Cardiac Transplantation and Mechanical Assistance

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The era of human heart transplantation began in 1967 by Dr. Christian Barnard in South Africa. Unfortunately, most patients died within the first year after transplantation from rejection or opportunistic infection, and the procedure was abandoned in all but a few centers. With the dedicated work of Dr. Norman Shumway from Stanford University, advances in immunosuppression and improved detection and management of rejection allowed heart transplantation to evolve from a laboratory curiosity into a clinical reality. Finally, with the introduction of the immunosuppressant, Cyclosporin A (CyA), in the 1980s the number of cardiac transplants being performed increased exponentially. Heart transplantation has entered the mainstream of surgical management of congestive heart failure and approximately 2000 procedures are performed annually in the United States and 3000 worldwide.

INDICATIONS AND OUTCOME

Primary treatment for end-stage heart disease is either medical (diuretics, digoxin, angiotensin-converting enzyme [ACE] inhibitors, calcium channel, or beta blockers), or high-risk reparative surgery (coronary revascularization, valve replacement) with combined cardiac rehabilitation and conditioning. Heart transplantation is offered to patients with end-stage cardiac disease who have an unacceptable lifestyle and cannot achieve palliation or prolongation of life with conventional medical or surgical therapy. Poor prognostic fac-

tors are (>50% one-year mortality rate) New York Heart Association class IV symptoms, low ejection fraction (ie, ejection fraction <20%), exercise oxygen uptake of <15 ml 02/min/kg, left ventricular end-diastolic pressure >20 mm Hg, and ventricular tachycardia.[1] Table 1 shows additional criteria that must be met when the decision has been made to proceed with transplantation from a cardiac perspective.

Although most recipients have idiopathic dilated cardiomyopathy or end-stage ischemic disease, transplantation may be appropriate for other conditions including congenital heart disease, post partum or valvular cardiomyopathy, and transplant arteriolar occlusive disease (Table 2).

When accepted for transplantation, the candidate is placed on a waiting list. The time period before a donor becomes available depends on ABO blood type (type O wait longest) and status (I—in the Intensive Care Unit on intravenous inotropes; II—all others). After patients are transplanted, they remain in the hospital for about two weeks, allowing for time to monitor heart function and establish a stable immunosuppression regimen.[2]

Chronic immunosuppression consists of CyA combined with Imuran (azathioprine) and steroids. CyA acts primarily by inhibiting the production of interleukin-2 (IL-2) and, thus, attenuating the recruitment of cytotoxic cells by helper-T lymphocytes and macrophages. The initial dosage of CyA is 6 mg/kg/day (administered either two or three times daily) and is then adjusted according to level, serum creatinine, side effects, and presence or absence of rejection. CyA levels can be measured by liquid chromatography or a monoclonal radioimmunoassay. The method of assay will affect the observed level. Liquid chromatography is specific for CyA, whereas the monoclonal radioimmunoassay will also detect metabolites of CyA and is, thus, less specific. The level sought is usually 300 µg/dL (whole blood TDx®—fluorescence polarization immunoassay) or lower with liquid chomatography.

Imuran blocks purine synthesis and suppresses hematopoietic cells. It is given at 2 mg/kg/day and is adjusted to keep the white blood cell count between 4000 and 6000 per cubic millimeter. Glucocorticoids block IL-1 and IL-2 production and are cytotoxic to lymphocytes and macrophages. They are given in large doses initially, and are tapered to as low as can be tolerated without rejection.

Rejection is detected by endomyocardial biopsies. Biopsies are done weekly after transplant and less frequently over two years. After two years, they are done semi-annually. Rejection is graded on a scale from 0 to 4 depending on the amount of lymphocytic infiltrate and myocyte necrosis (Table 3). Rejection greater than 3A or lower grade with hemodynamic compromise is treated. Treatment usually consists of a steroid pulse of either intravenous Solumedrol or oral Prednisone. Refractory rejection is then treated with cytolytic therapy (polyclonal ATGAM [antithymocytic globulin] or monoclonal OKT3), which are drugs that directly destroy lymphocytes.

Immunosuppressive agents may have many complications. CyA can lead to hypertension, renal and hepatic dysfunction, seizures, hirsutism, gingival hyperplasia, and lymphomas. Imuran can be hepatotoxic but is usually well tolerated. Steroids may lead to a cushingnoid appearance, osteoporosis, cataracts, peptic ulcer disease, mood swings, weight gain, hyperlipidemia, aseptic necrosis, and development of diabetes mellitus. Proper dosage is essential in preventing some of these complications while simultaneously preventing rejection.

Heart transplantation is now a well-accepted clinical entity with gratifying results. The one-year survival rate is 85% with greater than 90% of patients improving to functional New York Heart Association class I or II following transplantation, and greater than 90% of patients previously employed returning to work. The five-year actuarial survival rate is 65%.[2] Over the last 12 months (July 1992 to July 1993), 64 heart transplants have been performed at Temple University Hospital (TUH) with a 91% overall survival rate. Of all patients transplanted at TUH over an eight-year period, 72% remain alive.

Criteria For Heart Transplant Recipients

1. Severe, progressive heart disease unable to be improved or significantly palliated by medical or surgical therapy
2. Age less than 65 years*
3. Pulmonary vascular resistance less than 4 Wood units (with or without therapy)*
4. Absence of other permanent organ dysfunction (eg, liver, kidneys)
5. Absence of other life-threatening conditions (ie, active malignancy, active systemic infection,* diabetes with end-organ failure)
6. Strong support system
7. Absence of substance abuse
8. Ability to adhere to complex medical regimen

**Flexible, decided on an individual patient basis*

Table 1.

Causes of End-Stage Heart Disease

Disease	Percent
Ischemic heart disease	49.7
Cardiomyopathy	40.8
Valvular heart disease	3.4
Congenital heart disease	1.4
Rejection of previous transplant	2.7
Other	2.0
Total	**100.0**

Table 2.

FUTURE DIRECTIONS

Although successful in the treatment of congestive heart failure, heart transplantation has several limitations including donor organ scarcity, rejection/infection, and transplant arterial occlusive disease. It is estimated by the National Institutes of Health in the United States that 35,000 people less than 70 years of age will develop congestive heart failure and could benefit from heart transplant or a mechanical assist device. Unfortunately, only 2000 transplants are performed annually in the United States, a number that has not increased over the last three years.

This plateau is primarily attributed to a limited pool of donors. Due to the shortage of donor organs, the length of time on the waiting list for patients is increasing. Consequently, only 40% of patients who are listed for transplantation actually receive a new heart. Sixty percent never make it to transplantation. Of the remaining 60%, half will die while still on the transplant list. The mode of death is congestive heart failure or an arrythmia leading to sudden death. The remaining half are taken off the list for medical reasons that contraindicate cardiac transplantation and are presumed to die while off the list.

Methods to increase the donor pool have concentrated on educating the general population to donate organs and on instructing hospital personnel to contact proper procurement agencies when a potential donor becomes available. Another method to increase the donor pool is to use hearts that in the past would not have been used for transplantation.

Preservation solutions, such as the University of Wisconsin solution (UWS), improve cardiac preservation beyond the currently acceptable ischemic period of four hours. In experimental baboon transplants, hearts have been able to be preserved for up to 18 hours (compared to eight hours using a standard solution) with good myocardial function. This solution will allow for longer ischemic times so donor hearts can be obtained from further distances, allowing for flexibility in timing of donor and recipient operations. For example, a donor heart was obtained from western Canada and successfully transplanted at TUH. It had been turned down by other centers because of the long distance and subsequently extended ischemic time involved before transplantation. Furthermore, improved preservation will also allow use of hearts that may be at high risk for initial donor organ failure using conventional preservation techniques.[3]

Another reason hearts are not used is global myocardial dysfunction manifested by large inotropic requirement. This may occur in the setting of brain death due to neurohormonal disturbances and an altered hormonal milieu. Experimental studies from Novitsky and colleagues have shown that infusion of triiodothyronine (T3) into donors may improve myocardial function, and allow use of organs that might previously have been turned down for transplantation.[4]

Another reason to refuse a donor heart is the potential presence of atherosclerotic disease. At TUH, we have used angioscopy when donor hospital catheterization is unavailable to determine the presence and degree of coronary artery disease and procure organs from such donors with surprising salvage. If diffuse disease is present, the heart is not used. However, if focal lesions with good myocardial function are present on echocardiogram, bypass grafting during transplantation may be performed in the appropriate clinical situation.

Throughout a transplant patient's life, a delicate balance exists between rejection and infection. Many of the problems that occur from immunosuppression result because the actual immune response of the patient to the donor heart is not measured. Rather, what is measured is CyA levels and white blood cell count. Therefore, better methods to detect the immunosuppressive interaction between donor and recipient are needed. Until now, rejection is only detected with endomyocardial biopsies, which is an invasive procedure and exhibits rejection only after cellular injury is present. Therefore, other noninvasive methods to measure or predict rejection before the myocardium is significantly injured are essential. Some newer concepts include: the peak R wave amplitude, the change in refractory period needed to re-excite the atria, echocardiographic measurements such as wall thickness and time to diastolic relaxation, and possible use of magnetic resonance imaging (MRI) or position-emission tomography (PET) scanning to look for altered metabolism. Approaches that use immunologic markers have also been tried but have yet to be applied clinically. These include measurements of total lymphocyte count by flow cytometry, the ratio of the helper to the suppressor T-lymphocytes, and IL-2 receptor levels that are suppressed by CyA.

Finally, perhaps more focused methods of immunosuppression are being investigated to replace or add to the common triple regimen of CyA, Imuran, and steroids in an effort to fight rejection and decrease the observed incidence of infection. These newer experimental agents include FK506, which has been shown to have similar immunosuppressive effects to CyA. It is reported to have less nephrotoxicity and hepatotoxicity, but this has not been shown in a comparative clinical trial against CyA. Other potential immunosuppressive

Rejection as Measured by Endomyocardial Biopsy

Grade	New Nomenclature	Old Nomenclature
0	No rejection	No rejection
I	A = Focal (perivascular or interstitial infiltrate) B = Diffuse but sparse infiltrate	Mild rejection
II	One focus only with aggressive infiltration and/or focal myocyte damage	"Focal" moderate rejection
III	A = Multifocal aggressive infiltrates B = diffuse inflammatory process	"Low" moderate rejection "Borderline/severe"
IV	Diffuse, aggressive, polymorphous ± oedema ± hemorrhage ± vasculitis	"Severe acute" rejection
Denoted by a lesser grade		"Resolving" rejection
Denoted by Grade 0		"Resolved" rejection

Table 3.

drugs include Rapamycin, Cyclosporin G, and OKT4 (a monoclonal antibody against the T-helper lymphocytes). Although promising, none of these drugs have yet made a large clinical impact. Other methods for immunosuppression such as photophoresis have been tried. Photophoresis has been shown to reverse acute rejection without administration of steroids. This method of immunosuppression has been shown to be effective in treating the humoral component of rejection, but its effect on the cellular component still needs to be investigated.

The greatest limitation over longer periods for heart transplantation is the development of coronary arteriopathy, a concentric type of narrowing of the vessels that can be seen over a period of time. Approximately 40% of patients at five years have some degree of coronary arteriopathy that involves the small as well as large arteries and is not amenable to conventional revascularization. The only current treatment for graft atherosclerosis is re-transplantation. The cause of this vasculopathy is thought to be a chronic, low-grade cellular or humoral rejection not prevented or controlled by present immunosuppressive regimens. Currently, no acceptable methods exist to prevent transplant arteriopathy, but many ideas are on the horizon. They include attacking the humoral mechanism of rejection, better control of hypertension, better control of hyperlipidemia, and decreasing the vasoreactivity of CyA. At Temple University, we have started a systematic approach of early digital quantitative angiography on post-transplant patients, which is measured yearly or at shorter intervals if the patient's stress thallium test is abnormal. By doing quantitative digital angiography it is possible to detect even slight concentric hypertrophy in these coronary vessels and decide whether a patient is developing transplant arteriopathy. Several protocols in the process of being instituted for stabilizing transplant arteriopathy include: photophoresis, addition of methotrexate to the current immunosuppressive regimen, and pentioxifylline to decrease vasoreactivity of CyA.

Despite all these potential advances, immunology and donor organ shortage will always be limiting factors for transplantation. Unless immunologically nonreactive animals are discovered, xenotransplantation will not become a clinical reality. Cardiomyoplasty has not been shown to consistently produce objective improvements in cardiac function. Mechanical assist devices, however, may prove to be the best alternative to transplantation.

It would be difficult for a total artificial heart to ever become practical for chronic support because a completely reliable device without margin for mechanical failure could be an unattainable feat. Therefore, the best devices currently available are "assist devices" in that they do not replace the heart but augment ventricular function. If they do have mechanical failure, the patient's own heart will act as a backup until medical attention is sought. Of the devices available in the United States, the Thoratec® and the Abiomed VAD® systems are designed for short-term use as a "bridge to transplant" or postcardiotomy. Implantable devices offer the best scope as an alternative to transplant. The two devices that currently fit into this category are the Novacor 100P (Novacor Division, Baxter Healthcare Corporation, Oakland, Ca) and the TCI HeartMate systems (Thermo Cardiosystems, Inc., Woburn, MA) (Figure 1). They are both paracorporeal implantable devices used currently as "bridge to transplant." The most common complications are right heart failure (because these systems are only left ventricular systems), bleeding, and thromboembolism. The TCI device is superior with regard to a much lower rate of cerebrovascular accidents (3% vs. 25% with Novacor) despite anticoagulation. The TCI pneumatic device is approved for human use; the electrical system that will allow complete unteetered mobility is investigational. To date, ten patients have been supported with the electrical system—the longest supported for 504 days.[5] In addition to being readily available without donor issues and not requir-

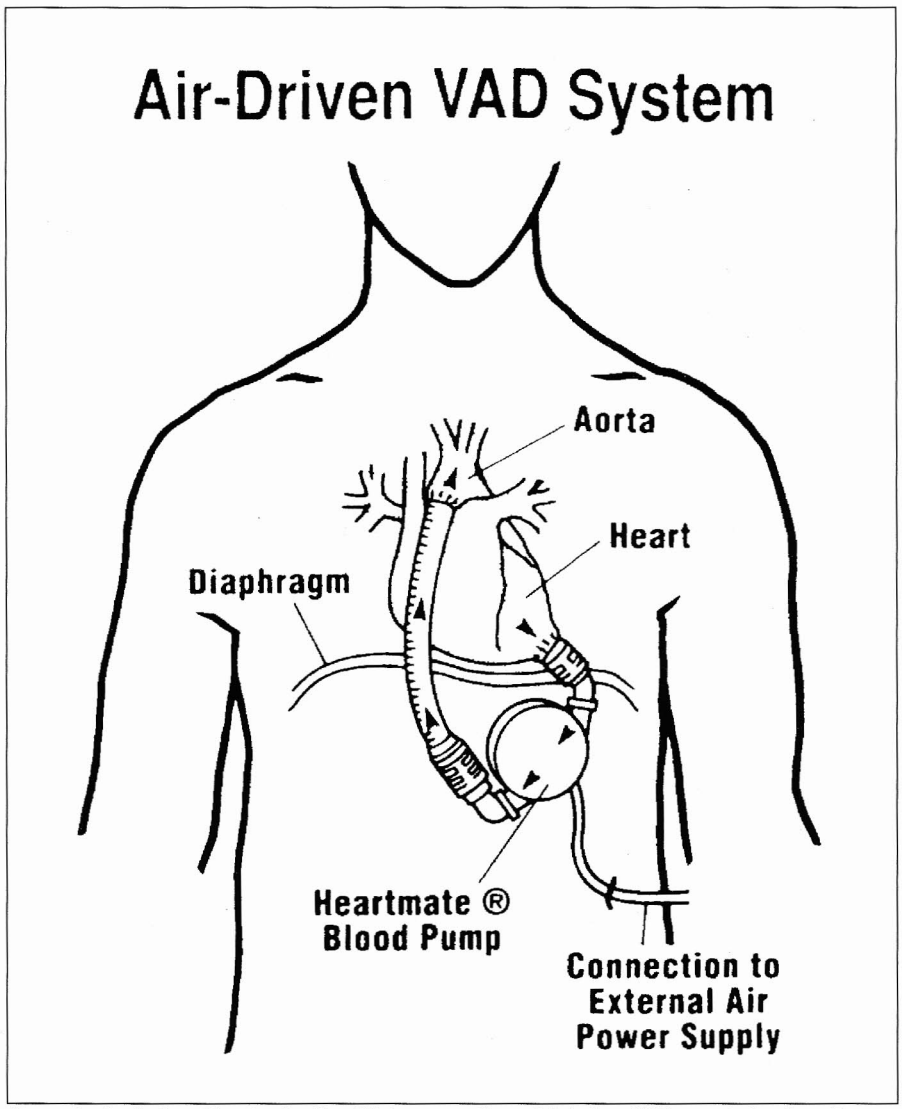

Figure 1. Implant position for the HeartMate pneumatic assist device. (With permission from Thermo Cardiosystems, Inc., Woburn, MA.)

ing immunosuppression, left ventricular assist device (LVAD) support will be cheaper than transplantation, especially considering the cost of cyclosporine and constant monitoring. Permanent mechanical circulatory assistance is clearly going to be a leading frontier of cardiothoracic surgery into the next century and beyond.

CONCLUSIONS

Heart transplantation is now a clinical reality and is the treatment of choice for end-stage heart disease that is refractory is maximal medical management. Active investigation continues by medical and research experts to expand the donor pool, improve tissue preservation, improve immunosuppression, and decrease transplant arteriopathy. Mechanical assistance looms in the near future as a potential alternative to transplantation and may eventually be in the forefront of surgical management of end-stage heart disease. STI

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