroconversion presently exceeds 90%.[64] This improved survival has shifted the profile of HIV infection from a rapidly fatal condition to a long-lasting, chronic ailment, with cardiovascular diseases now representing the leading cause of non–HIV-related death in these patients.[65] Several case reports[66,67] of HT in HIV-positive recipients have described good short-term outcome in these recipients. Recently, we reported a case series of 7 HIV-positive cardiac transplant recipients and reported 100% survival over a 5-year period without AIDS-related infections.[68] Immunosuppressive drugs were well tolerated, and HIV remained quiescent in these carefully screened patients who at the time of transplantation had low or undetectable viral loads without recent significant infections. Nevertheless, these findings require confirmation by other cardiac transplant centers.

Amyloid

Previously, infiltrative cardiomyopathies such as primary amyloidosis were considered a contraindication to transplantation because of recurrence of disease in donor organ and progression of disease in other organs. An Oregon survey of US centers that performed orthotopic HT without chemotherapy showed recurrence of disease, progression in other organs, and reduced long-term survival in 10 patients, with only a 39% survival at 48 months.[69] In a study of 24 cardiac amyloid patients transplanted in the United Kingdom,[70] 10 primary patients who received no chemotherapy had a median recurrence at 11 months, with 20% survival at 5 years. In contrast, median survival after transplantation increased to 29 months and 5-year survival to 36% in the 7 patients who received chemotherapy or stem cell transplants. The other 7 nonprimary amyloid patients had a 5-year survival of 64%.

Obviously, given the systemic nature of the disease, careful patient selection is needed to identify patients with predominantly cardiac amyloidosis. Proposed exclusion criteria include involvement of >2 organs and autonomic involvement with specific organ criteria such as creatinine >2.0 mg/dL, alkaline phosphatase >250 mg, large pleural effusions unresponsive to HF therapy, and significant autonomic dysfunction, ie, orthostatic hypotension.

Our center developed a protocol to perform orthotopic HT using extended-donor organs followed by high-dose chemotherapy and stem cell transplantation in patients with primary amyloid.[71] Twenty-five patients with systemic amyloidosis and HF were included in the study. Twelve patients with amyloidosis were transplanted. The 1-year survival after heart transplant evaluation was significantly greater in those receiving a transplant (75% versus 23%; $P<0.0001$), with survival of the amyloid transplant patients comparable to that of the other alternative heart list candidates. Combined cardiac and stem cell transplantation with extended-donor organs appears to significantly improve survival in systemic amyloidosis with HF, at least in the short to intermediate term. The use of extended-donor organs is a feasible strategy in these patients. Longer-term follow-up is needed to evaluate the prognosis of transplanted patients compared with those transplanted for other indications.

Familial amyloidosis is most commonly caused by a mutant form of the protein transthyretin produced in the liver and is associated with the more gradual onset of HF and a better prognosis than primary amyloidosis. Use of combined heart liver transplant has been shown to be effective for these patients at our and other institutions.[72,73] However, transplantation of patients with cardiac amyloidosis should be considered experimental and limited to institutions investigating this treatment option.

Extended Criteria (Marginal) Donor Heart or Alternative to HT

There are varying opinions of the ethical aspects of offering a donor heart to an elderly patient or a younger patient with significant comorbidities or requiring retransplantation when a large number of candidates await their first transplantation. For these borderline HT candidates, several large-volume HT programs in the United States offer extended criteria or "marginal" donor hearts that otherwise would not have been considered (noncritical coronary artery disease, moderate left ventricular hypertrophy)[74,75] (Table 7). In recent years, the option of permanent implantation of an LVAD as destination therapy has emerged as a viable alternative in some of these patients, particularly older patients with other comorbidities who often would not tolerate immunosuppressant therapy. Moreover, as more experience is gained from using these extended-donor organs with excellent outcomes, the question arises as to whether these donors represent a viable option for all patients.

Retransplantation

Cardiac retransplantation, first reported in 1977,[76] has long provoked ethical debate in the heart transplantation community. Recent improved survival after HT has resulted in an increased number of patients requiring retransplantation because of chronic allograft dysfunction. In 2007, retransplantation accounted for 4.4% of total heart transplantations in the United States and 3% worldwide.[77] It is anticipated that this percentage will increase as patient survival lengthens. Our center and others have previously reported poorer survival in cardiac retransplantation patients compared with de novo transplant recipients.[78–84] When selection criteria for retransplantation exclude primary allograft failure and refractory rejection in the first 6 months after transplantation, better prognosis has been reported.[85] One-year survival for retransplantation candidates has steadily improved from 52,7% for the cohort from 1982 to 1991 to 70.6% from 1992 to 2001 and most recently 81.2% from 2002 to 2007. Nonetheless, retransplantation is associated with a greater rate of comorbidities such as infections and malignancies from the heightened immunosuppression that negatively affects long-term survival.[86]

From available data, a working group on heart retransplantation[87] concluded that retransplantation should be considered only in patients with chronic graft dysfunction. However, these guidelines remain vague, and although HF, arrhythmias, and angina identify transplant vasculopathy at the highest risk, the timing of retransplantation for a long-term transplant survivor with 3-vessel coronary artery disease, prior stenting, and normal left ventricular function remains unclear. Identifiers of patients at greatest risk for sudden death are also undefined.

Table 7. Extended-Donor Criteria

Donor age >55 y
Cocaine use
Long-term alcohol abuse
Significant pressor or inotrope requirement (>10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dopamine or dobutamine)
ECG abnormalities (left ventricular hypertrophy, regional wall abnormality)
Long-standing diabetes mellitus
Death by poisoning (carbon monoxide, cyanide)
Prolonged ischemic time (>4 h)
Malignant brain tumors
Single-vessel coronary artery disease
Undersized organ (mismatch >30%), especially in patients with pulmonary hypertension

Congenital Heart Disease

Adults with congenital heart disease are the other growing subpopulation of patients being referred for cardiac transplantation as their long-term survival improves. Presently, 3% of patients undergoing cardiac transplant have complex congenital heart disease as the origin of their HF. Thirty-day survival after transplantation is significantly less in this group compared with patients with ischemic or dilated cardiomyopathies, generally because of intraoperative or postoperative bleeding. Previous Fontan procedure and older age at transplantation increase the perioperative risk.[88,89] One-year survival after transplantation has not increased significantly: 76% in the early era of 1982 to 1991 to 80% in 2002 to 2007.

However, if the congenital heart disease patient survives the surgery, then 10-year survival after transplantation is excellent regardless of age. Several special considerations need to be examined when an adult patient with congenital heart disease is examined. Evaluation of pulmonary vascular resistance is critical but often difficult in patients with a Fontan circulation. In patients with complex congenital heart disease, performing additional corrective surgeries needs to be balanced by potential detrimental effects of a prospective transplant. For example, a surgery strategy that may call for correcting a failed Glenn shunt with a Fontan procedure may result in increased pulmonary vascular resistance, other end-organ damage such as protein-losing enteropathy, or increased venous collateral circulation, all of which can complicate future cardiac transplantation.

Special considerations at the time of donor harvest and transplantation need to be made. Extended portions of veins, pulmonary artery, or aorta may be needed, and this may interfere with the procurement of other organs, especially the lungs. Creative approaches to the reconstruction of normal anatomy at the time of transplantation are frequently required. Adhesions from prior surgeries and an extensive collateral vessel network may predispose to excessive intraoperative and perioperative bleeding.

Conclusions

The selection of cardiac transplantation candidates continues to evolve. As new therapies become available and implantation of LVADs becomes more routine, there will be continued changes in the selection process. Presently, cardiac transplantation remains a life-saving therapy for patients with intractable HF not amenable to conventional medications or surgeries. With the scarcity of donor organs, it is anticipated that the trend for transplantation of only the sickest patients requiring continuous inotropic and/or mechanical support will continue.

Disclosures

None.

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