Current Status of Cardiac Transplantation and Mechanical Circulatory Support

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Cardiac transplantation and mechanical circulatory support are possible options for improving survival and quality of life in patients with isolated cardiac disease and end-stage heart failure. Transplantation is limited by donor availability but has a median survival of 10 years. Post-transplant immunosuppression is often transplant center dependent, but a tacrolimus and mycophenolate mofetil–based regimen may be preferred. Sirolimus may reduce the progression rate of transplant vasculopathy. There has been a trend toward continuous-flow left ventricular assist devices because of their increased durability and reduced size. A variety of surgical and percutaneous ventricular assist devices may be used as a bridge to decision on a patient’s candidacy for transplantation. Mechanical circulatory support as destination therapy has not been widely implemented because of poor device durability, but this is expected to change with newer devices. Mechanical circulatory support as a bridge to myocardial recovery has been successful only in a few patients.

Introduction
The prevalence and incidence of heart failure (HF) continue to expand worldwide. For over a decade, HF has been the single largest expense for Medicare in the United States and is the primary reason for hospitalization for more than 1 million hospitalizations on an annualized basis and is a contributor to many more hospitalizations annually. However, mortality continues to be excessively high despite advances in medical and device therapy for chronic HF. Despite these improved medical and device-based therapies for HF, the underlying pathophysiology contributing to the myopathic process is often unrelenting and progressive, leading to a gradual progression from stage B to stage D HF. Progress has not been as forthcoming in medical and device management of stage D HF as it has been for lower stages, and hospice care is often the only alternative for many patients in this category.

For patients with isolated cardiac disease, cardiac transplantation is the mainstay of therapy for stage D HF. However, the number of cardiac transplants occurring worldwide has declined considerably over the past decade. Because clinical outcomes with mechanical circulatory support as a bridge to cardiac transplantation or as destination therapy are improving substantially in terms of durability and efficacy, mechanical circulatory support will likely replace cardiac transplantation as the preferred therapy for such patients. This review focuses on these two forms of therapy for managing stage D HF.

Cardiac Transplantation
Indications and contraindications for cardiac transplantation
Patients with stage D HF who continue to have severe functional capacity limitations despite maximized medical and device therapy are potential candidates for cardiac transplantation. Medical and surgically reversible causes of HF should be corrected before cardiac transplantation is considered. There is great debate within the HF community on whether surgical correction of severe mitral regurgitation related to annular dilatation is warranted in patients with severe dilated cardiomyopathy [1,2]. Metabolic stress testing remains the definitive test in assessing the severity of functional capacity limitation, with a peak oxygen consumption of less than 14 mL/kg/min being an acceptable limitation warranting cardiac transplantation [3]. Some transplant centers have also used gender- and age-based criteria in which the potential recipient must have less than 55% of the average functional capacity for people of their age and gender.

At a few cardiac transplant centers, highly selected patients may be considered for a variety of combinations of organ transplants (eg, heart/kidney, heart/lung, heart/liver, and heart/bone marrow). However, the vast majority of cardiac transplant centers perform only isolated heart transplantations.
The primary contraindications for cardiac transplantation remain advanced age and medical comorbidities. The upper age limit for cardiac transplantation is set by individual transplant centers and may range from 60 to 75 years. Medical comorbidities that are relative contraindications to cardiac transplantation include severe pulmonary disease, chronic renal failure, and liver failure. Diabetes without noncardiac end-organ damage is no longer considered a contraindication to cardiac transplantation. Pulmonary hypertension secondary to HF deserves special mention because this is a contraindication to cardiac transplantation and is often readily reversible with medical therapy or mechanical circulatory support as a bridge to cardiac transplantation. At most centers, patients with a history of malignancy must be disease-free for at least 5 years before undergoing cardiac transplantation because of the potential for recurrence with immunosuppressive therapy after transplantation. However, many of these contraindications for cardiac transplantation are indications for consideration for mechanical circulatory support as destination therapy.

United Network of Organ Sharing and cardiac transplantation list prioritization

After a patient is deemed eligible for cardiac transplantation, he or she is entered into a national databank maintained by the United Network of Organ Sharing (UNOS) that allocates organs, including the heart. The UNOS list prioritizes organ allocation to the sickest patients within a geographic range of 500 miles. Prioritization of patients is achieved primarily by either the requirement for intravenous inotropic therapy or mechanical circulatory support. In many areas of the United States (particularly the Midwest, Northwest, and South), organ availability is so limited that potential recipients are unlikely to receive enough priority on the cardiac transplant list until they are sick enough to warrant mechanical circulatory support or intravenous inotropic therapy. Given the poor clinical outcomes associated with home intravenous inotropic therapy [4], most transplant centers have resorted to using mechanical circulatory support as a bridge to cardiac transplantation in patients for whom a suitable organ cannot be expeditiously found.

Immunosuppression after transplantation

Post-transplant immunosuppression seems to be determined primarily by individual transplant center protocols as opposed to data supporting one immunosuppressant over another. Induction therapy with either cytolytic therapy or interleukin-2 receptor antagonists immediately after transplant remains controversial unless it is used as a renal-sparing strategy in the setting of postoperative renal failure [5,6]. Approximately half of all heart transplant recipients receive one of these therapies postoperatively, although there does not appear to be any survival advantage despite the substantial costs associated with these therapies [7••]. There is a trend toward greater use of tacrolimus versus cyclosporine as the calcineurin antagonist of choice; however, no data exist comparing them directly. Mycophenolate mofetil has largely supplanted azathioprine as the second immunosuppressant in most transplant programs because mortality is reduced, albeit with a greater risk of opportunistic infections and increased cost [8]. Sirolimus has been shown to reduce the rate of progression of transplant vasculopathy [9], but it has not been shown to improve outcome when given de novo transplant recipients [10•]. Therefore, patients who develop transplant vasculopathy are often switched to sirolimus, but few patients are started on this immunosuppressant in the absence of transplant vasculopathy. Corticosteroids are the third immunosuppressant, primarily administered early post-transplant. Because of the deleterious long-term side effects related to corticosteroids, most transplant programs have instituted long-term steroid-sparing protocols, and some patients are weaned from them completely.

Outcomes following cardiac transplantation

The median survival after cardiac transplantation is approximately 10 years, and this continues to improve despite the gradual increase in illness severity of recipients at the time of cardiac transplantation (Fig. 1) [7••]. Newer immunosuppressive regimens have not been available long enough to influence these statistics; however, it is anticipated that survival will continue to improve as more patients are treated with these regimens. Survival appears to be similar in all age categories except those older than 70 years [7••]. However, survival in this age group remains superior to that of medical therapy, which has led to the concept of an alternate cardiac transplant recipient list in some centers where suboptimal donor hearts that are still viable are offered to alternate recipients who still benefit when compared with optimal medical therapy [11]. This approach has not been implemented at most centers, and no data exist comparing this approach to the alternative of mechanical circulatory support as destination therapy. Survival appears to be independent of the preexisting etiology of HF in recipients, with the only exception being a failed prior cardiac transplant, in which retransplantation survival is substantially worse [7••].

Long-term survival following cardiac transplantation appears to be limited primarily because of transplant vasculopathy and side effects related to chronic immunosuppressive therapy [7••]. One third of patients develop transplant vasculopathy within 5 years of transplantation and half within 10 years [7••]. Oral statin therapy appears to significantly reduce the incidence of transplant vasculopathy and therefore is prescribed in all cardiac transplant patients [12]. This effect appears to be at least partially independent of its effect on hyperlipidemia and may be related to an anti-inflammatory effect. Epicardial coronary transplant vasculopathy can be successfully intervened upon with balloon angioplasty and stenting [13]. Once vasculopathy has arisen, its progres-