

Review Article

Will Modern Miniaturized Left Ventricular Assist Devices Offer a Viable Alternative to Heart Transplantation?

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In the rapidly expanding field of mechanical circulatory support (MCS) the boundaries between bridging-to-transplantation (BTT), bridging-to-recovery (BTR) and permanent or destination therapy (DT) are becoming less distinct, since the initial intention to treat does not always coincide with the ultimate use of MCS and continuous crossover between strategies is commonly encountered, underscoring their imprecision.^{1,2} The heart failure signs and symptoms are similar in patients supported with different device implantation strategies, while the outcomes for BTT and DT appear similar. MCS is a dynamic state and recipients undergo frequent reevaluation.³ While BTT, DT and BTR are the main strategies for long-term MCS, in about 40% of recipients the initial implantation strategy cannot be categorized definitely into either bridge or destination. Clinical practice has led to innovative strategies, such as bridging to transplantation eligibility⁴⁻⁶ and bridging to decision.^{7,8} Newer indications might include “long-term MCS”, rather than premature assignment to transplantation with uncertain eligibility. Outcomes of long-term MCS can currently be evaluated in terms of duration of support, adverse events, survival and quality of life – regardless of the initial implantation strategy, which has become less relevant. Less reliance on terminology

as far as the initial intention to treat is concerned might improve patient care.³

Early results of long-term MCS with first-generation left ventricular assist devices

Although transplantation and BTT were established based on observational studies, the establishment of DT required survival benefit proven by the most robust form of study: the randomized clinical trial. The REMATCH trial¹⁰⁻¹² (1998-2001) randomized transplant-ineligible, end-stage heart failure patients to receive a left ventricular assist device (LVAD) or optimal medical therapy (OMT) and demonstrated a clinically significant 1- and 2-year survival benefit and an improved quality of life in LVAD-treated patients. This landmark trial remains the only randomized trial of MCS, and the LVAD used – the Heart Mate VE (Thoratec, Pleasanton, CA, USA; Figure 1), along with its improved model HeartMate XVE – remain even today the only devices for DT that have been approved by the United States Food & Drug Administration (FDA).

The 1- and 2-year survival rates of LVAD patients in the REMATCH trial were 52% and 23%, respectively (Table 1). The probability of device infection within 3 months was 28%, the frequency of bleeding within 6 months was 42%, while the

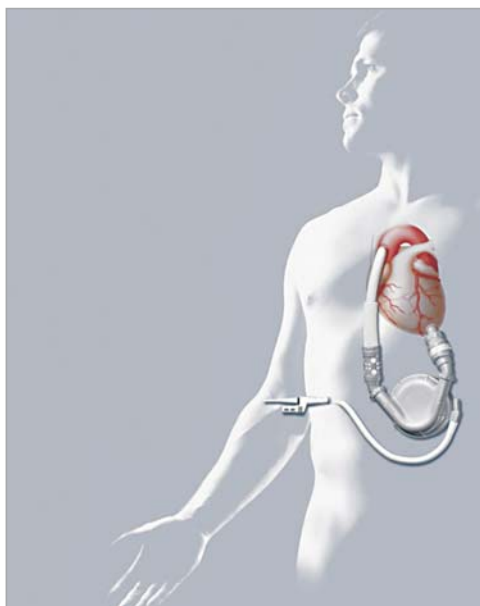


Figure 1. The HeartMate I, the most widely used first generation pulsatile left ventricular assist device. (Reprinted with permission from Thoratec Corporation.)

probability of device failure within 2 years was 35%. The main causes of death were sepsis, device failure, and cerebrovascular disease (accounting for 42%, 17%, and 10% of deaths, respectively).¹⁰

Retrospective analysis of DT with the HeartMate XVE in the USA in the early post-REMATCH era (between November 2001 and December 2005) showed slightly improved results, with 1- and 2- year survival rates of 56% and 31%, respectively (Table 1). Sepsis, multi-organ failure, stroke, right heart failure, and device failure were the main causes of death (accounting for 29.5%, 12.8%, 9%, 8.4%, and 6.4% of deaths, respectively). The probability of device replacement due to device end of life or fatal device failure was 18% and 73% at 1 and 2 years, respectively.⁷

The prospective, non-randomized INTrEPID trial¹³ (March 2000 to May 2003), which evaluated the outcomes of DT with the Novacor LVAD (World Heart, Oakland, CA, USA) in transplant-ineligible, end-stage chronic heart failure patients after repeated failure to wean from intravenous inotropes, reinforced the results of the REMATCH trial, demonstrating a significant 6- and 12-month survival benefit and an improved quality of life of LVAD-treated patients in comparison to the medically treated patients. The 1-year survival rate of the INTrEPID trial was 27% (Table 1). Cerebrovascular accidents (stroke or transient is-

chemic attacks) and infection were the most common serious adverse events and the main causes of death, accounting for 34% and 24% of deaths, respectively.

Improved results with pulsatile LVADs in recent years

The early survival of long-term MCS recipients has recently improved. According to the INTERMACS registry, long-term MCS recipients, implanted with FDA-approved, long-term VADs (mainly pulsatile VADs³) between June 2006 and March 2007 in the United States (n=156), had a 6-month survival of 75%. The main adverse events were infection (28.8%), bleeding (25.6%), respiratory failure (21.2%), neurologic dysfunction (15.4%), device malfunction (9.0%), and right heart failure (5.1%). The functional class of the patients was markedly improved 3 months after the initiation of MCS.²

Long-term MCS recipients, implanted between March 2006 and November 2007 (INTERMACS registry, n=348), had a 6-month survival rate of 74%, and a 9-month survival rate of 72%.⁶ Patients implanted between June 2006 and March 2008 (n=483) had a 6-month survival rate of 73%, a 9-month survival rate of 68% and a 1-year survival rate of 62%, whereas patients who received only LVAD support had a 1-year survival rate of approximately 70% (Table 1).¹⁴ There was no statistically significant difference in survival between DT and BTT.^{3,6,14}

Limited application of MCS as destination therapy

Despite the high estimated annual candidacy for MCS as DT,^{10,15} the number of patients actually supported with this implantation strategy has been limited.

The 1- and 2-year survival rates achieved with MCS as DT in the first half of the current decade, though dramatically better than the survival achieved with medical treatment, did not permit enthusiasm concerning the more widespread use of a costly technology that is associated with a high rate of adverse events. Another reason for the limited application of MCS as DT is the exclusion of large patient subpopulations. The first generation implantable LVADs cannot be implanted in patients with a small body surface area (BSA); thus, half the women candidates were excluded from MCS as DT. Furthermore, DT has been offered to transplant-ineligible patients, but ineligibility for transplantation usually meant ineligibility for MCS, since the contraindications for transplantation were more or less the same as those for MCS.¹⁵

Table 1. Results of long-term support.

Source of data, implantation period, device implanted, implantation strategy, number of patients	6-month survival LVAD vs. OMT or LVAD	1-year survival or LVAD LVAD vs. OMT	2-year survival LVAD vs. OMT or LVAD
REMATCH, randomized, 1998-2001, USA, HeartMate I, DT, (n=129, 68 LVAD/61 OMT) ¹⁰		52% vs. 25% p=0.002	23% vs. 8% p=0.09
REMATCH, subset analysis, inotrope dependent patients, (n=91, 45 LVAD/46 OMT) ¹¹	60% vs. 39%	49% vs. 24%	28% vs. 11% p=0.0014
REMATCH, subset analysis, non-inotrope dependent patients, (n= 38, 23 LVAD/15 OMT) ¹¹	61% vs. 67%	57% vs. 40%	22% vs. 16% p=0.55
INTRIPID, prospective, non randomized, 2001-2003, USA, Novacor, DT, (n=55, 37 LVAD/ 18 OMT) ¹³	46% vs. 22% p=0.03	27% vs. 11% p=0.02	
Post REMATCH, retrospective, 2001-2005, USA HeartMate I, DT, (n=280) ⁷		56% (LVAD)	31% (LVAD)
INTERMACS Registry, June 2006-November 2007, USA, FDA approved* long-term VADs, all strategies, (n=348) ⁶	74%†	–	–
INTERMACS, Registry, June 2006-March 2008, USA, FDA approved long-term VADs, all strategies, (n=483) ¹⁴	73%†	62%†	–
INTERMACS, Registry, June 2006-March 2008, US FDA approved long-term LVADs, LVAD support, all strategies, (n=362) ¹⁴		Approximately 68%† (285/362)	–
Prospective, non randomized, multicenter study, March 2005-May 2006, USA, HeartMate II, BTT, (n=133) ¹⁷	75%† Survival on support: 75%	Survival on support: 68%	–
Prospective, non-randomized, patients from both the pilot and pivotal trials of one participating centre, after Nov 2003 US, HeartMate II, (n=43, BTT 26/DT 17) ⁴⁶		80%†	–

*FDA approved durable devices as of March 2008 were the AbioCor TAH, HeartMate IP, HeartMate VE, HeartMate XVE, MicroMed DeBakey VAD - Child, Novacor PC, Novacor PCq, SynCardia CardioWest, Thoratec IVAD, Thoratec PVAD.³ In April 2008 the HeartMate II LVAD (Thoratec Corporation) received FDA approval for the BTT indication. The only currently FDA approved second generation long-term LVADs are the pediatric model of the MicroMed DeBakey and the HeartMate II (www.intermacs.org, accessed May 12, 2008). All devices are approved for BTT, apart from the HeartMate VE and XVE which are also approved for DT.³

†Cumulative survival of patients implanted with VADs, including patients who have undergone transplantation, recovery, or remained on ongoing support.

BTT – bridge to transplant; DT – destination therapy; LVAD – left ventricular assist device; OMT – optimal medical therapy.

MCS eligibility in transplant-ineligible patients

Advanced age is a contraindication for transplantation, because of the shortage of donor organs, but it is not a contraindication for MCS. However, significant comorbidities that make a patient ineligible for transplantation also preclude MCS.¹⁵ Thus DT was reserved for transplant-ineligible patients, but transplant-ineligible patients were usually deemed ineligible for MCS.

Contraindications for both transplantation and long-term MCS are severe lung, liver, kidney, or peripheral vascular disease, “fixed” pulmonary hypertension, a coexisting terminal condition, and a limited home environment.¹⁵ Thus, severe chronic obstructive or restrictive pulmonary disease, hepatic fibrosis and cirrhosis, “non-reversible” etiologies for renal insufficiency or failure, including diabetic nephropathy or

hypertensive renal disease, advanced metastatic cancer, uncontrolled active systemic infection, and major irreversible cognitive defects preclude both transplantation and long-term MCS.¹⁶

However, with increasing experience and improving results, MCS has recently been applied (as DT or as a bridge to transplantation eligibility) in patients with relative contraindications for transplantation, such as reversible pulmonary hypertension or organ damage.

In the early post-REMATCH era, patients implanted with LVADs for DT had at least one contraindication for transplantation, including advanced age (>65 years), pulmonary hypertension, insulin-dependent diabetes mellitus with end-organ damage, renal insufficiency, morbid obesity, and active malignancy. However, these patients were offered MCS (as DT), and furthermore 17% of them ultimately underwent

transplantation after a change in their transplant eligibility status during support. This was due to clinical improvement, including reversal of pulmonary hypertension, recovery of renal function, 5-year cancer-free survival, and weight loss.⁷

In 37.5% of the long-term VAD recipients of the INTERMACS registry implanted between March 2006 and March 2008, the pre-implant device strategy was “possible bridge to transplant”. Thus, 217 patients not listed for transplantation, who were considered “likely to become eligible” for transplantation, or as having a “moderate likelihood of becoming eligible”, or who were even “unlikely to become eligible”, received long-term MCS.¹⁴ These end-stage heart failure patients who had relative contraindications for transplantation were offered long-term MCS that was ultimately used as a BTT, BTR or as ongoing long-term MCS.^{3,14}

Despite the use of MCS in transplant-ineligible patients, due to the current application of less strict exclusion criteria for long-term MCS in comparison to the exclusion criteria applied for heart transplantation, MCS recipients with impaired pre-implantation organ function are at increased risk for early mortality and morbidity.¹⁶

While reversible organ damage is not a contraindication for MCS, severe irreversible organ damage and uncontrolled or irreversible illnesses that by themselves limit life expectancy may render the intervention futile and are still contraindications for MCS.¹⁶

Increased pulmonary vascular resistance (>6 Wood units) unresponsive to pharmacological intervention,¹⁷ renal dysfunction (with creatinine >3.5¹⁷ or 5 mg/dl¹³) and hepatic impairment (with total bilirubin >5 mg/dl^{13,17} or alanine aminotransferase, aspartate aminotransferase, or total bilirubin >5 times normal¹⁶) and INR >1.5¹⁶ have been used as exclusion criteria in studies of long-term MCS as DT^{13,16} or as BTT.¹⁷

Characteristics of first generation pulsatile LVADs

The previously reviewed studies and the INTERMACS registry included patients supported mainly by pulsatile VADs. The HeartMate VE and XVE, known as HeartMate I, and the Novacor are the most widely used and studied long-term implantable LVADs. They are first generation pulsatile LVADs, capable of providing flows up to 9-10 L/min, but typically providing flows of 5-7 L/min. They both have large pulsatile volume displacement pumps weighing 1.5-2 kg. The pumps include a compliance chamber receiving blood from the left ventricle, inflow and outflow one-way biological

valves, and large air-venting percutaneous drivelines. Pneumatic or electromagnetic (pusher-plate) compression of the compliance chamber ejects the blood into the ascending aorta, producing pulsatile flow. Implantation of these pumps is a difficult and lengthy procedure; the creation of a large sub-diaphragmatic pump pocket imposes an added risk of perioperative morbidity and mortality and is contraindicated in patients with a BSA of 1.5 m² or less.¹⁸

Pulsatile pumps are usually operated in an automatic fill-to-empty mode. They are preload-dependent; thus, adequate ventricular filling must be ensured. Blood is ejected into the aorta at a rate that is asynchronous to the intrinsic cardiac rate (although a degree of synchronicity might occur). These volume displacement LVADs fully unload the left ventricle, keeping the aortic valve usually closed, or allowing sporadic partial opening. Leaflet fusion and aortic root thrombosis can occur. Arterial pulsatility is maintained because of the pulsatile LVAD flow. Regular opening of the aortic valve of an LVAD operated in volume mode means device malfunction, or competitive ejection of the left ventricle (LV) and less device dependency. Since pulsatile LVADs require adequate LV filling (i.e. pump preload), decreased right ventricular output or volume depletion results in low LVAD flow and LVAD bradycardia. Volume overload results in high LVAD flow and LVAD tachycardia. Excessive LV volume offloading may result in the interventricular septum shifting to the left and precipitate right ventricular failure. Pulsatile pumps are not afterload sensitive, but hypertension should be controlled in order to decrease the risk of cerebral bleeding, to allow full emptying of the compliance chamber (thus avoiding blood stagnation and the risk of thromboembolism), and possibly to contribute to increased pump durability.^{8,19,20}

Characteristics of second generation continuous flow LVADs

Second generation implantable long-term LVADs were designed to address some of the problems related to the first generation implantable pulsatile devices,²¹ such as infection, bleeding, and device malfunction or failure. These devices have a simplified pumping mechanism with no requirement for compliance chambers, valves, or external venting.²² They evacuate blood from the left ventricle and pump it to the systemic circulation (the ascending or descending aorta) in a continuous flow pattern. Their basic prin-

ciple of function is based on the Archimedes screw,²³ which was designed in ancient Greece and used to pump water. Continuous axial blood flow is generated by a turbine impeller²³ rotating at high speeds on mechanical bearings. The pump output and flow pattern depend on the differential pressure (delta pressure) across the pump, and the rotational speed (rpm) of the pump. The delta pressure across the pump equals the pressure at the inflow site minus the pressure at the outflow site of the pump.²⁴

delta pressure = pressure at inflow site – pressure at outflow site

Assuming that the pressure drop inside the inflow and outflow conduits approximates zero, the pressure at the inflow site equals the LV pressure – representing the preload to the pump – while the pressure at the outflow site equals the pressure of the systemic circulation – representing the afterload to the pump.²⁴

delta pressure = LV pressure – systemic circulation pressure

Being preload and afterload sensitive, continuous flow pumps require adequate ventricular filling, and controlled systemic arterial pressure. At a given differential pressure the pump flow depends on the pump rotational speed, which should also be adjusted. Within limits, increasing the pump speed results in increased pump flows.²⁴

The flow created by axial flow pumps can be steady or pulsatile.²⁴ At high pump flows the aortic valve remains closed and there is a loss of arterial pulsatility. With progressively decreasing pump flow, if there is some ventricular contractility ventricular ejection through the pump and through the aortic valve occurs during systole; thus, a degree of pulsatility is produced. Ejection of the left ventricle through the device pump provides a degree of pulsatile flow, noted even with a closed aortic valve.^{8,20,24,25}

Intraoperatively, and when the chest remains open, the rotational speed should be low to avoid air suctioning.²⁵ After chest closure continuous flow pumps are usually operated at higher speeds early after initiation of support, to ensure good pump flow and tissue perfusion as well as adequate ventricular decompression to promote recovery. Excessive speed can cause septal deviation, tricuspid regurgitation, and right ventricular dysfunction. As a degree of cardiac recovery is achieved, the pump rotational speed, and thus the pump flow, is decreased, allowing ejection through the aortic valve.^{19,20,24-27} Decreased pump speed is desirable at least after the early post-implantation period, to encourage cardiac retraining and recovery, allow partial ejection and washout of the aortic valve, and some systemic pulsatility.²⁸ A pulse pressure difference >20

mmHg is usually correlated with partial aortic valve opening.¹⁹ Because of reduced arterial pressure amplitude, the pulse may not be palpable or audible with a sphygmomanometer and a stethoscope, and Doppler measurements might be required. When there is no improvement of ventricular function, opening of the aortic valve does not occur and the pulse pressure amplitude remains quite low (<10 mmHg).²⁹

Echocardiography can assist in adjusting the pump speed, by evaluation of right ventricular function, LV dimensions, septal deviation, and aortic valve opening. Excessive diminution of the LV cavity as well as overdistension (LV end-diastolic diameter >5.5-6 cm) should be avoided. Unlike the pulsatile pumps, newer generation devices can create high negative pressures and cause suction events.³⁰ If the pump is set at very high levels and/or the left ventricular filling is suboptimal, such as in excessive diuresis or bleeding, suction of the interventricular septum can obstruct the pump inflow and significantly decrease the LVAD outflow. In this case, volume to increase LV filling and/or decrease of the rotational speed is required.²⁴ Apart from hypovolemia, low LVAD flow can be the result of low right heart output due to decreased right ventricular contractility and/or increased pulmonary vascular resistance. Under these circumstances it is necessary to increase LV filling by improving the right heart output. Increasing the rotational speed hoping to enhance device output is hazardous, causing further LV diminution and worsening of the septal shift, thus further impairing right ventricular function. This vicious circle may require implantation of a right ventricular assist device in order to avoid a fatal outcome.²²

Unlike the first generation LVADs, continuous flow pumps, being valveless, allow regurgitant flow from the aorta to the left ventricle when they stop rotating or when they rotate at low speeds.³⁰ Excessive regurgitant flow via the pump when it is set at low speed may be a disadvantage if recovery is sought through progressively increasing the partial LV volume loading. Similarly, evaluation of recovery with the pump off or running at a low speed can be difficult when there is significant regurgitation via the pump.

Second generation, implantable, continuous flow pumps, such as the MicroMed DeBakey (MicroMed Technology, TX, USA),²⁴ the Thoratec HeartMate II (Thoratec Corporation, Pleasanton, CA, USA),^{28,31} and the Jarvik 2000 (Jarvik Heart, Inc, New York, NY, USA),^{22,25,26} typically deliver less output than their pulsatile predecessors.¹⁸ Although they are capable of

providing flows up to 7 L/min at a normal afterload, thus being able to offer full support for the majority of patients, creating a “relatively pulseless perfusion”,³¹ they typically deliver 3-5.5 L/min. Thus, they are usually operated as partial support devices, creating a “partial pulsatile flow”,²⁸ and have therefore been considered as assist rather than replacement devices.^{26,32}

The Micromed DeBakey

The Micromed DeBakey was the first newer generation, long-term, implantable, continuous axial flow LVAD to be used clinically, demonstrating that continuous “non-physiological” blood flow was compatible with sufficient end-organ perfusion and well tolerated in humans.^{24,33}

One hundred fifty patients underwent implantation of the Micromed DeBakey LVAD as a BTT in a prospective, multicenter trial between 1998 and 2002. Adverse events included reoperation for bleeding (32%), hemolysis (defined as plasma free hemoglobin >40 mg/dL, 12%), thromboembolic events (embolic stroke, transient ischemic attack, and peripheral embolism, 10.7%), pump thrombus (11.3%), device infection (3.3%), and pump failure (2.7%). The mean support time was 75 ± 81 days. Fifty-five per cent of patients were either BTT, BTR (n=1), or remained on support (n=1), and 45% of patients died.³³ This initial experience showed that the Micromed De Bakey, with its small, easily implantable, and silent axial-flow pump, provided adequate circulatory support and improved quality of life, with a low incidence of infection and device failure, but also highlighted a high incidence of pump thrombosis.³³

The Jarvik 2000

The unique design of the Jarvik 2000 (Figure 2) provides several potential advantages. The intracardiac positioning of the pump eliminates the need for pocket creation and therefore the risk of pocket infection. The absence of an inflow conduit eliminates the risk of inflow conduit thrombus or pannus formation.³⁴ The postauricular driveline exit provides fixation in a well vascularized area, decreasing the risk of exit site infection.³⁵ The intermittent low speed controller offers the advantage of periodically permitting the left ventricle to partially fill and partially eject through the aortic valve, ensuring aortic valve and root washout.²⁶ Human studies showed low regurgitant volume with the pump off.³⁶



Figure 2. Photograph of the pump, the outflow conduit and the percutaneous driveline of the Jarvik 2000, a second generation left ventricular assist device, before off-pump implantation in one of our patients. The pump itself is implanted inside the left ventricle; thus, there is no need for an inflow conduit or pocket creation.

The Jarvik 2000 offers flexibility of insertion, since it can be inserted via thoracotomy (with outflow graft anastomosis to the descending aorta) or via sternotomy (with outflow graft anastomosis to the ascending aorta), with or without the use of extracorporeal circulation.^{25,26,37,38} The simplified surgical implantation through a left thoracotomy is preferred in patients with previous sternotomy or when sternotomy is better avoided.¹⁸ The avoidance of cardiopulmonary bypass has several theoretical advantages, including less bleeding, right ventricular failure, and multiorgan injury.^{26,38} While in most very ill, but stable, class IV end-stage heart failure patients the Jarvik 2000 can be inserted off-pump via a left thoracotomy, this approach is not indicated in patients in extremis or cardiogenic shock, and in patients with suspected ventricular thrombus or requiring concomitant procedures.²⁶ Off-pump implantation of the Jarvik 2000 via median sternotomy in an inotrope-dependent patient with a gigantic heart has been reported, with application of a suction device and pharmacological management.³⁸ Although off-pump insertion through a sternotomy is possible with other implantable devices (such as the HeartMate I³⁹) the simplicity of the Jarvik implantation makes it particularly suited for this role.³⁸

The first permanent implant of the Jarvik 2000 was performed in the UK in June 2000.⁴⁰ This patient remained on support for more than 7 years and holds the record for LVAD support with the original device. In the collaborative feasibility study of destination therapy with the Jarvik 2000⁴¹ the pump was im-

planted in 17 selected transplant-ineligible end-stage heart failure patients. Actuarial 1-, 2-, and 3-year survival rates were 56%, 47%, and 24%, respectively. The median duration of support was 293 days. There was no mechanical failure of the implantable parts of the device during a cumulative support time of 15.9 years. Extradural hematoma at the postauricular power cable exit site, aortic root thrombosis, and insufficient output in a large patient with no recovery of an ischemic left ventricle, were some of the early adverse events related with poor outcome. Skull thickness measurements prior to the implantation, modifications of the skull pedestal instrumentation, improvement of the anticoagulation regime, and the new intermittent low speed controller, were adopted to overcome these device-related adverse events. The complication rate was lower in severely symptomatic but ambulatory patients who did not deteriorate into cardiogenic shock, than in terminally ill, hospital bound, transplant-ineligible patients.⁴¹ An earlier study also showed that the patients who benefited most from implantation of the Jarvik 2000 were those who required left ventricular assistance rather than total replacement. This continuous flow LVAD was most effective when there was residual native ventricular function to maintain aortic root ejection and pulsatility.⁴²

Further studies confirmed that the device was reliable and durable. Among 102 patients implanted with the Jarvik 2000 between April 2000 and December 2004 freedom from implantable component mechanical failure was 100%, during a cumulative patient support time of 59 years.⁴³ The UK experience showed a significantly higher discharge-to-home rate in Jarvik recipients in comparison to non-Jarvik MCS recipients.⁴⁴

Our own experience with the Jarvik 2000 has been excellent.²¹ We implanted the device via a left thoracotomy, off-pump, in 2 patients with acute decompensation of advanced chronic heart failure due to non-compaction cardiomyopathy and anticipated 6-month mortality higher than 50%. The intermittent low speed controller and postauricular pedestal cable exit were preferred. Care for the postauricular driveline exit site was minimal and wound healing was optimal. Both patients underwent early extubation and rehabilitation. The patients encountered minimal or no discomfort in daily activities and after 2-3 days of training they were comfortable with making all necessary changes of external components and battery charging. There were no major adverse events in the

whole period of support. Both patients are alive and well, 20 and 19 months post implantation, leading near normal lives, free of cardiac-related hospitalizations. The device can be used as destination therapy while recovery of the LV is evaluated. Heart transplantation also remains an option.

The HeartMate II

The HeartMate II (Thoratec Corporation, Pleasanton, CA, USA) (Figure 3) is another promising second generation LVAD that was redesigned to overcome device-related poor outcomes (mainly involving increased thrombogenicity of the inflow conduit) encountered during its first clinical use in a European study.²⁸

One hundred thirty-three patients with end-stage heart failure listed for heart transplantation were entered in a prospective, non-randomized, multicenter study without a concurrent control group and underwent implantation of the HeartMate II (as a BTT).¹⁷ Survival at 6 months, regardless of whether the patients had actually undergone transplantation, had ongoing mechanical support while remaining transplant eligible, or had cardiac recovery, was considered the principal outcome and occurred in 75% (100 patients) (Table 1). The duration of support ranged between 1 and 600 days (median 126 days, mean 168 ± 148 days). The survival rate during support was 75% and 68% at 6 and 12 months, respectively.¹⁷ Adverse events included bleeding requiring surgery (31%), ventricular arrhythmias requiring cardioversion or defibrillation (24%), local infection unrelated to the LVAD (28%), respiratory failure (26%), sepsis (20%), percutaneous lead infection (14%), renal failure (14%), and stroke (8%).¹⁷ LVAD therapy provided effective hemodynamic support and was associated with significant improvement in quality of life and functional status. Support by the second generation continuous axial flow HeartMate II in this study was associated with fewer infections, less incidence of right ventricular failure requiring right ventricular mechanical support, less bleeding, and less stroke compared with the first generation pulsatile flow HeartMate I, reported in a previous study.^{17,45} According to the company's data (www.thoratec.com, accessed May 22, 2008), in the BTT arm of the HeartMate II pivotal trial the cumulative survival (BTT, BTR, ongoing support) of 194 recipients at 6 months and 1 year was 80% and 77%, respectively.

Excellent results and excellent technical performance have been reported recently from the implan-



Figure 3. The HeartMate II, a second generation axial flow left ventricular assist device (LVAD). The HeartMate II has been recently (April 2008) approved by the FDA for bridge to transplant (BTT). Apart from the MicroMed DeBakey Child, it is the first FDA-approved newer generation continuous flow LVAD, and the first FDA-approved device for BTT since the inception of INTERMACS. All post market data will be collected using the INTERMACS registry and soon large scale data will be available (www.intermacs.org, accessed on May 12, 2008). (Reprinted with permission from Thoratec Corporation).

tation of the redesigned HeartMate II in 43 patients as a BTT (n=26) and DT (n=17). The mean duration of support was 258 days (1-761 days). Nine patients died, 4 patients were BTR, 3 patients were BTT, and ongoing support was reported in 27 patients (longest duration > 700 days). The Kaplan-Meier analysis showed an 80% overall 1-year survival rate, while the quality of life and the functional status were greatly improved after the perioperative period (Table 1).⁴⁶

Third generation devices

While continuous axial flow devices with mechanical bearings of the impeller have been characterized as second generation VADs, continuous axial or centrifugal flow devices with bearingless impellers or rotors based on magnetic or hydrodynamic levitation or a combination of the two have been characterized as third generation devices.⁴⁷

Long-term third generation devices with magnetic levitation technology (maglev) include the axial flow LVAD INCOR (Berlin Heart, Berlin, Germany) (Figure 4),⁴⁸ and centrifugal flow LVADs such as the DuraHeart (Terumo Heart Inc., USA),⁴⁷ the Heart Mate III (Thoratec, Corporation, Pleasanton, CA, USA),⁴⁹ and the Levacor (WorldHeart, Oakland, CA, USA).⁵⁰ The Ventrassist (Ventracor, Sidney, Australia),⁵¹ which includes a bearingless centrifugal pump with hydrodynamic rotor levitation, has also been classified as a third generation LVAD.

Third generation magnetically levitated devices have only one moving part (impeller or rotor) that is suspended within a magnetic field and has no direct mechanical contact with the pump's static components. This design aims to decrease mechanical friction, heat production and shear stress, and thus pre-

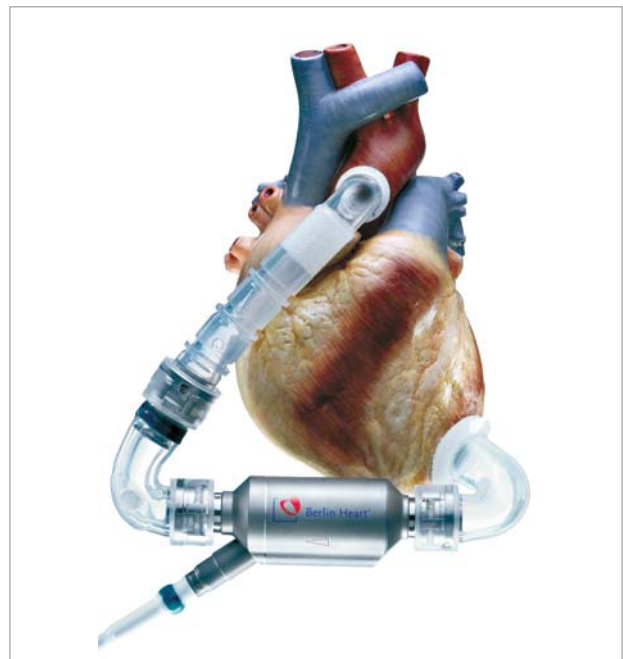


Figure 4. The Incor, a third generation left ventricular assist device, with a bearingless, magnetically levitated, axial flow pump implanted in the chest. (Reprinted with permission from Berlin Heart GmbH; www.berlinheart.com)

sumably results in increased durability, low energy requirements, and reduced damage to the blood components.⁴⁸

Although little explored in humans, the pump output and flow pattern of the third generation pumps resembles those of the second generation axial flow pumps. Suction events occurred with the InCor in dehydrated or generally hypovolemic patients, or during rising from supine to upright position. A newer version of the InCor system is equipped with an anti-suction algorithm, reducing the pump speed when detecting decreased pulsatility of the blood flow through the pump and automatically returning the speed to the preset level when the danger of the suction event is overcome, thus preventing regurgitant flow through the pump.⁴⁸

Skepticism has been expressed about the need of moving to third generation devices with complicated systems such as the maglev system while results with the second generation pumps are still promising.⁴⁷ The potential advantages of the third generation over the second generation LVADs will remain theoretical until clinical application proves substantially increased durability and biocompatibility, with less device malfunction and failure, minimized thromboembolic events, less anticoagulation requirement, and less hemolysis.

Elective bridging to recovery with a third generation LVAD

Our experience with a third generation LVAD, which has a bearingless, magnetically levitated, centrifugal pump, was excellent. We performed the first implantations worldwide in a human of the Levacor (World Heart, Oakland, CA, USA) (Figure 5) in two transplant-ineligible end-stage heart failure patients.⁵⁰ Despite good end-organ function, and the absence of major adverse events (such as sepsis, thromboembolic events, bleeding, clinically significant hemolysis, or device failure), the improved biocompatibility and durability of the newest LVADs in comparison to second generation devices remains to be proven.

Not only a novel device, but also a novel strategy of elective bridging to recovery (EBTR) was applied. Bridging to recovery is based on evidence that unloading the heart with an LVAD promotes reverse ventricular remodeling and myocardial recovery, which in a subgroup of patients is sufficient for device explantation, sustained for varying periods of time, sometimes over several years.⁵²⁻⁵⁴ Bridging to recov-

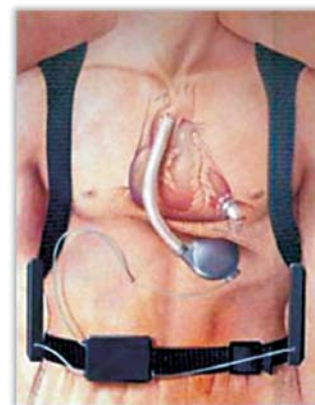


Figure 5. The Levacor left ventricular assist device, with a third generation magnetically levitated centrifugal pump. We first clinically implanted the Levacor as an elective bridge to recovery.⁵⁰

ery is an attractive implantation strategy, though one that is still at a rather early stage of investigation. The incidence of spontaneous myocardial recovery sufficient for device explantation is low. The subgroup of heart failure patients with high chances of recovery is not well defined; therefore, there are no well established patient selection criteria. Furthermore, the type and duration of mechanical support required for lasting recovery have not been clearly determined.^{53,55}

The incidence of recovery with MCS is higher in fulminant myocarditis, acute myocarditis, postpartum cardiomyopathy, and dilated cardiomyopathy, than in chronic ischemic cardiomyopathy with myocardial fibrosis. In general, long standing pathology, particularly ischemic, and advanced age of recipients are considered poor prognostic indicators for recovery.^{1,53-57}

According to the INTERMACS registry, BTR was the initial implantation strategy in less than 6% of long-term MCS recipients and had rather poor results.^{6,14} In a prospective, multicenter, observational study, only 6 (9%) of 67 patients who received long-term support as BTT and were regularly evaluated for cardiac recovery actually achieved full cardiac recovery and underwent device explantation.⁵⁶ In a retrospective study from an experienced centre, involving 970 chronic end-stage or acute heart failure VAD recipients, recovery sufficient for device explantation occurred in 76 patients (7.8%). In 72 of these 76 patients who were ultimately BTR the initial implantation strategy was permanent support.⁵⁸

Innovative combined strategies have been employed in an attempt to improve results. The Harefield protocol includes a combination of MCS and heart failure medication to maximize reverse remodeling, fol-

lowed by administration of clenbuterol (a selective β_2 -adrenergic receptor agonist) to promote physiologic cardiac hypertrophy.^{52,57} Eleven of 15 (73%) selected long-term LVAD recipients suffering from non-ischemic, and non-acute cardiomyopathy, who survived the perioperative period and in whom the combined protocol was applied, were successfully BTR. These 11 patients represented 46% of all LVAD recipients with non-ischemic cardiomyopathy.⁵⁷

Our protocol of elective bridging to recovery can be described as a multidisciplinary approach, combining reparative heart failure surgery, concomitant elective LVAD support, optimal heart failure medication, and cardiac resynchronization therapy. It was offered to two end-stage heart failure patients who were ineligible for transplantation, with heart failure symptoms in NYHA class IV (67 and 78 years old at implantation). Both patients suffered from long standing (>10 years) idiopathic dilated cardiomyopathy and had recently developed concomitant single vessel coronary artery disease. The downstaging of heart failure assured by the LVAD allowed: (1) extensive surgical repair (including mitral valve repair, revascularization and surgical ventricular reconstruction) in patients with high anticipated surgical morbidity and mortality; and (2) aggressive medical treatment that, because of the advanced disease, had been poorly tolerated prior to device implantation.⁵⁹ Both patients were successfully bridged to recovery after a rather short period of support (3 months) without occurrence of major complications. Cardiac recovery was achieved and sustained 24 and 22 months post device explantation. Larger scale application is required to validate our surgical approach to elective bridging to recovery.

Comparison of results with first and newer generation devices

The efficacy of continuous axial flow pumps compared with pulsatile, volume displacement pumps, with respect to the comparative outcomes (mortality, morbidity, adverse events), the characteristics of left ventricular unloading,⁶⁰ the hemodynamic and cellular responses,⁶¹ the end-organ function, and the exercise performance, remains largely unstudied.⁶² All comparative data come from non-randomized comparisons of small numbers of patients, and selection bias probably exists, since continuous flow pumps are considered as assist rather than replacement devices and are indicated for application in less sick patients.

A retrospective comparison of a small number of

patients implanted with either first generation pulsatile LVADs (HeartMate or Novacor) or the newer generation non-pulsatile Jarvik 2000 LVAD in similarly ill congestive heart failure patients showed a similar benefit from both non-pulsatile and pulsatile devices.¹⁸

Patients implanted with a continuous axial flow device (Micromed DeBakey or Incor, n=50) were compared with a matched control group implanted with a pulsatile device (Novacor or HeartMate, n=80). With similar duration of support, successful BTT, 30-day and long-term survival after cardiac transplantation were similar among the different LVAD groups. However, a greater incidence of post-transplant rejection was noted with the continuous flow devices.⁶³

A non-randomized comparison of a small number (n=31) of patients with similar baseline hemodynamic, echocardiographic, and clinical heart failure characteristics, who were BTT with long-term LVADs (10 nonpulsatile, 21 pulsatile), showed comparable preoperative and postoperative transplantation survival in the two groups. The degree of LV pressure unloading was identical in the two groups, but LV volume unloading was more pronounced with the pulsatile device because of a statistically significant higher pump output.⁶⁰

A non-randomized comparison of support with a pulsatile pump (HeartMate XVE, n=16) or a continuous axial flow pump (HeartMate II, n=18) showed significant and similar hemodynamic support and exercise capacity improvement. However the continuous flow LVAD was associated with lower left ventricular volume unloading and a greater mitral valve regurgitant volume.⁶²

A non-randomized comparison of 20 consecutive patients implanted with the pulsatile Novacor (n=12) or the continuous flow DeBakey (n=8) showed that both types of LVAD resulted in similar hemodynamic effects, with the exception of a greater degree of LV volume unloading on the echocardiogram with the pulsatile LVAD. Both forms of support effectively normalized the cellular markers of the failing myocardium phenotype.⁶¹

While the optimal degree of LV unloading during MCS remains unknown,⁶³ and despite a recent report of similar LV volume unloading with the HeartMate I and II,⁶⁴ it seems that the LV volume unloading with continuous flow pumps in common clinical practice is less than in pulsatile pumps. This may be related to the fear of ventricular collapse and suction events (associated with decreased pump output, pump failure,

right heart failure, hemolysis and thrombotic risk), so that continuous flow pumps were usually set at sub-maximal rotational speeds, thus producing sub-maximal flows. Integration into the pump controller of algorithms (mechanisms to detect ventricular suction and automatically decrease the pump rotational speed when adequate supply is not available)⁴⁸ will probably allow adequate unloading without the fear of ventricular collapse.

The flow pattern produced by continuous flow pumps seems to be tolerated well by the human organism.^{22,24-28} A retrospective comparison of patients bridged to transplantation and supported for >6 months with continuous flow devices (Jarvik 2000 or HeartMate II, n=12) or the pulsatile device HeartMate I (n=58) showed similar patient survival and a similar efficacy of pulsatile and non-pulsatile devices in providing adequate blood flow and maintaining proper end-organ function for prolonged periods of MCS (up to 15 months).⁶⁵

A similar increase of biochemical markers of brain injury was noted in the early postoperative course after implantation of a continuous flow LVAD (Micromed DeBakey with non-pulsatile flow in the early postoperative period, n=8) and a pulsatile flow LVAD (Novacor, n=7). This may indicate that the continuous flow noted in the early post device implantation period does not cause increased brain injury or permeability of the blood- brain barrier.⁶⁶

Discussion

The first generation LVADs are the most widely used and best studied devices. The recent results of long-term MCS, mainly with the use of pulsatile VADs reported from the INTERMACS-registered hospitals of the USA, have been substantially improved. One-year survival of about 70% of pulsatile LVAD recipients has been shown.

Although newer LVADs promised better results, more evidence is required to allow robust comparisons with the first-generation devices.⁴⁴ We need to obtain better knowledge about the large scale recent results from the implantation of newer generation pumps. Both published and anecdotal data from ongoing studies (announcements at congresses, data from companies' registries) show a tendency for improved early survival, and it is anticipated that 1-year survival may exceed 70%.

A European registry compatible with the INTERMACS registry is imperative so that we may

evaluate the results from the use of pulsatile and continuous flow technology in Europe. Several newer generation pumps have CE (Conformité Européenne) mark certification; thus, valuable information will be yielded by a European registry. Cooperation between academic and clinical researchers, public bodies and authorities, health insurance providers, and the industry's scientists, as well as the adoption of a common international language for the definition of adverse events and outcomes will all be required.

Improved models of the first generation pulsatile LVADs^{12,13,67} still have a role in MCS, especially when there is a perceived need for high pump output, such as in patients with a large BSA, in profound cardiogenic shock, lack of residual intrinsic LV activity, end-organ impairment, multiple comorbidities and refractory ventricular arrhythmias. The HeartMate XVE offers the advantage of requiring antiplatelet treatment only, so it can be used in patients with contraindications for anticoagulation.¹⁸

Newer generation, continuous flow LVADs are more silent and smaller (Figure 6), offer the advantage of simpler implantation techniques, require smaller or no pump pockets, decrease the surgical trauma, have thinner drivelines, and allow easier, faster, as well as less invasive or off-pump implantation.^{18,26,68} They can be implanted in smaller patients (BSA >1.2 m²), women and adolescents,¹⁸ while some of them have pediatric models. They have been considered as assist rather than replacement devices, acting synergistically with the LV, and are better applied at earlier stages of the disease in patients with some remaining pumping activity.^{18,24,26,41,42} There is evidence of a decreased likelihood of bleeding and infection^{17,33,35,69} and increased durability and reliability;^{33,43} thus, the use of newer generation LVADs will potentially decrease



Figure 6. The pumps and the drivelines of the HeartMate I and II. Note the smaller size of pump and driveline of the HeartMate II. (Reprinted with permission from Thoratec Corporation.)

morbidity and mortality from device-related infection and device failure, which is desirable in bridging strategies but imperative for successful destination therapy.

Despite the advantages offered by the axial flow technology, major disadvantages remain. Since most devices are still not fully implantable, a significant risk of infection remains.⁴⁴ Careful and precise anticoagulation is required to avoid the dreadful complication of stroke, which for the time being remains the Achilles' heel of MCS.

Although MCS is clinically effective and offers quality-adjusted life-years, it has been considered expensive and not cost-effective at traditional thresholds. Wider application and a reduced rate of adverse events will probably lower the costs, while improved survival and quality of life will increase the cost-effectiveness, which should be re-evaluated as results improve.^{70,71}

Conclusions

In the first half of the current decade the large scale documented survival with long-term MCS was far lower than the reported survival after heart transplantation (1-year survival of 80% post-transplantation).⁷² The shortage of donor hearts imposes the need for continuing research to offer alternative treatments to the thousands of patients dying from advanced chronic heart failure every year.⁷³ The epidemiological impact of transplantation is very low and is progressively declining, thus DT and BTR will progressively assume a major role in long-term MCS.

Patient selection plays a key role in improving results. Regardless of advances in technology, it remains difficult to achieve exemplary results in end-stage chronic heart failure patients who are ineligible for transplantation, in profound shock, right sided heart failure, or severe end-organ dysfunction.^{2,6,7,9,14,41} Implantation before the patients reach an irreversible catastrophic state could further improve the outcomes.

The results with the latest generation pumps do not at present allow characterization of these devices as "breakthrough" devices. The results of many ongoing trials that use newer generation devices will soon be available. Improved results are now anticipated, after the initial learning period, with improving device technology, and patient selection and management. Improved models of newer devices are increasingly used, allowing novel strategies of support.

Recovery of end-stage heart failure patients has

been achieved for the first time in the history of medicine, and bridging to recovery is a challenging and probably the most desirable outcome of MCS. Bridging to recovery with combined treatments (of MCS with pharmacological, surgical, or cell therapy), or by earlier elective application of miniaturized easily implantable LVADs capable of providing partial support, represent intriguing future perspectives. Long-term support as destination therapy, as a bridge to recovery, to decision, or to future therapeutic options will assume an increasingly important role. If the recently achieved improvement in 1-year survival, approximating 70%^{14,17} or even 80%,⁴⁶ is established, and if increased survival can be maintained for 2-5 years, long-term MCS as an equivalent alternative to transplantation (in transplant-eligible candidates) will be a viable consideration.

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