Mechanical Circulatory Support for Advanced Heart Failure

Where Does It Stand in 2003?

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Today, the lifetime risk of developing heart failure is 1 in 5 for both men and women. This high risk underscores the need for effective therapies to treat terminal heart failure unresponsive to conventional treatment. Cardiac transplantation, when possible, offers not only significant palliation but also a real opportunity for meaningful long-term survival. However, posttransplantation mortality and morbidity have improved little over the past decade, and because of the shortage of suitable donor organs, this therapy will never have more than a minimal epidemiological impact on heart failure.

To expand the therapeutic options for treating end-stage heart failure, the National Institutes of Health initiated research in the mid-1970s designed to develop mechanical circulatory support (MCS) devices that could provide destination therapy for this condition. The devices developed from this program were first used clinically, however, as bridges to transplantation in the mid-1980s. These implantable MCS devices have now been employed as a bridge to transplantation in more than 4000 patients worldwide. In 2002, on the basis of the results of the Randomized Evaluation of Mechanical Assistance for the Treatment of Chronic Heart failure (REMATCH) trial, implantable MCS systems were approved for destination therapy in patients who were not acceptable candidates for cardiac transplantation.

Despite these advances, numerous questions remain about the ultimate goals of MCS and the role of this technology in treating heart failure. Who are the best candidates for these devices, and what should be the therapeutic goals in each case? What adjuncts can be expected to maximize the benefits of MCS? How can future devices best be developed and studied? To illustrate where this technology stands in 2003 and how it can be expected to develop, we will consider its present and future capabilities in light of these questions.

What Are the Goals of MCS?

The first use of MCS resulted from the observations by Spencer, Dennis, DeBakey, and others that some cardiac surgery patients who could not be weaned from cardiopulmonary bypass (CPB) postoperatively might subsequently be weaned if they were kept on the heart-lung machine for longer periods to allow for rest and recovery of the heart. This observation stimulated the development of MCS as a bridge to recovery. Then, as now, the main barrier to long-term use of the heart-lung machine for cardiac recovery was the physiological and hematologic trauma caused by the oxygenator. If the patient’s own lungs could be used for oxygenation and a cardiac assist device could be used to maintain circulation for more prolonged periods, then the potential for cardiac recovery might be enhanced. Research efforts at Baylor College of Medicine, in Houston, Tex, under the direction of Drs Michael DeBakey, Domingo Liotta, and William Hall, led to the first use of an implantable left ventricular assist device (LVAD) in 1963. A similar device was successfully implanted in 1966 in a young woman who was supported for 10 days and became the first long-term survivor of the use of this technology. In a classic article published in 1971, DeBakey reviewed his experience in the
1960s with this technology and outlined the main barriers to its wider use: lack of a portable control mechanism and power source, lack of a nontraumatic blood–biomaterial interface, the need for extensive implant surgery, and prohibitive cost.

In the late 1960s and early 1970s, the failure of cardiac transplantation to fulfill its initial promise stimulated the development of implantable cardiac assist pumps for destination therapy, as an alternative to cardiac transplantation. This was the original goal outlined in a 1976 request for proposal (RFP) issued by the National Heart, Lung, and Blood Institute, which offered major funding in this field. The original RFP was for a pump that could provide support for up to 2 years without external venting. Current devices such as the Novacor Left Ventricular Assist System (World Heart, Inc), the HeartMate implantable LVAD (Thoratec Corporation), and the Thoratec Ventricular Assist Device System (Thoratec Corporation) evolved from this program.

Among the first patients to undergo successful bridging to transplantation were 3 patients at our hospital, 2 of whom received a total artificial heart (TAH) (in 1969 and 1981) and 1 of whom had an LVAD implanted (in 1978). Although device function was satisfactory in all instances, these patients subsequently died of infectious complications related to the immune suppression necessitated by the transplant. In the early 1980s, however, introduction of the immune-sparing drug cyclosporine allowed several newer technologies to be successfully used for bridging to transplantation: the Novacor (1984), the Jarvik-7 TAH (Jarvik Heart, Inc) (1985), and the HeartMate (1986). Since the mid-1980s, the use of MCS for this purpose has steadily increased. In 2001, approximately 20.1% of all heart transplant recipients in the United States underwent MCS before transplantation (personal communication, L. Edwards for United Network for Organ Sharing, unpublished data, April 2003). The National Heart, Lung, and Blood Institute goal of 2-year in vitro pump performance has been achieved by both the implantable Novacor and the heartMate, despite the fact that the US Food and Drug Administration (FDA) had approved these pumps only for 30-day implants. As of January 2003, the HeartMate LVAD had been used to support 217 patients for more than 1 year, 33 patients for more than 2 years, and 3 patients for more than 3 years, all on an outpatient basis. These patients initially received the HeartMate as a bridge to transplantation and remained on the transplant waiting list. The Novacor implantable pump has a similar record, 1 patient having been supported by it for more than 4.5 years.

Because of the widespread use and success of MCS for bridging to transplantation, valuable experience has been gained with the use of these technologies. In fact, the >2-year durability and reliability of the HeartMate pump was demonstrated because of the prolonged waiting times endured by bridge-to-transplantation patients, and these waiting times will likely continue to increase. In 2000, the average waiting time for O–blood-type patients was 869 days in those fortunate enough to receive a transplant.

The first patient to be discharged from the hospital with an electrically powered, untethered LVAD occurred in 1991 and was reported by Texas Heart Institute researchers in 1994. Other patients were soon able to return to productive work while awaiting transplants as outpatients. In 1995, one of our patients worked productively for 6 months before receiving a transplant. In these cases, MCS offered long-term effectiveness and the potential to return patients to full, active lives. Currently, most patients who need MCS for more than 90 days are discharged from the hospital. Recently, the Berlin group described 38 MCS recipients who had lived outside the hospital for a mean of 454 days (range, 20 to 769 days). These patients had minimal complications and a satisfactory quality of life.

Because the 1976 RFP had called for destination therapy, yet the only approved indication for an implantable LVAD was bridging to transplantation, researchers believed that a controlled study (REMATCH) should be undertaken with destination therapy in mind. This study, which was completed in 2001, yielded statistically favorable results for recipients of the HeartMate LVAD. A similar study of destination therapy is now being undertaken with the Novacor device.

Who Are the Best Candidates for MCS?

A substantial number of heart failure patients could potentially benefit from long-term MCS. At present, the most appropriate candidates for MCS are patients who are facing imminent death from heart failure but who still have adequate end-organ function. To achieve benefit, an MCS device must be associated with minimal operative risk of implantation, and its long-term use must have an acceptable level of late complications. As these devices have shown excellent long-term reliability both in vitro and in vivo, the main risk of implantation is associated with patient factors. The current implantable devices require that patients be at least of average size, and the most important limitation of short-term survival (30-day mortality) remains the level of derangement of end-organ function before implantation. Therefore, in selecting the best candidates for this therapy, we must find the right balance between those who are too sick and those who are too well.

Currently, long-term MCS is indicated for patients with chronic heart failure whose hemodynamic status deteriorates despite maximal drug therapy and/or intra-aortic balloon pump assistance. Candidates should have a pulmonary capillary wedge pressure of >20 mm Hg, a cardiac index of ≥2 L · min⁻¹ · m⁻², and a systolic blood pressure ≥80 mm Hg. Temporary use of inotropic agents may be considered for advanced heart failure therapy, but early weaning should be attempted. If this attempt proves unsuccessful, MCS should be instituted before further end-organ deterioration occurs.

The current practice of outpatient intravenous therapy with milrinone or dopamine has not improved survival, and the precipitous deterioration that frequently occurs in these patients limits the timely application of MCS and frequently
will adversely affect its successful use. To be considered for destination therapy, patients must be ineligible for transplantation, have a very poor quality of life despite optimal medical management, and have an acceptable risk for device implantation. However, as the REMATCH study demonstrated, if patients are unacceptable for transplantation, they may well have an unacceptable risk for the extensive surgery required for device implantation.

In addition, patients’ hemodynamic profiles can be difficult to interpret. For example, hemodynamic profiles may be the same in patients with severe end-organ dysfunction who will not survive and in patients with retained end-organ function who can undergo implant surgery with acceptable results. For acceptable short-term and long-term survival, the critical factor is the patient’s general overall condition, ie, end-organ function and nutritional state. Cardiac cachexia invariably adversely affects results. As with cardiac transplantation, device selection should include factors other than absolute cardiovascular hemodynamics, ie, cardiac reserve measured by VO₂max and degree of renal and hepatic dysfunction. In fact, the hemodynamic criteria that are still used in patient selection are those that were determined more than 25 years ago by Norman’s group for assessing postcardiotomy (acute) heart failure. These criteria, however, have little significance for patients with chronic heart failure, either for those who are outpatients working part-time or for those who are inpatients on maximal intra-aortic balloon pump and pharmacological therapy in an intensive care unit.

The most important factor in successful device implementation remains timing of the operation. Because of the disparity between actual patient selection and the specific FDA requirements for device implantation, physicians involved in device selection must possess a satisfactory depth of relevant clinical experience in this complex field. They must not only know medical options but also understand suitability of the various devices available as well as the role of transplantation in treating these patients. Experience with a variety of these technologies is essential, as a single device may not be the best for all patients. The establishment of physician credentials in this field is long overdue, as there are currently no criteria scrutinized by appropriate professional societies that physicians must meet in order to use these devices or to interface with transplantation. The United Network for Organ Sharing criteria for transplantation certification only require participation in a certain number of transplantation procedures.

Once a specific device has been matched to the size and cardiac condition of a particular patient, actual device implantation should yield a marked survival benefit. In the only study with a concomitant control group, the rate of survival to transplantation of the MCS group was 71%, compared with a survival rate in the control group of 30%. The study also showed a 90% one-year survival rate after transplantation in the MCS group and a 67% one-year survival rate after transplantation in the control group. These data would be even more meaningful today because the average waiting time to transplantation for the control group was only 5 days in this historical study, whereas today, the waiting times are much longer for even the highest-priority categories for transplantation.

What Adjuncts Can Be Expected to Maximize the Benefits of MCS?
The initial role of MCS was to allow recovery of the failed ventricle (from prolonged ventricular arrest) after CPB. In some cases, success was achieved. This recognized benefit has been broadened today to include patients with chronic heart failure undergoing long-term MCS. We first reported this observation in 1994 in bridge-to-transplantation patients. Subsequently, a number of patients have had their devices removed, generally because of device malfunction, and were able to survive with conventional medical therapy and without transplantation or additional device support. To date, the number of patients treated in this manner has been limited, but numerous studies from a wide range of transplantation centers have reported improvement histologically, biochemically, neurohormonally, and ultrastructurally in the bridge-to-transplantation patient population. Adjunctive therapy may further enhance the chance of ventricular recovery. For example, cell transplantation at the time of LVAD implantation may enhance myocardial functional recovery, and the use of the β-antagonist clenbuterol has been reported with promising results by Yacoub in Great Britain. Controlled clinical studies encompassing a wider range of patients will further define the role of ventricular recovery with MCS.

How Can Future Devices Best Be Developed and Studied?
Current MCS devices offer hope to otherwise terminally ill patients (Figure). Initiation of therapy at an earlier stage in the patient’s illness would result in a better long-term outcome. However, early initiation of MCS can be justified only if smaller, safer pumps are developed that can be implanted with a lower mortality and fewer late complications. Today’s continuous-flow pumps are most promising in this regard. In suitable patients, these small pumps can be implanted with a high degree of safety and minimal late complications. In fact, the author (O.H.F.) has implanted the Jarvik 2000 LVAD without the use of CPB. By eliminating CPB, operative risk and morbidity in these critically ill patients should decrease. Continuous-flow pumps offer promising long-term reliability, as well. The Jarvik 2000 LVAD has now supported 12 patients for more than 1 year, and 1 patient (among the first to undergo LVAD implantation for destination therapy) has been supported successfully for 3 years. In all instances, the

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*In this FDA study for approval of the pneumatic HeartMate, the control group consisted of patients who were approved for device implantation (from 1988 to 1993) but who did not have a device implanted because a device was not available; they remained on the transplant list until death or transplantation.
operative survivors who were discharged from the hospital returned to New York Heart Association functional class I status. Like the other currently used continuous-flow pump, the MicroMed DeBakey VAD (MicroMed Technology, Inc), the Jarvik 2000 has not been associated with significant infections.

These 2 implantable nonpulsatile devices seem to offer the best results in homebound patients with advanced heart failure. Such patients have enough cardiac reserve to allow a return to the normal Starling mechanism when the failed heart is unloaded by a continuous-flow device. Therefore, these small, continuous-flow pumps are most effective when used as true assist devices. The early success of continuous-flow pumps may allow a broadening of their indications to include class III and IV homebound outpatients, who could lead active, meaningful lives with such support.

Many patients die because their heart damage exceeds any potential for partial device support. Most of these patients develop acute heart failure secondary to coronary artery disease, need total ventricular replacement, and could be saved by an off-the-shelf TAH like the AbioCor TAH (Abiomed, Inc). Successful long-term in vitro and in vivo performance of the AbioCor TAH has been achieved, and clinical trials are now underway. Current indications allow for implantation only in patients with severe chronic heart failure who are not suitable transplantation candidates.

As the treatment of heart failure becomes more complex, physicians are finding it harder to perform controlled, relevant studies designed to guide device selection. Part of the challenge involves determining how to evaluate these devices in the clinical setting, how to benchmark the performance of a new device, and how to compare such a device to previous pumps or to medical therapy in populations that are hard to standardize. These issues must be addressed by regulatory agencies and clinicians in such a way as to preserve the viability of the device industry. To date, this industry has not been very profitable. Therefore, economic barriers to device development are as real and important as medical and scientific barriers.

The current cost of LVADs includes the accrued cost of years of research and not the actual costs to produce the technology. Like all medical devices, LVADs will cost less with time and increased use. Some of the smaller pumps currently can be manufactured for less than $10 000 in actual costs. Although charges today are much higher, they do not reflect costs. In addition, when applied to the proper patient cohort, the current axial flow pump technology will significantly reduce inpatient costs for patients with congestive heart failure. This has been demonstrated in a pilot study in Great Britain. One of the patients in that study was hospitalized 6 times for congestive heart failure in the 9 months before the pump was implanted. In the 3 years since, he has been hospitalized only once, and that hospitalization was not related to congestive heart failure. He remains in NYHA class I; he was in NYHA class IV at the time of implantation.

**Conclusion**

In the coming decades, device technology, implantation techniques, and patient management will undoubtedly improve to the point where MCS will be a therapeutic option for many patients with advanced heart failure. Mechanical devices may potentially replace transplantation altogether in selected patient groups. On the basis of individual device characteristics and the level and type of heart failure, we must determine which population of patients will benefit most from which devices. Quality of life after implantation also must be considered for these patients. All of today’s implantable devices are approved for outpatient use, allowing many patients to return to productive work while awaiting transplantation. Clearly, the survival benefit and life quality of these patients validate the importance of MCS in this patient population.

Because transplantation requires an immense societal effort and is limited in its application and long-term results, destination therapy is an essential goal of MCS technology. Newer devices promise to expand and augment the clinical application of MCS. Smaller, implantable, continuous-flow pumps can be safely implanted before heart failure and end-organ dysfunction become irreversible. In addition, the timely application of a TAH can be lifesaving when used as a rescue device for patients with acute biventricular failure. Industry, clinical investigators, and regulatory agencies must work together to produce new, more widely applicable technologies and to facilitate their meaningful evaluation.

In discussing the rules of acting, Shakespeare’s Hamlet said that one must “suit the action to the word, the word to the
action; with this special observance that you o’erstep not the modesty [limits] of nature.” 22 Similar advice may be applied to MCS technology. The medical challenge is to match the right technology to the right patients at the right time, observing and respecting nature’s limit, ie, advanced end-organ failure, thereby maximizing the chance of a successful outcome.

References
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