Status of Cardiac Transplantation with a Report of the First Year's Experience at Henry Ford Hospital

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Cardiac transplantation is now widely accepted as effective treatment for selected patients with end-stage heart disease. Improvements in immunosuppressive treatment and monitoring in the past 15 years have resulted in impressive one-year and five-year survival rates of 80% and 60%. In general, survivors have enjoyed a considerably improved quality of life. A cardiac transplantation program was initiated at Henry Ford Hospital in 1985, and a total of 15 patients received heart transplants in the first 12 months. Fourteen patients are currently alive and well at various stages posttransplant. This early clinical success has prompted the consideration of both combined heart-lung transplantation and mechanical left ventricular support at Henry Ford Hospital in the future. (Henry Ford Hosp Med J 1986;34:197-201)

After nearly a decade, cardiac transplantation reemerged in the late 1970s as effective treatment for selected patients with end-stage cardiac disease. Since then a rapid increase in both the number of recipients and transplant centers has occurred. An international registry for heart and heart-lung transplant recipients was established in 1984 (1). The number of patients in the registry currently exceeds 2,800; over 700 were accounted for in 1985 alone. Some authorities predict that as many as 2,000 cardiac transplants per year could be performed in the United States using current recipient and donor selection criteria (2,3).

The major stimulus for renewed interest in cardiac transplantation is the increased survival and freedom from morbidity afforded by cyclosporine immunosuppression. Expected survival rates for cardiac transplant recipients in 1986 are 80% and 60% at one and five years, respectively. The quality of life is clearly improved following cardiac transplantation, and many recipients resume full-time employment.

The cardiac transplantation program at Henry Ford Hospital was initiated in 1985. This was a cooperative multilevel and multidisciplinary venture throughout the hospital. After three months of laboratory experiments, the first human cardiac transplant at Henry Ford Hospital was performed in April 1985. A total of 15 patients received transplants during the first 12 months of the program. To date, 14 of these 15 patients are alive and well at various stages of posttransplant; the one death was attributed to disseminated aspergillosis. This presentation outlines some of the important issues in human cardiac transplantation and discusses the results of the recent Henry Ford Hospital experience.

Recipient Selection

Careful recipient selection is one of the most important determinants of success in a cardiac transplant program. Medical, psychosocial, and financial issues must be considered. At Henry Ford Hospital a pretransplant evaluation is performed by a committee which consists of the medical-surgical group, a social worker, psychiatrist, and chaplain. Full support of the transplant committee must be obtained before an individual is added to the list of patients awaiting transplantation. Additional input is obtained from specialists in infectious diseases, immunopathology, pathology, hypertension/nephrology, nursing, and rehabilitation.

Cardiac transplantation is considered for patients with end-stage cardiac disease only when other, more conventional treatment has failed or is contraindicated. As a group, these patients have an extremely poor prognosis. Data from Stanford University show a mean survival rate of six weeks for patients who have been accepted for transplantation but for whom no suitable donor can be found (4). Despite this survival advantage, the main reason for cardiac transplantation at Henry Ford Hospital is the symptomatic relief of severe congestive heart failure.

The primary diagnoses of the 15 patients who received transplants at Henry Ford Hospital in 1985 are listed in Table 1. Na-

Table 1
Primary Diagnosis

Idiopathic cardiomyopathy	4 patients
Ischemic cardiomyopathy	8 patients
Valvular heart disease	2 patients
Other	1 patient

Table 2
Criteria for Recipient Selection: Optimal Conditions

Age less than 55 years
Terminal cardiac disease despite optimal conventional medical/surgical therapy
Life expectancy less than one year
Noncardiac function normal or reversibly impaired
Pulmonary vascular resistance less than 2 Wood units
No active infection, cancer, or other systemic illness
Good psychosocial profile
Good record of medical compliance
Adequate finances
Well-informed and motivated

Table 3
Recipient Demographics

Age	45 years (mean)	29 to 58 years (range)
Sex (No.)	Males (13)	Females (2)
Race (No.)	Caucasian (12)	Black (3)

tionally, ischemic cardiomyopathy is probably the most frequent indication for cardiac transplantation, and more patients are being referred after unsuccessful myocardial revascularization with or without concomitant valve or aneurysm procedures. Moribund patients with an intraaortic balloon pump and receiving inotropic support or other mechanical support are also a growing fraction of the cardiac transplant population. Overall, clinical judgment is probably as important in determining the optimal timing for transplantation as are the objective measures of cardiac failure, such as cardiac index, ejection fraction, and end-diastolic pressure. The optimal recipient criteria based on current opinion are outlined in Table 2 (5).

The age criteria for transplantation have been challenged by many groups. Patients older than 55 years have had transplants and, if otherwise carefully selected, do as well as their younger counterparts. Undoubtedly, the upper age limit at an institution is partly determined by the number of available donors and the number of young recipients already on the waiting list. The demographics of the cardiac transplant recipients at Henry Ford Hospital are provided in Table 3.

Elevation of the pulmonary vascular resistance detected at the time of right heart catheterization is a significant concern for patients with long-standing congestive heart failure. The orthotopically transplanted heart is poorly prepared to function acutely with a high afterload on the right ventricle. Fortunately, patients rarely have fixed elevations of pulmonary vascular resistance even in the setting of long-standing heart disease. At Henry Ford Hospital an attempt is made to normalize pulmonary resistance during catheterization by administration of oxygen and systemic vasodilators. Alternately, these patients might be considered for combined heart and lung transplantation or heterotopic heart transplantation.

The goal of cardiac transplantation is successful rehabilitation of the patient with a return toward a normal level of activity. Since life expectancy after cardiac transplantation is unlikely to be normal when compared with age-matched controls, the transplant recipient should be highly motivated and have a realistic attitude and definite ambition. Stress is always present, and good emotional and family support is essential. Alcoholism and drug abuse are contraindications for transplantation. The best recipients are mature, intelligent individuals with a good record of medical compliance and a short history of disability.

Donor Selection

Current optimal donor criteria are presented in Table 4 (6,7). Coronary artery disease is so prevalent in North America that

generally only younger donors are chosen. Nevertheless, a growing donor shortage and increasingly ill recipients have forced some groups to extend the donor age criteria. In most cases, a careful review of the donor's history, physical examination, electrocardiogram, and echocardiogram is sufficient to detect significant cardiac abnormalities. Cardiac catheterization and coronary angiography are rarely indicated. Though it is not critical, an attempt is made to match the size of donor and recipient. Long-standing cardiac failure and pulmonary hypertension result in global cardiomegaly and frequent enlargement of the great vessels. In these circumstances it is technically easier to graft a heart from a larger donor. Similar allowances are also made for recipients with high pulmonary vascular resistance.

The donor's and recipient's ABO systems must be compatible, but matching the minor blood group antigens is unnecessary. HLA matching is probably beneficial for cardiac recipients, but time constraints and the limited donor pool prevent routine use. Prospective HLA antibody screening is performed for all potential cardiac recipients. Fortunately, cytotoxic antibodies against HLA antigens are much less common in cardiac than in renal transplant candidates. Results of the formal donor-recipient cross-match are unnecessary preoperatively unless screening indicates recipient positivity against 15% or more of a panel of random donor lymphocytes. We have yet to encounter a patient with this degree of positivity. Donors are also screened for the presence of potentially transmissible diseases such as AIDS, hepatitis-B, and nonprimary central nervous system cancer. A significant history of recent drug abuse, particularly intravenous drugs, precludes cardiac donation.

The mechanism of brain death has not been shown to influence the results of organ transplantation. In our experience at Henry Ford Hospital, the two major causes of brain death have been traumatic brain injury and cerebral hemorrhage from vascular abnormalities. Brain death sets in motion a complex chain of physiologic events which ultimately result in cardiovascular collapse and arrest of the circulatory system. The potential organ donor requires careful monitoring to maintain homeostasis. Fluid balance and electrolyte management are complicated by the presence of diabetes insipidus. Temperature regulation is disturbed with the appearance of either hyperthermia or hypothermia. Sepsis from pneumonia, urinary tract infections, or traumatic or surgical wounds must be treated aggressively with appropriate antibiotics. Initially, hypotension resulting from fluid restriction, diabetes insipidus, or diuretic therapy can be reversed by fluid administration. Judicious use of dopamine and colloid are also beneficial in maintaining cardiovascular stability. The dosage limits or duration of dopamine administration have not been clearly established. However, most cardiac groups find that doses of over 5 µg/kg/min are excessive.

Table 4
Criteria for Donor Selection: Optimal Conditions

Age: Males less than 35 years of age, females less than 40 years of age.
Size: Within 20% body weight of the recipient.
ABO blood group compatible.
Hemodynamically stable: Dopamine less than 5 μg/kg/min.
Absence of significant cardiac history or injury.
Absence of transmissible diseases: hepatitis, AIDS, cancer, etc.

Table 5
Biopsy Interpretation

Grade	Histology
No rejection	No infiltrate
Mild rejection	Mononuclear infiltrate
	Perivascular to interstitial location
	No myocyte necrosis present
Moderate rejection	Mononuclear interstitial infiltrate
	Mild to moderate myocyte necrosis
Severe rejection	Marked myocyte necrosis
	Infiltrate with polymorphonuclear leukocytes or hemorrhage

Not enough thanks can be given to the families of the donors who make these unselfish gifts at a time of great personal grief. Increasing public awareness of the success of transplantation combined with progressive policy decisions on the part of government at multiple levels have helped increase the number of organ donors. We expect that required-request legislation will have a further positive effect. Each hospital must formulate its own definitions of brain death, although nationally recognized guidelines are available (8,9). Contact with a number of excellent regional organ procurement networks ensures optimal utilization of the organs to be donated once brain death has been established.

Cardiac Transplantation: The Operation

The surgical procedure for orthotopic cardiac transplantation was originally described by Lower and Shumway (10) and later modified by Barnard (11). Initially, simultaneous donor and recipient operations were performed in adjacent operating rooms to minimize the period of cardiac graft ischemia. Current hypothermic cardioplegic techniques ensure good myocardial preservation for periods of up to four hours in humans and considerably longer in animals. This has increased the donor pool by allowing donor organ procurement up to 1,000 miles from the site of implantation (12,13). Close coordination between donor and recipient teams is required to minimize graft ischemic times, particularly at these long distances. Fortunately, our transplant program has been able to secure all donors from within a 250 mile radius. Mean ischemic time was 107 minutes with a range of 53 to 184 minutes.

Cardiac recipients present challenging problems to the anesthetist. The induction and prebypass phases require careful monitoring and titration of anesthesia to maintain hemodynamic stability. Recipients at Henry Ford Hospital have their blood ultrafiltered during cardiopulmonary bypass. Our clinical impression is that this reduction in total body water improves pulmonary function and facilitates early extubation postoperatively. The most frequent intraoperative problem in this group of patients is bleeding. Major risk factors that cause bleeding are reoperation, preoperative anticoagulant therapy, and congestive hepatic dysfunction.

All grafts have functioned sufficiently after implantation to allow weaning from cardiopulmonary bypass. Patients routinely receive small doses of inotropes postoperatively. Early in our experience at Henry Ford Hospital, we learned that right-sided hemodynamics were equally if not more important than left-sided hemodynamics after cardiac transplantation. Consequently, a pulmonary artery thermodilution cardiac output catheter is now inserted routinely before separation from cardiopulmonary bypass. Reduction of right ventricular afterload with nitroglycerin or prostaglandins has been helpful in some patients.

Immune Suppression

Early in the cardiac transplant experience the two major sources of morbidity and mortality were rejection and infection. The 12-month survival rate in 1968 was 20%, with almost all of the deaths occurring from rejection and infection within the first three months after transplantation. Clearly, the antirejection protocols available then had too narrow a margin between over and under immune suppression.

In the 1970s cardiac transplantation fell into disfavor, and only a few groups continued this procedure. Two notable achievements were made at Stanford University during this period: introduction of endomyocardial biopsy as a routine clinical tool in the evaluation of rejection (14), and development of antihuman thymocyte sera for prophylaxis and treatment of rejection (15). By the mid-1970s, the 12-month transplantation survival rate at Stanford improved to 60%, and other American, European, and South African centers began to report similar results. Endomyocardial biopsy is the "gold standard" against which all other diagnostic techniques for rejection must be compared. It is a simple and relatively safe procedure that can be repeated as often as necessary. The histologic classification of cardiac rejection has been well described (16) and is presented in Table 5.

Although the threat is always present, the incidence of rejection declines markedly after the first three months (17). Presently, almost all patients have at least one histologically diagnosed acute rejection episode in the first three months posttransplant. Antirejection surveillance, therefore, is most intense during this period, and endomyocardial biopsies are repeated every one or two weeks. Beyond the three-month period, the interval between successive biopsies is gradually extended; currently, one-year survivors at Henry Ford Hospital are biopsied every three months.

Another major advance in the history of cardiac transplantation was the discovery of cyclosporine, a naturally occurring peptide isolated from two species of soil fungi. This remarkable drug has potent and specific effects on cell-mediated immunity. Initially, cyclosporine was used as the sole immunosuppressive drug, but clinical experience has shown it to be most effective

Table 6
Immune Suppression: Regimen for Cardiac Transplant Recipients

Steroids	Methylprednisolone intravenously. 500 mg intraoperatively. 100 mg every 8 hours for 24 hours. 50 mg every 8 hours for 24 hours. Prednisone orally 1 mg/kg/day tapered to 0.2 mg/kg/day by 4 to 6 weeks.
ALG	10 to 15 mg/kg/day intravenously to reduce total peripheral blood lymphocytes less than 200. Stop when serum cyclosporine level greater than 100 ng/mL.
Cyclosporine	6 to 8 mg/kg/day orally. Start when taking fluids orally and renal function adequate. Adjust every 12-hour dose to obtain targeted trough serum level.
Azathioprine	1 to 2 mg/kg/day orally. Start when taking fluids orally and maintain total leukocytes greater than 5,000 and platelets greater than 100,000 in peripheral blood.

when combined with either prednisone or azathioprine. The immunosuppressive protocol in use at Henry Ford Hospital is presented in Table 6.

Cyclosporine therapy has been responsible for the latest 15% to 20% across-the-board improvement in survival rates following cardiac transplantation. It has narrowed the success rate differences between experienced centers and those just starting transplant programs. This has encouraged rapid proliferation of transplant centers worldwide.

When cyclosporine therapy is compared with "conventional" immunosuppressive regimens (those used in the pre-cyclosporine era), mortality from rejection and infection is dramatically reduced (17). The incidence of acute rejection is probably unchanged, but the rejection process is slowed and more amenable to reversal. Preservation of humoral and non-specific immunity also results in fewer deaths from infection, although the overall incidence of infection probably remains unchanged.

Complications of long-term immunosuppressive therapy include an increased risk of opportunistic infections and cancer (18). The development of accelerated atherosclerosis within the graft is one complication specific to cardiac transplantation and is a leading cause of late death. Routine, annual coronary angiography is performed to detect this complication, and significant coronary lesions are an indication for retransplantation. Cyclosporine has its own special long-term problems, notably nephrotoxicity and the almost universal incidence of hypertension among cardiac transplant recipients. Acute cyclosporine nephrotoxicity is frequently observed posttransplant in patients with preoperative renal dysfunction (19). This complication is usually manifested as acute oliguric renal dysfunction in the immediate posttransplant period. For this reason, we avoid the perioperative use of cyclosporine and rely on antilymphoblast globulin for immune suppression during the first two to three days. Cyclosporine is administered when cardiorespiratory, gastrointestinal, and renal function have stabilized. Cyclosporine levels are monitored daily, and the dose is adjusted frequently to ensure optimal efficacy and minimum toxicity. When more insidious chronic nephrotoxicity of cyclosporine occurs after several months of therapy, serial monitoring of renal function reveals slow deterioration. This has been the subject of much recent concern and research. Cyclosporine analogs, multidrug protocols, and determination of optimum long-term cyclosporine levels should diminish this problem in the future.

Future Directions

The major breakthrough for solid organ transplantation will come with the development of methods for inducing specific tolerance. This will obviate the need for long-term immunosuppressive therapy and eliminate the associated problems of infection, cancer, and adverse drug reactions. Much experimental progress should affect clinical practice soon.

New analogs of cyclosporine which are undergoing clinical trials may or may not have advantages over the parent compound. Monoclonal antibodies against specific classes of human T-cells are now available for clinical use and are effective in treatment of resistant-rejection episodes. Their ultimate role, however, remains to be defined. Other forms of immune modification by pretransplant blood transfusion or total lymphoid irradiation are beneficial for renal transplantation but are not yet widely practiced in cardiac transplantation.

Short-term mechanical support or replacement of the heart is viewed as a bridge to cardiac transplantation. These devices are effective in salvaging patients until suitable donors can be found, but the demand for cardiac donors already exceeds the supply. Thus, the "bridge" concept does not solve the problem; it merely increases the number of seriously ill patients awaiting transplantation. Xenografts and a new generation of totally implantable mechanical devices are potential sources for cardiac replacement in the future.

The first year's experience in cardiac transplantation at Henry Ford Hospital has been exceptionally gratifying for everyone involved. Future directions for the program include the initiation of combined heart-lung transplantation and temporary left ventricular support with a mechanical device. We expect the next 12 months to be equally exciting.

Addendum

Twenty-five patients have undergone orthotopic cardiac transplantation at Henry Ford Hospital as of August 1986. Five patients have been followed in excess of one year, and all survivors are currently well.

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