Clinical Cardiology: New Frontiers

Mechanical Circulatory Support and Cardiac Transplantation

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Congestive heart failure is not a specific disease but rather a clinical syndrome of diverse etiologies. This syndrome is characterized by ventricular dysfunction leading to decreased cardiac output; consequent neurohumoral activation leading to salt and water retention, with congestion in the pulmonary and systemic circulation; a “vicious circle” of blood-flow maldistribution; and eventual hypoperfusion of vital organs. In North America, the most common underlying cause of CHF is atherosclerosis resulting in ischemic dysfunction of the myocardium. A second important underlying cause is valvular malfunction leading to pressure and/or volume overloading of the ventricles. Other important causes of CHF include primary myocardial disease (idiopathic, infiltrative, or inflammatory) and congenital cardiac malformations.

The incidence of heart failure is increasing, probably not only because of aging of the population, but also because effective palliative therapies are extending the lives of many CHF victims. In addition, many patients have undergone successful emergency intervention for otherwise fatal acute coronary events only to develop CHF at a later date. The American Heart Association estimates that at least 400,000 new cases of CHF are diagnosed each year. In the United States, more than $34 billion is spent each year for the medical care of CHF patients. Despite the advent of more effective therapy, CHF is the principal cause of 40,000 deaths per year in the United States and is a contributing factor in another 250,000 deaths.

The short-term goal of CHF therapy is to improve the patient’s quality of life by relieving his or her symptoms. Current medical therapy is highly successful in achieving this goal. Such therapy has also had limited success in achieving the longer-term goal of extending these patients’ lives. Despite these advances, however, most patients eventually succumb to CHF. Many patients, because of their relative youth and lack of comorbid conditions, become candidates for cardiac replacement therapy, which is currently limited to allotransplantation. Transplant candidates whose disease reaches its final stage before an appropriate donor heart becomes available are considered eligible for temporary MCS. The long-term MCS systems presently in clinical use serve as temporary “bridges” to transplantation. In the future, such devices will likely become viable alternatives for permanent nonbiological cardiac replacement; indeed, the Institute of Medicine estimates that between 35,000 and 70,000 Americans each year could benefit from long-term MCS. Genetically altered animal organs may also eventually provide another alternative for biological replacement of the heart.

Over the past 4 decades, MCS and cardiac transplantation have evolved, somewhat in parallel, toward the goal of lowering the mortality and morbidity associated with CHF. By combining these two surgical interventions, physicians have improved the length and quality of many lives, and additional patients are potentially treatable with these methods. This review describes the current status of cardiac transplantation and mechanical circulatory assistance, examines the major persisting clinical problems in these fields, and discusses the clinical advances to be expected during the coming years.

Mechanical Circulatory Support

Background

MCS was first used clinically in 1953 with the implementation of cardiopulmonary bypass. This breakthrough led to numerous surgical treatments for a variety of cardiac disorders. The success of cardiopulmonary bypass stimulated research into other innovative techniques for supporting the circulation. Counterpulsation with the intra-aortic balloon pump was first applied clinically in 1967 to support patients with acute heart failure. In the 1960s, CHF patients occasionally were temporarily supported by cardiopulmonary bypass, an implantable VAS, or a TAH. Although the overall success rate was limited, this early experience did prove that MCS could adequately sustain a patient’s circulation until cardiac function recovered or a donor heart could be obtained. During the 1970s, major hurdles related to immunosuppression prevented heart transplantation from becoming a reasonable treatment option. During this time, research efforts, made possible by support from the NHLBI, were directed toward producing MCS systems for long-term use or for permanent cardiac replacement. In the early 1980s, the introduction of cyclosporine-based immunosuppression allowed heart transplantation to become a widely accepted therapeutic alternative. During that same decade, clinical
trials were initiated to evaluate the safety and efficacy of MCS systems in supporting terminally ill transplant candidates until a suitable donor heart could be found. Today, after nearly 30 years of research and development, MCS systems are in widespread clinical use as bridges to transplantation or myocardial recovery. Despite numerous design modifications and refinements, an ideal system has not yet evolved; nevertheless, current systems can adequately support many heart failure patients.

MCS Systems
The MCS systems currently being used as bridges to transplantation resulted from the NHLBI program for the development of long-term circulatory support initiated in the 1970s. Two of these systems, the HeartMate (Thermo Cardiovascular Inc) and the Novacor (Baxter Healthcare Corp), are fully implantable LVASs, which permit mechanical “bypass” of the left ventricle without removal of the native heart. The Thoratec VAS (Thoratec Laboratories, Inc) is a paracorporeal system that can provide univentricular or biventricular support. The implantable CardioWest TAH replaces the entire native heart during the support period. All 4 of these systems can provide physiological circulatory support for extended periods, yet each has unique advantages and disadvantages. As the waiting time for donor hearts has lengthened, physicians have gained increased experience with the long-term benefits and problems of MCS.

HeartMate LVAS
The HeartMate is an implantable, pulsatile LVAS designed to be portable and easy to operate. The blood-contacting surfaces that line the blood pumps are textured to encourage the deposition of circulating cells. A uniform autologous tissue lining is established on all the blood-contacting surfaces of the pump, minimizing thrombus formation and bacterial colonization. The inflow and outflow conduits each contain a 25-mm porcine valve to ensure unidirectional blood flow. Presently, 2 versions of the HeartMate (Figures 1 and 2) are in clinical use: an implantable pneumatic version (IP-LVAS) and a vented electric version (VE-LVAS). The 2 models use the same blood pump and differ primarily in their method of actuation. With the IP-LVAS, an external drive console sends pulses of air that cause the pump’s flexible diaphragm to move upward, pressurizing the blood chamber and causing the ejection of blood into the aorta. In contrast, with the VE-LVAS, diaphragm movement and blood ejection depend on an electric motor positioned below the diaphragm. An external vent equalizes the air pressure and permits emergency pneumatic actuation. The external system controller and batteries in the VE-LVAS are small and lightweight, allowing the patient nearly unlimited mobility.

The patient is on cardiopulmonary bypass when the HeartMate is implanted. The pump is positioned below the left hemidiaphragm, either within the peritoneal cavity or in a preperitoneal pocket. The inflow tube crosses the diaphragm and is inserted in the apex of the left ventricle; a 20-mm Dacron outflow graft exits from the pump, crosses the diaphragm, and is anastomosed to the ascending aorta. After it has been externalized through the right or left abdominal wall, the driveline is connected to the external power and control unit. The maximum blood flow possible is 11.6 L/min for the IP-LVAS and 9.6 L/min for the VE-LVAS. An automatic mode may be used to maximize pump flow, or a fixed-rate mode may be used to provide a preset flow rate. During normal operation, the pump completely unloads the left ventricle and supports cardiac output at physiological levels. Because of the portability and ease of operation of the HeartMate, patients can be discharged to await heart transplantation outside the hospital.

The HeartMate IP-LVAS is approved by the FDA for use as a bridge to transplantation. As of April 1998, it had been...
used for this purpose in 944 patients worldwide. Owing to the unique lining and flow characteristics of this pump, only minimal anticoagulation (with aspirin or other platelet inhibitors) is required. Patients can be supported for extended periods with a relatively low risk of thromboembolism or mechanical failure.

**Novacor LVAS**

The Novacor LVAS is a portable, implantable pump designed for long-term use (Figure 3).\(^{20}\) It differs significantly from the HeartMate in its method of pump actuation and use of a smooth blood-contacting surface. During pump systole, 2 opposing pusher plates compress a seamless polyurethane blood sac, causing ejection of blood. Unidirectional flow is achieved with 21-mm bioprosthetic valved conduits. A percutaneous lead contains the necessary electrical wires and a vent. Transducers within the pump send signals to the external control unit to regulate the pumping rate and to display the pumping parameters. The system can be operated in either fixed-rate, synchronous, or fill-to-empty mode. In 1993, the Novacor LVAS was converted from a console-operated system into a wearable or portable system. The wearable system eliminates the need for a bulky console by incorporating a compact controller and rechargeable power packs that are worn on the patient’s belt.\(^{21}\) The wearable system is designed for out-of-hospital use and can be monitored with a bedside monitor.

The Novacor pump is surgically placed in a preperitoneal pocket just anterior to the posterior rectus sheath, between the left costal margin and the iliac crest.\(^{22}\) Cardiopulmonary bypass is necessary during implantation, and the surgical inflow and outflow connections are similar to those described for the HeartMate. A percutaneous driveline is brought out through the right abdominal wall and attached to the external control console. The synchronous and fill-to-empty modes provide sufficient and variable cardiac output by responding to increased physiological demands. During device use, anticoagulation with heparin and later with warfarin and antiplatelet agents is necessary to prevent thromboembolism. During long-term support, ambulatory patients can be discharged and live outside the hospital while awaiting a suitable donor heart.\(^{23}\)

**Thoratec VAS**

The Thoratec VAS is a paracorporeal, pneumatically powered system configured for univentricular or biventricular support (Figure 4).\(^{24}\) It features a seamless polyurethane blood sac within a rigid polycarbonate housing. An external drive console sends pressurized air to the pump, which compresses the blood sac and causes blood to be ejected. Bjork-Shiley concavo-convex tilting-disk valves within the inflow and outflow conduits ensure unidirectional blood flow. The Thoratec VAS can be operated in fixed-rate, volume, or synchronous mode. Volume mode is preferred because it maximizes support of the cardiac output. Synchronous mode is intended for weaning patients from support. Although the console can function automatically to achieve maximum pump flows, the operator must adjust the systolic driving pressure and diastolic vacuum pressure. The pump has a maximum stroke volume of 65 mL and a maximum flow of 6.5 L/min.

The Thoratec VAS is implanted through a median sternotomy, but cardiopulmonary bypass is not required in all cases.\(^{25}\) For left ventricular support, the pump inflow cannula can be placed in the left ventricular apex or the left atrium, and the pump outflow conduit is anastomosed to the ascending aorta. For right ventricular support, a large-bore cannula is placed in the right atrium, and the outflow conduit is sewn to the main pulmonary artery. After they have been externalized subcostally, the inflow and outflow cannulas are connected to the pump(s), which reside(s) externally on the anterior surface of the abdomen. During the support period, anticoagulation with dextran, heparin, warfarin, and dipyridamole is required. Patients may be ambulatory,\(^{26}\) but their mobility is limited by the size of the drive console and the paracorporeal position of the pump(s).

The FDA has approved the Thoratec VAS for use as a bridge to heart transplantation. In the future, use of this system may be extended to include patients with acute heart
failure, including postcardiotomy cardiogenic shock. New system designs that are currently being tested include a small, portable drive console and implantable blood pumps.

CardioWest TAH

The CardioWest TAH, formerly called the Jarvik or Symbion TAH, is a pulsatile biventricular cardiac replacement system (Figure 5).27 Its rigid polyurethane pump contains a smooth, flexible polyurethane diaphragm that separates the blood and air chambers. Two Medtronic-Hall mechanical valves provide unidirectional blood flow. Compressed air from the external drive console moves the diaphragm upward, pressurizing the blood chamber and causing ejection of blood. The pump has a maximum stroke volume of 70 mL and a maximum flow rate of 15 L/min, although the average flow rate is $\ldots$ 28 L/min. The operator can adjust the pump rate, duration of systole, and driving pressure to achieve optimal flow conditions.

The TAH is surgically implanted in the mediastinal space after the ventricles have been excised, with atrial cuffs retained. The pneumatic drivelines are externalized percutaneously and attached to the drive console. Anticoagulation with dipyridamole, heparin, and warfarin is necessary to prevent thrombus formation. Patients may be ambulatory, but their mobility is greatly restricted by the large drive console.

The CardioWest TAH is currently undergoing an FDA-approved clinical investigation at select institutions in the United States. In other countries, this TAH is being used at some centers as a bridge to heart transplantation. A small, portable drive console is being developed for out-of-hospital use.

Major Differences Between MCS Systems

The Novacor and HeartMate systems are very similar with respect to function, implantation techniques, and intended use. The HeartMate is different in that it uses textured blood-contacting surfaces to allow the development of a “pseudoneointimal” lining that enhances biocompatibility. All the other MCS pumps have smooth blood-contacting surfaces that necessitate anticoagulant therapy. During prolonged HeartMate support, patient care can be managed safely with minimal or no anticoagulation.13,29 Another important difference concerns the availability of these systems in the United States. The FDA has approved the Thoratec VAS and HeartMate IP-LVAS for commercial use in bridge-to-transplant cases only. The Novacor LVAS, HeartMate VE-LVAS, and CardioWest TAH currently remain in clinical trials under an investigational device exemption, which limits their use to selected centers. Whereas the Novacor and HeartMate provide left ventricular support, the Thoratec and CardioWest systems offer biventricular support. The most important difference between the Thoratec VAS and the CardioWest TAH involves pump position and the need for removal of the native heart when the TAH is used. The Thoratec pump(s) reside(s) extracorporeally, and the CardioWest TAH is placed within the mediastinal space. Moreover, the Thoratec system can be used for right-ventricular, left-ventricular, or biventricular support, but the CardioWest TAH offers only biventricular support.

MCS: Clinical Results Summary

Over the past 15 years, extensive clinical experience has been gained with the above-described bridge-to-transplant systems in the United States and Europe (Table 1). The European30 and international31 voluntary registries have reported similar results with numerous systems. The overall bridge-to-transplant population is supported by a wide variety of MCS systems. The transplantation rate, or percentage of patients who eventually undergo transplantation, ranges from 62% to 69%, and the rate of hospital discharge after transplantation is 65% to 69%. In a subset of patients supported by systems

<table>
<thead>
<tr>
<th>System</th>
<th>Clinical Trials Initiated, year</th>
<th>No. of Patients Supported</th>
<th>Cumulative Experience, y</th>
<th>Regulatory Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>HeartMate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP-LVAS</td>
<td>1986</td>
<td>865</td>
<td>185</td>
<td>Approved 1994</td>
</tr>
<tr>
<td>VE-LVAS</td>
<td>1991</td>
<td>336</td>
<td>101</td>
<td>Approval pending</td>
</tr>
<tr>
<td>Novacor</td>
<td>1984</td>
<td>768</td>
<td>177</td>
<td>IDE in progress</td>
</tr>
<tr>
<td>Thoratec VAD</td>
<td>1982</td>
<td>620</td>
<td>50</td>
<td>Approved 1995</td>
</tr>
<tr>
<td>CardioWest TAH</td>
<td>1993</td>
<td>101 (198*)</td>
<td>10 (13*)</td>
<td>IDE in progress</td>
</tr>
</tbody>
</table>

*IDE indicates investigational device exemption; VAD, ventricular assist device.

These figures reflect experience gained from 1985 to 1992, when this pump was known as the Symbion TAH.
designed specifically as bridging devices, the transplantation rate is similar (60%), but the hospital discharge rate is 89%.28 Patients who require only isolated left ventricular assistance rather than biventricular assistance have much better rates of transplantation and discharge. Those who require isolated right heart support or biventricular support with hybrid MCS systems have transplantation rates of 30% to 40% and hospital discharge rates of 0% to 60%. For patients with the 4 systems described above (except those undergoing biventricular support with the Thoratec VAS), the hospital discharge rate after cardiac transplantation ranges from 89% to 93%. This rate is comparable to that seen in the general cardiac transplant population not requiring preoperative MCS. The primary reason for the better survival rate with the implantable LVAS is that patients can be safely supported for longer durations, allowing complete physical rehabilitation before heart transplantation.32,33 In 1 series, LVAS recipients in NYHA functional class I at the time of transplantation had survival rates of 100% at 2 years.34

The only controlled study of the effects of LVAS support in bridge-to-transplant patients was performed with the IP-LVAS.32 The control group met all the criteria for MCS, but because of logistical problems, no device was available for them. These patients were compared with a similar cohort that underwent MCS during the same period. Despite the added morbidity and mortality associated with a major surgical intervention, the device-supported patients had a significantly better survival rate than did the control group (71% versus 36%, respectively, 90 days after transplantation). Interestingly, the surviving control patients all received a heart transplant within 12 days of becoming eligible for the study.

Complications
In the bridge-to-transplant population, the most frequent complications are bleeding, infection, thromboembolism, renal failure, hemolysis, technical problems, and neurological dysfunction.30,31 The most prevalent and important complications are bleeding and infection. Bleeding rates, which are as high as 60%,30,31,35 are related to coagulopathy due to hepatic dysfunction, the extensive surgical procedures required for MCS, and the combined effects of cardiopulmonary bypass and blood-pump rheology on platelet activation. Patients who require biventricular assistance are more susceptible to bleeding complications than those who need univentricular assistance.9 Infection rates generally range from 30% to 40%,35–37 and contribute to significant morbidity.38 Although infections can be frequent and severe during MCS, they do not preclude successful cardiac transplantation.39–41 Severe infections typically occur in patients with comorbidities such as bleeding and multiple organ failure.32,43

Recovery and Rehabilitation
Over the past decade, the duration of pretransplant MCS has lengthened considerably because, as a whole, transplant candidates are waiting longer for donor organs. Moreover, experienced physicians have gained confidence in the reliability of MCS systems; with these systems and improved medical management, patients can safely wait for many months until a donor heart becomes available. For those with multiple organ dysfunction secondary to prolonged heart failure, complete recovery of secondary organ function may necessitate weeks to months of MCS.32,33 The duration of circulatory assistance required for end-organ recovery and physical rehabilitation varies greatly from 1 patient to another and is somewhat dependent on the duration and severity of CHF. Patients who return to NYHA class I during MCS may await a suitable heart donor while living outside the hospital.19,23 In these cases, hospital discharge improves the patient’s psychosocial status, reduces costs, and decreases the incidence of certain serious complications such as nosocomial infections.44,45

Patients who have significant improvement in their physical status while undergoing MCS often have a similar degree of improvement in their psychological status. However, those who are not rehabilitated fully and who have frequent medical complications may experience stress, major depression, organic mental syndromes, and adjustment disorders.46 The required degree of psychosocial support varies greatly between patients and changes with the duration of MCS. Patients who remain hospitalized for extended periods become more susceptible to stress and depression. Generally, patients readily accept MCS because they strongly believe that it is lifesaving. Patients and their family members rarely complain about the inconvenience imposed by MCS and its associated equipment.

The anxiety of awaiting a suitable donor heart can be severe for patients and their families. By returning to a relatively normal lifestyle during the MCS period, patients have a greatly reduced level of anxiety, stress, and depression. Presently, recipients of the HeartMate and Novacor LVASs can live outside the hospital, in their own homes, while awaiting heart transplantation. In many of these cases, patients have been able to participate in social events and return to employment. As a result, their quality of life has been greatly enhanced.19,47

Cardiac Transplantation
Allocation of Donor Hearts
Although, as noted above, potentially 40 000 patients per year die of heart disease that might otherwise be treatable with transplantation,48 only ~2500 donor hearts become available annually.49 Because of this disparity between demand and supply, recipient selection criteria and donor allocation decisions are crucial medical, ethical, and societal issues. The need for a fair, consistent, and ethical system of donor allocation was the main factor that led to establishment of a national organ procurement and distribution network, UNOS. Since 1986, this private organization has had a federal contract within the United States to maintain an organ procurement and transplantation network and a scientific registry for organ transplantation. The organization’s policies are under direct review by the US Department of Health and Human Services and are administered by that department’s Division of Organ Transplantation. UNOS maintains a national computerized list of patients awaiting various organs, and it coordinates organ allocation according to established,
consistent, frequently reviewed criteria. Policy decisions are made in public forums, with input from a variety of medical, legal, and patient constituencies. Currently, allocation of available donor hearts is based on the severity of the recipient’s illness, the recipient’s length of time on the waiting list, ABO blood-type compatibility between donor and recipient, and an overall body-size match between donor and recipient. Priority is given to those who require significant inotropic support or MCS: all others are accorded secondary consideration, on an equal basis.

Because of the limited ischemic times allowed for heart allografts (maximum, ∼6 hours), a truly national donor-heart distribution scheme is impossible in a country as large as the United States. Instead, allocation is prioritized geographically, with preference given to local recipients or, when no local recipients exist, to those within areas in succeeding 500-mile radii from the donor hospital. Because of time limitations, as well as the relatively small numbers of organs involved, many nuances of donor/recipient screening (such as matching for human lymphocyte antigens and cytomegaloviral status) are not practical.

Recipient Selection
Owing to the lack of suitable donor hearts and the improving survival prospects for CHF patients, it has become increasingly important to stratify the risk of patients referred for heart transplantation. For critically ill patients who require prolonged hospitalization for inotropic support or MCS, eligibility is limited only by contraindications to transplantation. For patients who are less severely ill, greater selectivity is needed, and a variety of guidelines have been proposed. In deciding to place a patient on the waiting list for heart transplantation, the physician must weigh the magnitude of the patient’s need against the potential benefits of transplantation. When a patient is first considered for heart transplantation, the initial consideration is to exclude (or treat) any potentially reversible causes of heart failure. Treatment options may include high-risk revascularization for ischemic heart disease in patients with a viable myocardium, surgery for severe valvular lesions that may be causing ventricular dysfunction, or medical therapy for inflammatory or primary myocardial disease. In patients with nonischemic cardiomyopathy, an endomyocardial biopsy may confirm or exclude other potentially reversible causes of myocardial dysfunction, such as hemochromatosis or sarcoidosis; the biopsy can also diagnose conditions that may preclude heart transplantation, such as amyloidosis, which recurs frequently in allograft recipients and may be rapidly fatal.

Once the patient’s therapy has been maximized, assessment of his or her prognosis without transplantation can rely on the following objective measurements: left ventricular ejection fraction (the prognosis is markedly worse for patients with an ejection fraction <20%), level of exercise tolerance (the prognosis is very poor for patients with a V̇O₂ max <14 mL·kg⁻¹·min⁻¹ during formal exercise testing), hemodynamic data, and parameters of neurohumoral activation. No single test or measurement can identify end-stage heart failure involving an extremely poor short-term prognosis. In assessing ambulatory transplant candidates, physicians generally rely on several or all of the above-mentioned factors.

The most common indications for transplantation are idiopathic dilated cardiomyopathy and ischemic heart disease with left ventricular dysfunction, each of which accounts for nearly half of the transplant population in any given year. Less common indications for transplantation include congenital malformations, giant cell myocarditis, unetectable cardiac tumors, isolated cardiac sarcoidosis, and restrictive or hypertrophic cardiomyopathy.

Once a patient undergoing optimal medical management is deemed to have an extremely poor prognosis, other criteria are applied to determine whether the patient can be expected to benefit from cardiac transplantation. Unfortunately, many patients with chronic heart failure develop pulmonary hypertension. Early in the heart transplant era, physicians discovered that a normal donor right ventricle is not always able to increase its external workload acutely in response to elevated pulmonary pressures. There is no single specific level of PVR beyond which the donated right ventricle will always undergo acute failure, but most programs defer patients with a PVR in excess of 4 to 6 Wood units, and many programs limit the transpulmonary gradient as well. In recent years, physicians have accepted the concept that some reversibility of elevated PVR is possible in patients with chronic heart failure, and patients with reversible PVR elevation have done well after transplantation. Therefore, those with an elevated PVR during catheterization of the right side of the heart should undergo pharmacological maneuvers with prostacyclin or nitroprusside during catheterization in an attempt to demonstrate reversibility of the PVR elevation. Patients whose PVR can be reduced to the acceptable range without concomitant severe systemic hypotension are suitable candidates for transplantation.

A number of other contraindications to transplantation are generally accepted, some being relative and others absolute. Most of these factors have been discussed by the American Heart Association Committee on Cardiac Transplantation and the American College of Cardiology’s Bethesda Conference on Cardiac Transplantation. With time and increasing experience, several of the original exclusion criteria, such as older age and the presence of insulin-requiring diabetes, have been challenged; nevertheless, elderly or diabetic patients are carefully screened with respect to physiological status and secondary organ or vascular complications. Because of the limited donor supply, there probably should be an upper age limit for transplant candidates, but there is no consensus in the United States regarding what that limit should be. Some experts have proposed that age be considered in organ allocation, so that older organs would be given to older recipients. To do so, however, would further complicate an already difficult medical and ethical decision-making process.

Absolute contraindications to heart transplantation include other medical conditions that would markedly and separately limit the patient’s survival, such as ongoing malignancy or irreversible pulmonary, hepatic, or neurological disease. Active infection is usually a temporary contraindication to transplantation because immunosuppression would make any...
infection difficult to control. Currently, HIV infection is probably the only infectious problem that is a permanent contraindication. Relative contraindications include severe obesity or osteoporosis, psychosocial instability or substance abuse, active peptic ulcer disease, a history of malignancy with an uncertain prognosis for recurrence, and severe peripheral vascular disease.

Survival Rates
As of 1982, meaningful numbers of cardiac transplant procedures began to be accrued into the registry of the International Society of Heart Transplantation. Since that time, these numbers have been updated annually. According to the most recent data, based on >40,000 patients treated over a 15-year period, 1-year survival rates after orthotopic heart transplantation have averaged 79%. Figure 6 shows the actuarial survival rates for the overall patient population of 34,180 persons. The survival rate markedly improved for patients undergoing transplantation after 1986, but no further increase in survival rate has been seen in the more recent cohorts, here defined as patients operated on after 1991. Figure 7 shows similar actuarial survival curves for the pediatric population, which is divided into subsets according to age at the time of transplantation. The highest mortality occurred in the youngest patients; older children (5 to 16 years of age) had survival rates almost identical to those of adults. Figure 8 shows actuarial survival curves for the adult population, which is subdivided according to age. The survival rate decreased for each succeeding decade of life, and the cohort over age 65 years had a highly significant decrease in survival.

Rehabilitation Rates
Figure 9 shows data from the registry of the International Society for Heart and Lung Transplantation regarding rates of rehabilitation of heart transplant recipients between 1994 and 1996. Most patients returned to NYHA class I status and resumed their normal occupational, physical, and social pursuits. Ninety percent had no limitations in activity at 1 and 2 years postoperatively. In the United States, however, the healthcare system makes it hard for transplant recipients to obtain health insurance, and such insurance is generally tied to employment. Therefore, many able-bodied transplant recipients are virtually unemployable, with only 30% working full-time 1 year after transplantation and 34% working full-time at 2 years (Figure 10).

Causes of Death
Causes of death after heart transplantation vary according to the posttransplant interval. Most deaths during the first postoperative month are due to acute rejection, nonspecific graft failure, or multisystem organ failure. After the first month, infectious complications emerge as a major cause of morbidity and mortality. After the first postoperative year, malignancy and graft coronary disease become the main causes of death. It is hoped that more specific immunosuppressive modalities will soon become available to prevent these conditions and permit much longer survival.

Major Clinical Problems
As is evident from the causes of death noted above, several major clinical problems remain. The primary one, which

![Figure 6. Actuarial survival curves for heart transplant recipients, overall and divided into subsets according to year of transplant. (Reproduced with permission from Hosenpud et al.)](image)

![Figure 7. Actuarial survival curves for pediatric heart transplant recipients, divided into subsets according to age at time of transplant. (Reproduced with permission from Hosenpud et al.)](image)

![Figure 8. Actuarial survival curves for adult heart transplant recipients, divided into subsets according to age at time of transplant. (Reproduced with permission from Hosenpud et al.)](image)

![Figure 9. Heart transplant recipient functional status, United States data reported to the Registry of the International Society for Heart and Lung Transplantation between April 1994 and December 1996. (Reproduced with permission from Hosenpud et al.)](image)
TABLE 2. Typical Regimen for Surveillance Endomyocardial Biopsies After Heart Transplantation*

<table>
<thead>
<tr>
<th>Time</th>
<th>Frequency</th>
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</thead>
<tbody>
<tr>
<td>1st month</td>
<td>Weekly</td>
</tr>
<tr>
<td>2nd month</td>
<td>Biweekly</td>
</tr>
<tr>
<td>3rd to 6th month</td>
<td>Monthly</td>
</tr>
<tr>
<td>6th to 12th month</td>
<td>Quarterly</td>
</tr>
</tbody>
</table>

*Biopsies are also performed after each course of rejection therapy and as needed for clinical suspicion of rejection.

diffuse, concentric, and longitudinal distribution of the condition, angiography provides only a gross underestimate of its severity. Nevertheless, angiographic results have been correlated with an extremely poor prognosis. Although several measures have been shown to effectively decrease the incidence of this vasculopathy, effective strategies for treating or palliating established cases do not exist, and retransplantation is the only definitive therapy. Unfortunately, retransplantation is associated with decidedly inferior graft and patient survival rates. For this reason, experts have major ethical reservations about using scarce donor organs for this purpose.

Future of Cardiac Transplantation

Two factors can be expected to influence the future of cardiac transplantation. The first factor will be the advent of improved methods for suppressing the immune system, preferably with drugs or other less toxic modalities that entail less tendency toward graft vascular disease or chronic rejection. Although once thought to be unrealistic, induction of specific immune tolerance of a donor organ may become possible as the immune response becomes better understood and manipulated. The second influential factor will be the development and validation of alternatives to cardiac allotransplantation, as discussed below. Even if optimally utilized, available human donor hearts will never meet the increasing demand for cardiac replacement. For this reason, attention has become focused on alternative possibilities, including genetically altered animal organs and permanently implantable mechanical devices.

Issues and Controversies

MCS Use and Patient Selection

No current single MCS system is capable of treating the full spectrum of heart failure. At this time, it is neither financially nor technically feasible for all cardiovascular care centers to use all the available MCS systems. Ideally, transplant centers should have implantable systems for long-term support, short-term systems for acute heart failure, and a system capable of providing temporary right ventricular support. Other considerations include anticoagulation (if any), device portability, and the patient’s ability to leave the hospital during the support period.

Patient selection is a complex process, and universal criteria do not exist; experts generally agree, however, that the timing of device implantation in transplant candidates is crucial. For patients with acutely exacerbated heart failure, hasty implantation may be as unwise as waiting too long before implantation. For patients with a severely deranged coagulation profile and/or renal failure and fluid overload, the most prudent course is to resolve these conditions before implantation. Heart transplantation is least likely to be successful in CHF patients who have severely impaired renal, hepatic, and pulmonary function perioperatively. However, recovery from such secondary end-organ dysfunction occurs in many patients during MCS, so failure of 1 or more organs is not necessarily a contraindication to MCS. Risk factors that may lessen the patient’s chance of surviving to transplantation include coagulopathy, previous cardiac sur-
gery, pneumonia, and hepatic dysfunction. No reliable predictors have been found that can identify patients unlikely to survive MCS. Ambulatory CHF patients at high risk of sudden death or acute decompensation appear to be good candidates for support. In fact, these patients may avoid cardiac transplantation by undergoing long-term MCS followed by eventual removal of the device. With this ambulatory population, the greatest challenge is appropriate identification of candidates.

Alternatives to Cardiac Transplantation
Possible alternatives to cardiac allotransplantation include xenotransplantation, cardiomyoplasty, left ventricular reduction surgery, and long-term MCS. Another possibility is “bridging to recovery,” in which the MCS device would be electively removed after months or years of support, when sufficient cardiac function had been regained.

Xenotransplantation involves the replacement of a human heart with a nonhuman one. Strong immunologic barriers currently limit the use of nonhuman hearts, but pioneering genetic researchers are producing transgenic animals whose genetic materials incorporate important human epitopes. When expressed, several of these epitopes may ameliorate or abrogate the intensity of hyperacute xenograft rejection. Because rejection depends on the activation of complement, one current approach is to insert regulatory proteins for human complement into the porcine genome; the altered pigs might be controlled by conventional immunosuppression is uncertain. It also remains unclear whether fundamental physiological incompatibilities may preclude adequate functioning of a cardiac xenograft. Recently, however, the Cambridge group documented survival and normal function of a porcine orthotopic cardiac xenograft in a nonhuman primate model for several months. Although xenotransplantation may be a common clinical practice someday, it is hard to predict when that day may be; when it does occur, organ replacement will have a giant leap forward. Currently, concerns about the epidemiological risks of xenosis, or the transfer of animal infections to the human population, have led to calls for a moratorium on human xenotransplantation until these ethical, societal, and medical issues are resolved.

Cardiomyoplasty is a surgical procedure that involves translocation and wrapping of the latissimus dorsi muscle pedicle around the heart to assist the cardiac pumping action. The “trained” latissimus dorsi muscle is electronically paced and contracts synchronously with the heart to augment systolic function. Postoperatively, there is a 3-week delay before the latissimus dorsi begins to augment blood flow in response to increased work. Therefore, there is a functional delay in circulatory assistance when this approach is used. Cardiomyoplasty has been shown to improve the patient’s symptoms and quality of life but does not appear to improve survival. The improvement in symptoms may relate not only to improved systolic function but also to a reduction of ventricular wall stress owing to diastolic “girdling.” Cardiomyoplasty does not appear to have a lasting effect on primary myocardial disease, and progressive heart failure limits postoperative survival. During the first year after surgery, survival rates range from 75% to 80%. During the subsequent 2 or 3 years, however, there is a consistent decrease in survival rate. Outcomes are affected by the severity of heart failure at the time of the cardiomyoplasty. Determination of the appropriate role of this procedure awaits the results of randomized prospective studies.

Partial left ventricular reduction (the Batista procedure) entails removing a segment of the left ventricular myocardium and repairing the mitral valve. The objective of the operation is to reduce the diameter of the left ventricular cavity and to decrease mitral regurgitation. Ventricular pressure and wall stress are decreased after this operation, and patients with dilated cardiomyopathy have significantly increased left ventricular ejection fraction and cardiac index and improved NYHA status in the short term. In Brazil, where this procedure was devised, the operative mortality is 15%; in the United States, however, the operative mortality seems lower, probably because of the availability of MCS and transplantation as “rescue” modalities after failed procedures. Controlled studies involving sufficient patients to allow a critical assessment of this operation are lacking. Before left ventricular reduction can become a routine treatment for CHF, long-term follow-up studies are needed to determine the clinical utility of the procedure and the appropriate criteria for patient selection.

There are 2 possible approaches to the use of MCS as an alternative to cardiac transplantation. In the first approach, a long-term implantable system may be used to support patients for an indefinite period. Patients who are discharged from the hospital and return home will have an enhanced quality of life and will possibly live longer than with medical therapy alone. Over the past 15 years, experience with the bridge-to-transplant population has allowed investigators to gain considerable confidence with regard to MCS. Two systems, the HeartMate and Thoratec, have proved safe and efficacious by FDA standards. Because the HeartMate was originally envisioned as a permanent system, a randomized, multicenter clinical trial is under way to evaluate the VE-LVAS for long-term use in NYHA class IV patients who are not transplant candidates. The REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) Trial, initiated in 1996, is designed to compare medical management and VE-LVAS support with respect to mortality, quality of life, and cost. On the basis of a pilot series, a revised REMATCH protocol was approved by the FDA, and enrollment has recently begun. The results, which are unlikely to be known until after the year 2000, should reveal the long-term capabilities of the VE-LVAS and similar MCS systems.

The second potential approach for using MCS systems as alternatives to transplantation involves bridging to recovery of myocardial function in CHF patients. Long-term MCS is known to improve the clinical and histological signs of CHF. Chronic unloading of the left ventricle decreases cardiac dimensions, enhances ejection fraction, and lowers...
pulmonary capillary wedge pressure and pulmonary vascular resistance.\textsuperscript{101,102} Myocytolysis is consistently reduced in patients with idiopathic cardiomyopathy who are supported by an LVAS for prolonged periods. So far, reports concerning LVAS removal after prolonged support have been anecdotal.\textsuperscript{102,103} In 1 series,\textsuperscript{102} 5 patients who had significant cardiac recovery and underwent LVAS removal were all doing well many months later. However, reimplantation, with exacerbated CHF symptoms, and death have also been observed after MCS removal.\textsuperscript{99}

In the authors’ experience, 2 young patients, 1 with idiopathic cardiomyopathy and the other with peripartum cardiomyopathy, were supported for 16 months and 5 months, respectively, before VE-LVAS removal. Both patients were in NYHA class I 18 and 15 months, respectively, after device explantation. They represent a population likely to benefit from bridging to recovery. Indeed, young patients with severe CHF have a limited life expectancy even with cardiac transplantation and may have a better long-term prognosis and quality of life without transplantation. Nevertheless, many questions remain: Which patients are most likely to have sufficient cardiac remodeling to allow removal of the MCS system? How long will adequate cardiac function be maintained? Do practical measures of myocardial recovery exist, and can the degree of recovery be assessed? Controlled trials designed to answer these questions are urgently needed.

Comments

In the absence of a definitive cure for the primary diseases that lead to CHF, combined medical and surgical therapy will continue to be the standard of care. Cardiac transplantation and MCS will continue to evolve in parallel, and ongoing refinements in these modalities will improve patient survival and quality of life. Other future therapies may be based on gene therapy, new pharmaceutical agents, and improved biomaterials. Because cardiac transplantation is limited by the insufficient supply of human donor organs, better immunologic manipulation is needed to enhance graft survival and possibly expand the donor pool to include other species. Future blood pumps must be smaller and totally implantable, as well as more efficient, biocompatible, and reliable. In this era of rapid technological progress, the main obstacles to major advancement are societal, financial, and regulatory barriers. Fortunately, these barriers are not insurmountable, and there is every reason to believe that they will eventually be overcome.

References


Mechanical Circulatory Support and Cardiac Transplantation


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