Management of Advanced Heart Failure

The Role of Heart Transplantation

Michelle M. Kittleson, MD, PhD; Jon A. Kobashigawa, MD

Case presentation: A 65-year-old man with idiopathic dilated cardiomyopathy is referred to an advanced heart failure center for heart transplant evaluation. He presented with decompensated heart failure 2 years earlier. At that time, an echocardiogram demonstrated a left ventricular ejection fraction of 25% with a left ventricular end-diastolic diameter of 6.3 cm, mild mitral regurgitation, and mild tricuspid regurgitation. A coronary angiogram demonstrated normal coronary arteries. Further evaluation revealed no evidence of thyrotoxicosis, and the patient denied alcohol use. Because the suspicion for amyloidosis, hemochromatosis, and sarcoidosis was low on the basis of laboratory findings, endomyocardial biopsy was not performed. The cardiomyopathy was presumed to be idiopathic. Lisinopril, carvedilol, and furosemide were started, and an implantable cardiac defibrillator was placed for primary prevention.

The patient’s symptoms resolved over the next few weeks. His ejection fraction on echocardiogram 6 months after the initial presentation was unchanged at 25%, but he was able to return to work as a financial analyst and to perform a regular exercise program of walking 30 minutes daily. He had no limitations until 3 months before presentation, when he noted the gradual onset of progressive dyspnea on exertion.

At the time of his presentation to the advanced heart failure center, he noted dyspnea with showering and dressing, and he was sleeping in a recliner owing to orthopnea. On examination, the heart rate was 90 bpm and regular, and his blood pressure was 88/64 mm Hg. The jugular venous pressure was 16 cm H₂O, and there was an S₃ gallop and 2+ pitting lower extremity edema. Laboratories demonstrated creatinine of 2.0 mg/dL. On echocardiogram, the ejection fraction was 15%, and the left ventricular end-diastolic dimension was 7.5 cm.

The goal of a heart transplant evaluation is determine whether (1) the patient’s cardiac status, with optimal medical therapy, is limited enough to benefit from heart transplantation; (2) the patient has comorbidities that would preclude heart transplantation; and (3) the patient demonstrates compliance and possesses adequate social support. Figure 1 summarizes this approach, outlined in detail below.

Optimal Medical Management of Advanced Heart Failure

Advances in medical therapy have dramatically improved the survival of patients with end-stage heart failure. Given the relative scarcity of donor organs, it is essential to determine whether end-stage heart failure patients are truly refractory to maximal medical therapy and merit transplant evaluation. At an advanced heart failure center, patients may undergo pulmonary arterial catheterization for optimization of filling pressures and cardiac output, high-risk revascularization of coronary artery disease, or ablation of ventricular tachycardia before heart transplantation is considered.

In ambulatory patients, evaluation will also include cardiopulmonary exercise stress testing to determine whether a patient’s cardiac status is limited enough to merit heart transplant evaluation. The cardiopulmonary exercise stress test measures maximal oxygen consumption (VO₂max), which is proportional to cardiac output. A VO₂max <12 mL · kg⁻¹ · min⁻¹ with adequate effort in a compensated patient indicates poor survival over the
next year and is an indication to proceed with evaluation. Adequate effort is defined as the patient’s achievement of anaerobic threshold, at which point CO₂ production exceeds O₂ consumption (indicated by a respiratory exchange ratio \( \frac{V_{CO_2}}{V_{O_2}} < 1 \)).

At an advanced heart failure center, end-stage patients may also be evaluated for mechanical circulatory support. Mechanical circulatory support is used for end-stage heart failure patients as (1) a bridge to recovery, for those individuals who require temporary circulatory support and are expected to recover; (2) a bridge to transplantation, for those patients with progressive decline in organ perfusion on escalating inotropic therapy while awaiting transplantation; and (3) destination therapy, for those individuals with contraindications to heart transplantation, including advanced age. The decision to proceed with mechanical circulatory support in the form of a left ventricular assist device or biventricular assist device as a bridge to transplantation will vary from center to center, depending on the patient’s projected waiting time to transplantation and degree of hemodynamic compromise. In general, heart transplantation is the preferred option for end-stage heart failure patients, and ventricular assist device support is reserved for those patients who are not candidates for transplantation or who cannot survive until a heart becomes available.

It is unclear if the functional status of the patient in the clinical vignette is limited enough to merit heart transplant evaluation, because he is decompensated and would benefit from optimization of his volume status and hemodynamics. The need for pulmonary artery catheterization is debatable; randomized trials show no benefit in length of stay or rehospitalization with pulmonary artery–guided therapy. Thus, it would be reasonable to reserve use of the pulmonary artery catheter for refractory volume overload associated with progressive renal dysfunction or hypotension, in which case an accurate assessment of the cardiac output and systemic vascular resistance would be used to guide the use of intravenous inotropes and vasodilators.

In addition to diuresis, it is important to identify the precipitant for the decompensation, because it may be treated or avoided in the future. Precipitants include ischemia, arrhythmias, valvular heart disease, infection, dietary indiscretion, and medication noncompliance (Table 1). Medication noncompliance is crucial, because it would impact the patient’s transplant candidacy. When no clear precipitant is identified, this is most concerning, because it indicates the patient’s tenuous cardiac function.

Once the patient is compensated on a stable diuretic regimen, medical therapy should be optimized (Figure 2). When given in addition to an angiotensin-converting enzyme inhibitor and β-receptor antagonist, spironolactone improves symptoms and survival in patients with New York Heart Associ-
Table 1. Precipitants for Decompensated Heart Failure

<table>
<thead>
<tr>
<th>Nonadherence</th>
<th>Medication noncompliance</th>
<th>Dietary indiscretion</th>
<th>Arrhythmias</th>
<th>Atrial fibrillation/atrial flutter</th>
<th>Ventricular tachycardia</th>
<th>Infection</th>
<th>Ischemia</th>
<th>Valvular disease</th>
<th>Mitral regurgitation</th>
<th>Aortic stenosis</th>
<th>Thyroid disease</th>
<th>Renal failure</th>
<th>Anemia</th>
</tr>
</thead>
</table>

Case Presentation: Workup and Management

The patient was admitted for intravenous diuresis. No precipitant for the decompensation was identified. By the time of discharge from the hospital, he had lost 10 kg, with a jugular venous pressure of 8 cm H₂O and creatinine of 1.5 mg/dL. He was already taking stable doses of an angiotensin-converting enzyme inhibitor and β-receptor antagonist and tolerated the addition of spironolactone 12.5 mg daily and digoxin 0.125 mg daily with a digoxin level of 0.6 ng/mL. The QRS was 110 ms, and cardiac resynchronization was not performed. Right-sided heart catheterization when he was clinically euvolemic demonstrated right atrial pressure of 6 mm Hg, pulmonary artery pressure 38/18 mm Hg, and pulmonary capillary wedge pressure of 15 mm Hg, with a cardiac index of 1.9 L·min⁻¹·m⁻². Cardiopulmonary exercise stress testing demonstrated a \( V_{O2\text{max}} \) of 10.4 mL·kg⁻¹·min⁻¹ with a respiratory exchange ratio of 1.1.

Assessing the Indications for Heart Transplantation

Despite advances in pharmacological and device treatment of chronic heart failure, long-term morbidity and mortality remain unacceptably high; the 5-year mortality rate for patients with symptomatic heart failure approaches 50% and may be as high as 80% at 1 year for end-stage patients.¹ Over the last 4 decades, cardiac transplantation has become the preferred therapy for select patients with end-stage heart disease. Approximately 2400 heart transplants are performed annually in the United States. The median survival of patients after transplantation is 10 years and up to 13 years for those who survive the first year after transplantation, a significant improvement over that provided by medical therapy.¹³

The 3 major indications for heart transplantation are heart failure, angina, and ventricular arrhythmias refractory to maximal medical therapy.¹⁴ The most common indication for heart transplantation is intractable heart failure. Patients with severe angina in the absence of heart failure are often not considered for transplantation because the survival benefit is unclear. Intractable ventricular arrhythmias, commonly referred to as VT storm, may merit evaluation for a heart transplant, and often urgent listing and consideration of mechanical circulatory support given the associated hemodynamic compromise.

Once a patient is euvolemic with optimal medical management, one can assess whether he or she is limited enough to merit transplantation. Of course, the inability to initiate optimal medical therapy because of progressive renal dysfunction or hypotension indicates poor reserve and is also an indication for transplantation,¹⁵ as are frequent episodes of decompensation despite medical compliance. Objective measurements that may help stratify the severity of illness include right-sided heart catheterization and cardiopulmonary exercise stress testing. The performance of right-sided heart catheterization once the patient is euvolemic is helpful to assess the degree of fixed postcapillary pulmonary hypertension and cardiac output at rest. A cardiac index \(<2.5\) L·min⁻¹·m⁻² suggests poor reserve and the need for transplant evaluation,¹⁴ as does a \( V_{O2\text{max}} \) \(<12\) mL·kg⁻¹·min⁻¹.²

Case Presentation: Management Decision

The patient in our clinical vignette, despite achieving euvolemia, has a low
cardiac index and low maximal oxygen consumption with good effort, which indicates that his cardiac function is limited enough with optimal medical management to consider heart transplant evaluation. Given that he has stabilized without requiring ongoing inotropic therapy, he is not considered a candidate for a left ventricular assist device as a bridge to transplantation.

The patient undergoes a heart transplant evaluation, including assessments by a cardiothoracic surgeon, psychiatrist, and social worker. His past medical history is significant for prostate cancer status after radical prostatectomy 5 years earlier. He quit smoking cigarettes 10 years ago, does not drink alcohol, and has never used illicit drugs. He had a normal screening colonoscopy 1 year ago. He works as a financial analyst and lives with his wife of 38 years. They have 1 son, who lives nearby.

### Assessing the Contraindications to Heart Transplantation

The 2 major categories of contraindications for heart transplantation are medical and social/psychological (Table 2). Many of these factors are not absolute and need to be considered in the context of the severity of the patient’s heart disease and associated comorbidities.

#### Age

In general, patients should be considered for heart transplantation if they are 70 years of age or less, because advances in posttransplantation care have shown that survival in the older age group is comparable to that of younger recipients. Patients over 70 years of age have also been reported to have acceptable outcome, but careful consideration of associated comorbidities is essential. At some centers, such patients are offered nonstandard donor hearts, including those with coronary artery disease, mildly decreased left ventricular ejection fraction, left ventricular hypertrophy, or age >55 years. This practice allows older patients to undergo heart transplantation without denying the scarce resource to younger potential recipients, with comparable outcomes.

#### Obesity

Obese patients have a greater risk of poor wound healing, infections, and pulmonary complications after cardiac surgery, although the outcomes in heart transplant recipients are less clear. Nevertheless, it is recommended that patients achieve a body mass index <30 kg/m² before listing. This may be difficult to achieve in patients with poor functional status, and at our center, we will consider patients with BMI <35 kg/m².

#### Malignancy

Active neoplasm, excluding nonmelanoma skin cancer, is an absolute contraindication to heart transplantation. However, heart transplant candidates with cancers in remission or that are low grade, such as prostate cancer, are often acceptable. Because immunosuppressive therapy may reactivate a prior malignancy, consultation with the patient’s oncologist is essential to perform an accurate risk assessment.

#### Pulmonary Hypertension

Right-sided heart failure contributes to morbidity and mortality after heart transplantation that is related to preoperative pulmonary hypertension. Contraindications to transplantation include (1) transpulmonary gradient >15 mm Hg and calculated pulmonary vascular resistance >5 Wood units, (2) pulmonary artery systolic pressure >60 mm Hg in conjunction with 1 of the above findings, and (3) the inability to achieve pulmonary vascular resistance <2.5 Wood units with vasodilator or inotropic therapy. In such patients, long-term unloading with a ventricular assist device may be required to achieve an acceptable pulmonary vascular resistance.

#### Diabetes Mellitus

Diabetes that is uncontrolled or associated with end-organ damage (proliferative retinopathy, severe neuropathy, nephropathy, peripheral vascular disease) is often considered a contraindication to transplantation. At our institution, patients will ideally achieve control with a hemoglobin A1c <7.5% before they are listed for transplantation; ongoing collaboration with an endocrinologist is helpful in achieving this goal.

#### Renal Dysfunction

Renal dysfunction is no longer considered an absolute contraindication to

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**Table 2. Contraindications to Heart Transplantation**

<table>
<thead>
<tr>
<th>Contraindication</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Over 70 y is a relative contraindication depending on associated comorbidities</td>
</tr>
<tr>
<td>Obesity</td>
<td>BMI &lt;30 kg/m² is recommended; most centers will tolerate BMI &lt;35 kg/m²</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Active neoplasm, except nonmelanoma skin cancer, is an absolute contraindication; cancers that are low grade or in remission may be acceptable in consultation with an oncologist</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>The inability to achieve PVR &lt;2.5 with vasodilator or inotropic therapy is a contraindication; such patients may benefit from long-term unloading with a ventricular assist device</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Uncontrolled diabetes or that associated with significant end-organ damage is an absolute contraindication</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>If due to diabetes, may be an absolute contraindication</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>Severe disease not amenable to revascularization is an absolute contraindication</td>
</tr>
<tr>
<td>Infection</td>
<td>HIV and hepatitis C are absolute contraindications at most centers</td>
</tr>
<tr>
<td>Substance use</td>
<td>6 Months of abstinence from smoking, alcohol, and illicit drugs is required; in critically ill patients, consultation with psychiatry and social work is essential</td>
</tr>
<tr>
<td>Psychosocial issues</td>
<td>Noncompliance, lack of caregiver support, and dementia are absolute contraindications; mental retardation may be a relative contraindication</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; PVR, pulmonary vascular resistance.
heart transplantation, unless the renal dysfunction is due solely to diabetes, because in this situation, it is a sign of advanced diabetes with end-organ damage. If the renal dysfunction is related to poor cardiac function, it may improve after transplantation, and for some patients, heart-kidney transplantation is considered.

**Peripheral Vascular Disease**

There is little consensus on the impact of cerebrovascular and peripheral vascular disease in heart transplant candidates. Clinically severe disease that is not amenable to revascularization is an absolute contraindication. However, asymptomatic disease that can be addressed before transplantation should be considered within the context of other risk factors.

**Infections**

Active infection is an absolute contraindication to heart transplantation. Certain chronic infections are also considered contraindications in most centers, including HIV and hepatitis C. Chagas disease, although uncommon in the United States, is a common indication for transplantation in South America, and reactivation of disease can occur. The decision to proceed with transplantation in these situations must be made in collaboration with an infectious disease specialist well-versed in transplantation.

**Substance Use**

Active cigarette smoking is a relative contraindication to heart transplantation, and smoking during the previous 6 months before transplantation is a risk factor for poor outcomes. At our institution, patients must display abstinence from smoking for 6 months, documented by urine cotinine screens, before they are listed for transplantation. Addiction to alcohol or illicit drugs is an absolute contraindication, because it suggests that these patients will have poor compliance after transplantation, and 6 months of abstinence with participation in counseling programs is required. This assessment may be difficult to make in the critically ill patient in whom transplantation cannot be delayed for 6 months. In this scenario, consultation with social work and psychiatrist specialists is essential in gauging the patient’s commitment to abstinence.

**Psychosocial Evaluation**

Patients must be able to demonstrate the ability to comply with medications and follow-up after transplantation, which includes social support with a dedicated caregiver. Patients have been denied transplantation because of a lack of compliance and social support. Mental retardation and dementia are relative contraindications to heart transplantation, the former because of concerns about compliance and the latter owing to overall poor prognosis.

**Case Presentation: Outcome**

The patient demonstrated no absolute contraindications to heart transplantation. Although he had a history of prostate cancer, he was deemed by his urologist to be acceptable to proceed for transplantation given that he had a radical prostatectomy with no recurrence. The renal dysfunction was not concerning, given his improvement with diuresis and optimization of his medical management, which suggested a cardiorenal syndrome that would improve with transplantation, and he had excellent social support. He was listed as Status 2 for heart transplantation.

After a 6-month wait, a suitable donor became available. The donor was a 40-year-old man who presented with brain death due to a subarachnoid hemorrhage caused by a ruptured cerebral aneurysm, without any past medical history. The patient’s postoperative course was unremarkable, and he was discharged home 1 week after heart transplantation. Two years after heart transplantation, he has had no evidence of rejection or significant infection. He has returned to work as a financial analyst and continues to do well.

**Conclusions**

Despite advances in medical and device therapy, end-stage heart failure carries significant morbidity and mortality. The greatest challenge for a cardiologist caring for patients with advanced heart failure is recognizing when to refer the patient to an advanced heart failure center for evaluation for heart transplantation or ventricular assist device support. At the advanced heart failure center, the role of the heart failure specialist is to determine whether the patient’s cardiac status is limited enough, with optimal medical management, to merit transplantation and to determine whether there are comorbidities that would preclude transplantation.

**Disclosures**

None.

**References**

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