



## Devices as destination therapy

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The quest for the artificial heart, or a device that could support a patient's circulation in case of heart failure, has been ongoing for half a century. Since Gibbon's introduction of cardiopulmonary bypass in 1953, heart surgeons have pursued this goal with the first successful human implantation of a left ventricular assist device (LVAD) in 1963 [1]. In 1969 a total artificial heart (TAH) was used as a bridge to transplantation [2], and subsequent growing interest in the field led to government support and involvement of the National Heart and Lung Institute and growth of this field. Research in TAH and LVADs progressed simultaneously. In 1982, Dr. DeVries implanted a TAH into a critically ill patient with subsequent survival for 112 days [3]. Plagued by thromboembolic and infectious complications, these devices, at the time, were criticized by the community as not being ready for human use [4,5]. During the same period of time, the LVADs were showing greater promise and improved outcomes for a majority of patients in need of circulatory support. It became apparent that most heart failure patients did not need biventricular support. The LVADs were initially approved for use as a bridge to transplantation. However, their use in this capacity did not relieve the short supply of heart transplants, and as a result only increased the recipient pool by allowing patients to survive until a donor heart was found. As the experience with the devices grew, so did the indication for implantation and the desire to see these machines used as a permanent support system for the heart.

Throughout the 1990s, these devices underwent continued modification not only to improve reliability and reduce complications but also to improve utility and ease for the patient living with the device. Power and regulatory units were modified and reduced in size thus allowing for greater patient mobility. The improved reliability and mobility of the units allowed outpatient care and significantly altered the quality of life for these patients. As the devices evolved, so did our understanding of their potential. In the late 1990s, several studies were undertaken to evaluate the efficacy of these machines as destination therapy. At the same time the artificial heart once again made headlines with hopeful results in terminal patients in need of biventricular support. In discussing the topic of circulatory support as destination therapy, we must evaluate the various devices, indications, patient selection, clinical trials, and the future of this therapy.

### Destination devices

#### *Pulsatile LVADs*

Pulsatile LVADs are extensively discussed in the previous chapter. Since the growth of this field in the 1980s, several manufacturers have played an important role not only in the supply and refinement of current ventricular assist device (VAD) technology, but also in the development of the future devices which will some day play a greater role in this field. In talking about devices used as destination therapy, we must focus on intracorporeal units. Several paracorporeal machines are widely used for both short-term and long-term therapy; however, due to the physical constraints, they have not played a key role in their use as destination therapy. Three companies lead the way

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in the field of pulsatile LVAD use as an alternative to transplantation: the Thoratec Corporation (Pleasanton, CA) with its HeartMate LVAD, the World Heart Corporation (Ottawa, ON, Canada) with their Novacor device, and the Arrow LionHeart LVD-2000 designed through a collaboration between Pennsylvania State University and Arrow International (Reading, PA).

The HeartMate is an LVAD backed by an extensive clinical experience. Originally designed in 1975, it has undergone numerous modifications of both pump and controller console throughout the 1980s and 1990s. In 1991, a clinical trial of the electric-vented model showed good reliability and improved mobility over the original pneumatic system [6]. Used primarily as a bridge to transplantation, the pump showed a 60% to 70% survival rate to transplantation with an average implant duration of 80 to 100 days and a maximum time on support of more than 2 years [7–9]. Due to the extensive experience and positive outcomes with the device, it was evaluated for use as an alternative to transplantation in a study begun in 1998. The outcomes of the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial will be discussed later. However, the positive outcomes of the trial led to the present approval of this pump by the FDA as a permanent treatment of end-stage heart failure in patients who do not qualify for heart transplantation [10].

The Novacor pump, in a similar manner, has been used extensively as a bridge to transplantation. Developed by Peer Portner and Stanford University, the pump was first successfully used in 1984 as a bridge to transplantation [11]. Like the HeartMate system, it is currently available with a wearable controller and has proven to be reliable with 60% to 70% of patients surviving to transplantation. The median time of LVAD support is 100 days with a long duration of 1512 days reported [11–13]. The company currently claims a >90% 3-year pump reliability [14]. As with the HeartMate device, the Novacor pump has undergone a clinical trial to evaluate its efficacy as destination therapy. The INTrEPID trial (Investigation of Non-Transplant-Eligible Patients who are Inotrope Dependent) also evaluated the use of an LVAD as an alternative to medical treatment in end-stage heart failure patients. This study is currently near the point of completion and has shown to work without failure an average of 4 years in 12 patients [15].

These two devices with their trials have paved the way toward the clinical use of LVADs as destination therapy in treatment of heart failure.

The Arrow LionHeart pump is a system specifically designed with the goal of destination therapy. Being a completely implantable system, it uses a transcutaneous energy transmission system (TETS) and an implantable compliance chamber to deliver therapy with no percutaneous connections. The pump delivers flow at a maximum of 8 L/min [16]. The compliance chamber loses gas over time and requires replenishment of once a month [17]. Battery recharging is achieved through a transcutaneous system with a wand overlying a subcutaneous recharging coil. This system allows the patients to be completely disconnected from external power for short periods of time. This new transcutaneous technology is currently being developed by the majority of pump manufacturers to provide an improved quality of life with a lower infection rate to the device-supported patient population.

#### *Rotary pumps*

Considered the “next generation” LVADs, these pumps have emerged as a possible alternative to the large pulsatile devices. Continuous circulatory flow is a concept dating back as far as the invention of the heart-lung machine in the 1950s. Having the advantage of reduced size and noise, these devices were developed in the 1980s and early 1990s primarily by two manufacturers. The MicroMed-DeBakey VAD (Houston, TX) (Fig. 1) and the Jarvik 2000 pump (Jarvik Heart, Inc., New York, NY) (Fig. 2) are the two main devices in clinical use in the US bridge-to-transplant trials today. Both systems are small axial pumps based on an impeller rotating at high revolutions per minute (rpm). The DeBakey VAD is 3 inches long and capable of pumping 10 L/min [18]. The Jarvik unit is equally as small and produces a flow rate of 7 L/min [19]. Both pumps produce a low-pulsatile flow with the pulsatility diminishing with the rise in the rpm. A unique feature of the Jarvik pump is its intraventricular position and its skull-fixated percutaneous controller and energy connector. The outflow tract of the Jarvik VAD is also usually connected to the descending aorta as opposed to the ascending aorta as in the majority of VADs. Although neither of the systems is currently undergoing a formal trial for evaluation as destination therapy, both devices have shown promise in long-term

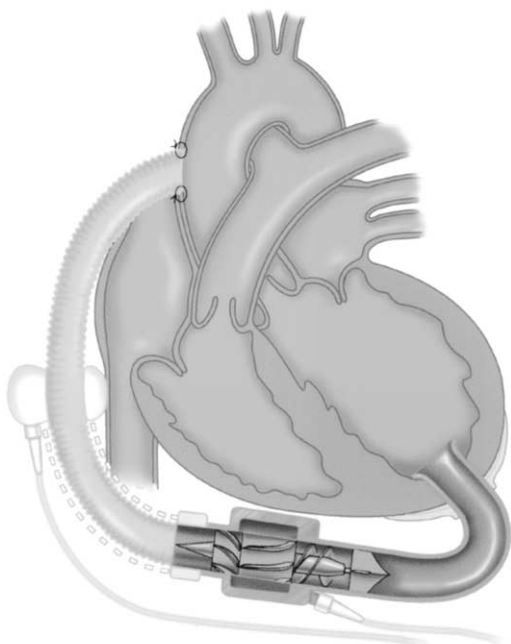


Fig. 1. MicroMed-DeBakey, VAD. (Courtesy of Micro-Med Technology, Inc.)

reliability. The DeBakey VAD has shown a longest duration of greater than one year, and the Jarvik pump has been implanted as destination therapy in a number of patients in England

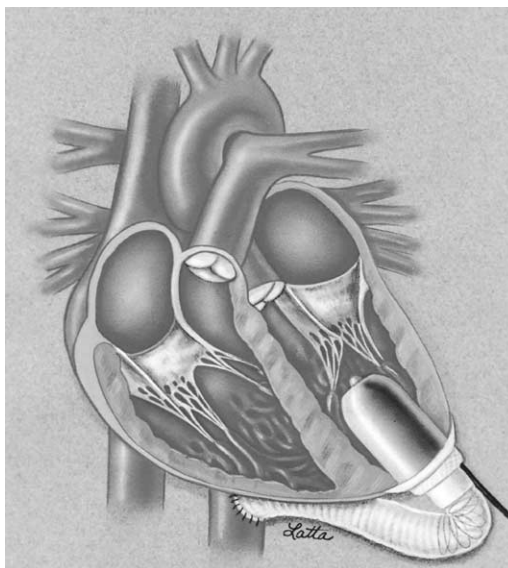


Fig. 2. Jarvik 2000. (Courtesy of Texas Heart Institute.)

[19,20]. A third pump, the HeartMate II LVAD (Thoratec Corporation, Pleasanton, CA) like the two previously mentioned pumps, is an axial flow pump from the makers of the widely used HeartMate pulsatile VAD (Fig. 3). Like the DeBakey pump, this device is also small with an inflow cannula implanted in the left ventricular

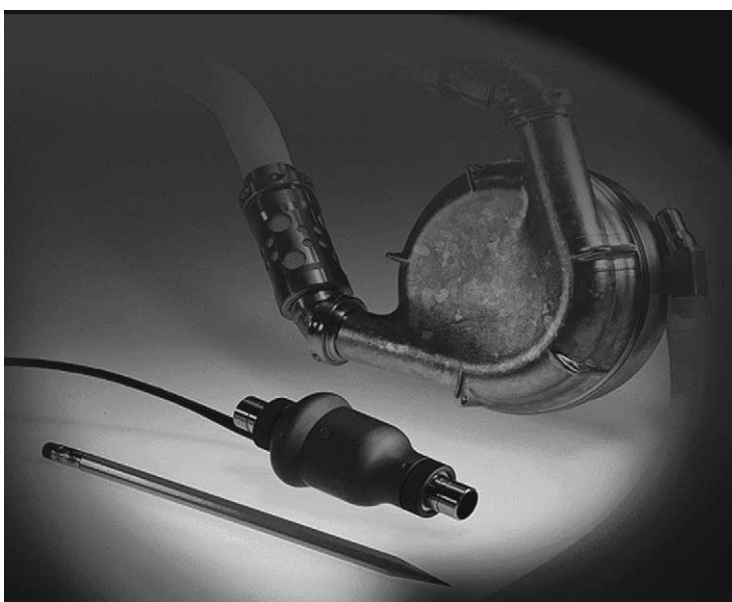


Fig. 3. The HeartMate® I and II ventricular assist systems. (Courtesy of World Heart Corp.)

apex and the outflow graft connected to the ascending aorta. To improve reliability of continuous flow throughout the cardiac cycle and prevent ventricular collapse, the intraventricular portion of the inflow tract has been elongated and as a result tends to stent open the middle of the ventricle [21]. This device has also not undergone trials specifically with the focus of destination therapy, however, all of these pumps offer attractive features for patients looking for long-term support. Their small size coupled with the low noise and energy expenditure make these pumps very appealing in the long-term quality-of-life assessment.

### *Total artificial heart*

Total artificial hearts have been used as bridge to transplantation and as destination therapy for a couple of decades. The indication for the use of the pump centers around patients who will need prolonged biventricular support. Two companies are currently leading the way in the development of these devices, the CardioWest Total Artificial Heart (TAH; CardioWest Technologies, Tucson, AZ; see Chapter 11 this issue) and the AbioCor TAH (ABIOMED, Danvers, MA; see Chapter 12 this issue). The CardioWest TAH is the result of continuous development of the original Jarvik-7 TAH used in the early 1980s [22]. The device has been used extensively worldwide as a bridge to transplantation. The pump is pneumatic and is driven by a large console thus limiting its use in the outpatient setting. A smaller controller is in the works; however, at present, the device plays a limited role in its use as destination therapy. The AbioCor TAH is a new device undergoing testing as destination therapy in a select patient population. The device is currently undergoing an FDA-approved multicenter trial involving patients with limited life spans who are not candidates for heart transplantation. The first patient to receive the heart on July 2, 2001, was kept alive for 5 months [23], despite substantial preoperative morbidity. The pump is completely implantable with no percutaneous drive lines. It uses the TET coil system to deliver power and control to the pump.

### **Device and patient selection**

In choosing the type of device to use as part of destination therapy, the primary question to answer is whether the patient needs biventricular

support or will an LVAD provide appropriate therapy. Currently no intracorporeal system is widely available for separate right and left ventricular support. In most instances, heart failure patients improve with the unloading and support of the left ventricle. In case of perioperative right heart failure, a temporary paracorporeal right ventricular assist device (RVAD) is used until the right side recovers or a donor heart becomes available for transplantation. However, a patient population exists that does require biventricular support, thus creating a need for a total artificial heart. A decreasing cardiac index in the setting of high pulmonary arterial (PA) and central venous pressures, low left atrial pressures, and low cardiac index all point to possible right heart dysfunction [24]. However, care must be taken not to assume normal right heart function in the setting of normal preoperative pulmonary pressures. With low cardiac output states, a patient may display normal PA pressures, which then increase dramatically after the cardiac output increases following VAD support. Kavarana et al reported no significant difference in preoperative hemodynamic parameters between patients who suffer from right ventricular failure after LVAD implantation and those who maintain adequate right heart function [25].

Another consideration in this matter is the size of the patient. The two currently tested TAHs described previously require a recipient to have considerable chest volume. Patients receiving the CardioWest heart require a 10-cm anteroposterior chest cavity diameter [22]. The currently available pulsatile LVADs also require a body surface area of greater than 1.5 m<sup>2</sup>. For smaller patients, axial rotary pumps may be the best option.

Appropriate patient selection is a challenge, especially as currently successful systems achieve FDA approval. The trials currently evaluating these devices as destination therapy include patients who otherwise do not fit the criteria to undergo heart transplantation. In many cases, particularly in the case of the TAH trials, these patients are very ill with significant comorbidities including end-organ dysfunction. In some cases, these patients are too old to undergo transplantation. In either situation, it is difficult to say whether these are the ideal patients to receive this therapy, which causes further insult to an already fragile system. Patients who receive device support as destination therapy should meet certain criteria that may predict initial survival after implantation. We have created a scoring system

Table 1  
Risk factors for poor survival after left ventricular assist device placement

Risk factor	Score
Mechanical ventilation	4
Reoperation	2
Previous LVAD	2
Central venous pressure > 16 mmHg	1
Prothrombin time > 16 seconds	1

*Adapted from Rao V, Oz MC, Flannery MA, et al. Revised screening scale to predict survival following left ventricular assist device insertion. J Thorac Cardiovasc Surg, in press.*

to predict which patients would survive device implantation. The initial scale, created in 1995, was recently revised to better reflect the current extensive LVAD experience (Table 1). The positive and negative predictive value of the current scoring system is 79% and 70%, respectively. Using the scale, a score of > 5 corresponds to a 47% mortality compared with a 9% mortality for a score of < 5 [26]. Renal failure, previously considered as a major comorbidity, has recently been shown to play less of a role in the prediction of overall survival. In many cases, increased cardiac output due to circulatory support improves renal function after VAD implantation. Liver failure, with subsequent coagulopathy, may lead to increased perioperative bleeding with subsequent correlation to increased right heart failure. These selection criteria were developed after evaluating patients who received the device as a bridge to transplantation. As a result, the selection process may need further revision when considering patients who will be treated with destination therapy.

Many questions still remain as to the ideal population that would survive and benefit from this technology. Further evaluation of the clinical trial results combined with cautious and judicious use of this treatment option is warranted to answer the question of which patient population would benefit the most from the use of circulatory assist devices as destination therapy.

### Clinical trials

The most significant trial to test circulatory assist devices as an alternative to transplantation was the REMATCH trial mentioned previously. The study was undertaken in 1998 with 129 patients in 20 centers. The patients enrolled included

adults with end-stage (NYHA class IV) heart failure who did not qualify for heart transplantation. The patients were randomly assigned to either LVAD implantation or optimal medical therapy. The Thoratec HeartMate LVAD was the device used in the trial. Death was the primary end-point of the study; however, multiple secondary end-points were evaluated including quality of life, complications, and hospitalizations [27]. The study was concluded in July 2001 with data presented at the annual American Heart Association Scientific Assembly Meeting in November 2001. The results showed that the two groups were matched in pre-study characteristics. The LVAD-treated group showed a 48% reduction in risk of death compared with the medically treated group. The disturbing finding was the 1-year and 2-year survival of this patient population. The medically treated patients showed a 25% 1-year survival and 8% 2-year survival with the LVAD patients surviving 52% and 23% of the time, respectively [10]. These results not only demonstrated the potential of the circulatory assist devices as an alternative to medical therapy in this patient population but also highlighted the morbid outcome of the natural course of this disease. Further analysis of the REMATCH data is ongoing, and new data examining this issue should be available shortly.

Another trial currently near its conclusion is the INTrEPID trial using the Novacor device. Similar to the REMATCH trial, this trial is looking at the use of the Novacor device as destination therapy and as an alternative to medical therapy in an inotrope-dependent patient group not eligible for heart transplantation. The results of this study may further point to the potential and benefits of circulatory assistance therapy.

The AbioCor TAH trial is another trial currently underway to evaluate the efficacy of device support as destination therapy. The initial trial is conducted by a limited number of centers with more centers to be included in the second larger trial. Currently, patients included in the study must have an estimated life expectancy of 30 days or less and not be eligible for heart transplantation. One of the patients has been supported on the device for more than 200 days and has been discharged home on the device. Further experience with this device is necessary before we can clearly define the patient population that would benefit from this therapy.

All of the currently proposed devices will need to undergo challenging clinical trials before

obtaining FDA approval. We believe that a modified regulatory process will be required for device companies, because the financial constraints of the large randomized evaluations are overwhelming to the small companies involved in this field. Innovative approaches could include creation of a generally agreed-upon control population such as the REMATCH trial optimal medical management group or a group of patients gathered from subgroups of each company's randomized trial.

### Summary

The use of circulatory support as destination therapy has been a goal for the treatment of end-stage heart failure for several decades. Current investigations are evaluating several circulatory pumps with that particular objective. With continued modification of design, the current and future pumps will become more reliable and provide improved quality of life to patients in need of mechanical circulatory assistance. The new pumps on the horizon specifically address reliability, size, and cost, and are based on the centrifugal system. These devices use the Maglev (Magnetic Levitation) concept that allows for frictionless pumping, low thrombogenicity, minimal noise, and increased durability. Further research with this goal in mind and support from the federal government will be the key to the future use of circulatory assistance as destination therapy for heart failure patients. In addition, the cost-effectiveness of these devices will need to be maintained as the technology improves, as in any new technology that confronts a more intuitive option like the native heart.

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