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Implantable left ventricular assist devices

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Congestive heart failure (CHF) is a major cause of morbidity and mortality in Canada. The syndrome is characterized by a reduction in cardiac output and ineffective emptying of the left ventricle during systole. This results in lower systemic perfusion pressure to vital organs, an elevation of the left ventricular end-diastolic pressure (LVEDP), and neurohumoral activation. The increase in LVEDP impairs left atrial emptying causing an increase in pulmonary venous pressure and, subsequently, pulmonary congestion. Further increases in LVEDP decrease the coronary artery perfusion gradient, further restricting cardiac function. Ultimately, the syndrome culminates in refractory hypotension, hypoxemia, arrhythmias, and death.

Heart failure is the only major cardiovascular disorder that is increasing in incidence and prevalence today. This is a reflection of the aging population and the effective palliative medical therapies available. In addition, many patients have undergone successful emergency interventions for otherwise fatal acute coronary events only to develop CHF at a later date. According to the Heart and Stroke Foundation of Canada, an estimated 420,000 Canadians were living with heart failure in 1997. In that same year, 48,000 deaths were attributed to CHF in Canada. These values reflect a prevalence of 1-2% in the general population with an increase to 6 -10% in patients older than 65 years.

Medical therapy is effective at improving the quality of life of patients with CHF[1] and has achieved limited success in extending the lives of these patients.[2,3] Unfortunately, many ultimately succumb to the disease. In this regard, the median survival after diagnosis is 1.7 years in men and 3.2 years in women with a 5-year survival of <50%.[4] Cardiac transplantation, however, is a very effective therapy for end-stage heart failure. Transplantation survival rates are currently approximately 85% in the first year and 50% at 10 years.[5] Unfortunately, a large and increasing discrepancy exists between the number of patients who could benefit from transplantation and the number of available donor hearts. For instance, since 1993, the number of heart transplants performed per year in Canada has remained constant at 160-180/year. At the same time, the number of patients waiting for cardiac transplantation has increased from 78 in 1991 to 112 patients in 1997, with a mortality rate of 10-15% while awaiting a donor organ. Since efforts aimed at increasing the supply of donor organs have failed,[6] alternative therapies for CHF must be pursued. Mechanical support, by means of an implantable left ventricular assist device, represents an underutilized and promising alternative for a large number of Canadian patients.

Implantable left ventricular assist devices

Left ventricular assist devices (LVADs) are mechanical pumps that restore normal hemodynamics, and therefore end organ perfusion, in patients with profound myocardial dysfunction.

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Figure 1: The HeartMate Vented Electric LVAD

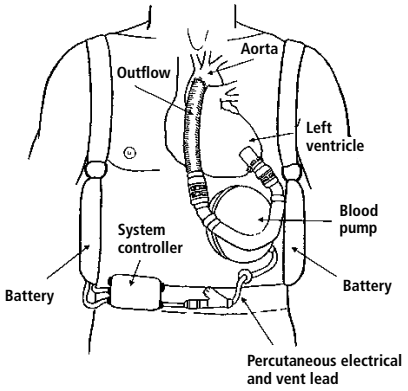
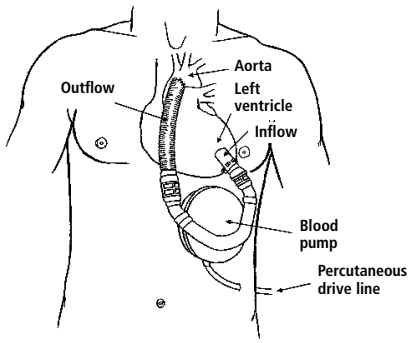


Figure 2: The HeartMate Implantable Pneumatic LVAD



The array of ventricular assist devices available today include:

- extracorporeal membrane oxygenation (ECMO) devices
- uni- and biventricular extracorporeal nonpulsatile devices
- extracorporeal and implantable pulsatile devices, and
- the total artificial heart.

As discussion of each of these support modalities is beyond the scope of this review, it will focus on recent technical and clinical advances pertaining to the implantable, pulsatile left ventricular devices.

During the past 5 years, LVADs have revolutionized the treatment of patients with chronic end-stage heart failure. LVADs have been inserted to bridge hemodynamically unstable patients to transplantation. In addition, more recent indications for device use in Europe include temporary bridging while awaiting myocardial recovery and insertion as a long-term therapeutic modality.[7] With respect to the latter, certain advantages can be envisioned by this treatment strategy in patients who are not transplantation candidates and have failed medical therapy. These include earlier hemodynamic support prior to irreversible end organ damage, lack of immunosuppressive medications and rejection, and the unlimited availability of devices.

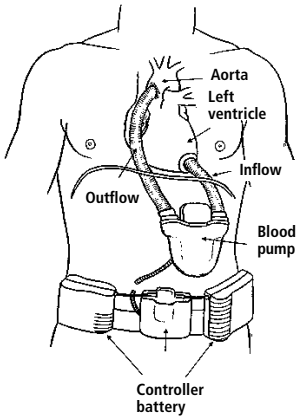
Technological advances in miniaturization have resulted in the development of electrically powered, wearable devices. These highly portable, implantable LVADs have enabled patients to leave hospital and return to work or school while awaiting transplantation. They provide pulsatile flow resulting in high cardiac outputs (>9 L/min) for prolonged periods of time. Implantable left ventricular assist devices available today for clinical use include the Novacor N100 (Baxter Healthcare), and the HeartMates 1205 VE and IP (ThermoCardiosystems). A fully implantable LVAD, the HeartSaver VAD (Ottawa Heart Institute and WorldHeart Inc.) developed in Canada, will be assessed in humans this year.

HeartMate LVADs

The HeartMate LVADs are implantable, pulsatile, assist devices designed to be portable and easy to operate (Figures 1 and 2). The HeartMate systems are implanted through a median sternotomy. The pump is placed below the left hemidiaphragm, either within the peritoneal cavity, or in a preperitoneal pocket. The inflow cannula extends from the apex of the left ventricle, across the diaphragm, and into the pumping chamber. A 20-mm Dacron outflow graft exits from the pump, crosses the diaphragm, and is anastamosed to the ascending aorta. The inflow and outflow conduits each contain a 25-mm porcine valve to ensure unidirectional blood flow. A drive line is externalized through the right or left abdominal wall from the pumping chamber and connected to the external power supply and control unit. Drive lines are covered with polyester velour that promotes bonding to the skin to reduce the risk of infection. The device has the advantage of a textured blood-contacting surface which encourages endothelial cells to form a pseudo-neointimal lining in the pumping chamber to reduce the risk of bacterial colonization and thromboembolism.[8,9]

Two HeartMate LVADs are in clinical use today, and although both use the same pump, their methods of actu-

Figure 3: The Novacor wearable LVAD



ation differ. The implantable pneumatic (IP) version (Figure 2), the HeartMate IP, is attached to an external drive console that sends pulses of air to move the pump's flexible diaphragm upward, thereby pressurizing the blood chamber. Diaphragmatic movement results in blood ejection into the aorta. Clinical trials of this device began in 1986 and it was the first implantable system to receive U.S. Food and Drug Administration approval for support of patients awaiting heart transplantation. The HeartMate IP has been used in more than 1000 patients at 120 centres worldwide.

The more compact and lightweight HeartMate VE (vented electric) contains a rotary electric motor positioned below the diaphragm in order to move the diaphragm rhythmically (Figure 1). This motion results in the ejection of blood into the aorta. The HeartMate VE is lightweight and small, allowing the patient nearly unlimited mobility in contrast to the pneumatic version which requires an accompanying large console. The HeartMate VE has an external vent to equalize the air pressure and permit emergency pneumatic actuation. Two rechargeable batteries provide 4-6 hours of charge. Clinical trials were initiated in January 1991 and the first patient to be discharged from the hospital with an implantable mechanical circulatory support system to await a donor heart at home did so with this device in 1994. The lightweight, portable features of the HeartMate VE and lack of anticoagulation make it a popular choice.

During normal operation, the HeartMate pumps completely unload the left ventricle and support cardiac output at physiological levels. A maximum blood flow of 11.6 L/min can be realized with the HeartMate IP in comparison to a pump output of 9.6 L/min obtained using a HeartMate VE. Pump output can be regulated by programming an automatic mode format or fixed rate mode.[10] In an automatic mode setting, the device ejects when the pump is 90% full or when it senses a decreased filling rate. Thus, when the patient's activity increases, the pump fills faster, and the rate automatically increases, resulting in increased pump output. Since the aortic valve rarely opens in patients supported with an LVAD, pump output is synonymous with cardiac output.

Novacor LVAD

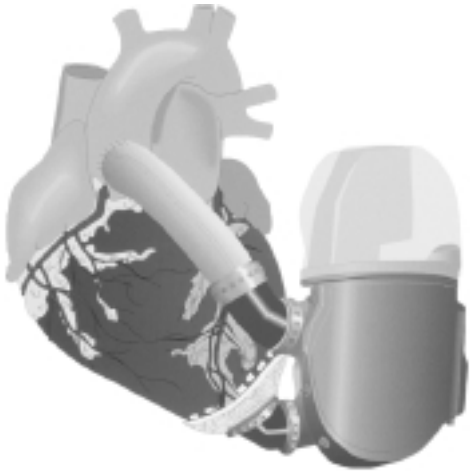
The Novacor LVAD is a portable, implantable pump designed for long-term use (Figure 3).[11] It differs significantly from the HeartMate in its method of pump actuation and use of smooth blood contacting surfaces. During pump systole, two electrically-operated opposing pusher plates compress a seamless polyurethane blood sac resulting in ejection of blood. Unidirectional flow is achieved with 21-mm bioprosthetic, valved conduits. The pump is implanted in the abdominal wall just anterior to the posterior rectus sheath. The externalization of the drive line and mode functions are similar to the HeartMate design. In 1993, the Novacor LVAD was converted from the console-operated system to the wearable system. Like the HeartMate VE, the small controller and battery packs provide unlimited patient mobility.

The FDA granted approval to conduct clinical trials in 1984 with the Novacor system. Subsequently, the world's first successful bridge to transplantation operation was conducted at Stanford using this device. In April, 1999, Baxter Canada received Notice of Compliance from Health Canada for the Novacor device. It is approved as a bridge to transplantation. Similar approval was granted in the United States by the FDA in September, 1998. In Europe, however, the Novacor device has been marketed since 1994 both as a bridge to transplantation and as a long-term alternative for patients who are not transplantation candidates and have failed medical therapy.

Over 1000 patients have received a Novacor LVAD. Baxter reports that one patient is entering the fifth year of support, while two in Europe have surpassed 3 years of continuous support. Six others have exceeded 2 years, while 50 individuals have been supported longer than 1 year.

Anticoagulation is necessary, however, to prevent thromboembolism with this device. Stroke volumes and

Figure 4: The HeartSaver Fully Implantable LVAD



maximum flow rates are similar to those achieved with the HeartMate LVAD. During long-term support, ambulatory patients can be discharged from the hospital and engage in their usual activities while awaiting a donor heart.

HeartSaver VAD

Several major limitations in the design of wearable LVADs, described previously, have been identified. First, the position of the pumping chamber in the abdomen can lead to complications with adjacent organs and result in diaphragmatic defects.[12] In addition, the externalization of the drive line accounts for a high incidence of infection. A fully implantable system could reduce the incidence of this complication significantly.[13,14] Finally, remote monitoring and programming could facilitate more patient freedom and improve the cost-effectiveness of longer-term follow-up. The HeartSaver VAD, designed and tested by a collaborative team at the The Ottawa Heart Institute and WorldHeart Inc., is a fully implantable VAD that may overcome these obstacles.[15] The HeartSaver VAD combines total implantability with an intrathoracic position, transcutaneous power transfer, and remote communication capability.

The current implantable HeartSaver VAD, version 5.1, consists of a 70 ml blood chamber with a flexible polyurethane diaphragm within a rigid housing (Figure 4). The silicone-based hydraulic fluid is pumped during systole through an energy converter consisting of a bidirectional, brushless motor, a bladed impeller, and a bladed housing. The hydraulic fluid actuates the flexible blood chamber diaphragm that ejects blood from the chamber. The blood chamber fills passively during diastole with the hydraulic fluid returning to the volume displacement chamber through a one-way valve. Bioprosthetic valves are mounted in the inflow and outflow cannulas to ensure unidirectional flow.

The HeartSaver has been shaped to fit within the thorax, which may provide several advantages over the implantable, wearable VADs. These include a shorter inflow cannula to improve blood inflow characteristics and a secure thoracic anchor (rib cage) to prevent device migration. Importantly, the issue of external venting for the compliance chamber is overcome by the intrathoracic position. In this regard, all pulsatile systems require a compliance chamber to compensate for air displacement.[16] As a result, an externalized venting drive line has been a necessity. To eliminate the need for percutaneous venting, a volume displacement chamber was integrated into the HeartSaver unit. This allows displacement of the hydraulic actuating fluid during device diastole. The hydraulic fluid chamber and flexible diaphragm are in contact with the lung tissue which is, in turn, in contact with atmospheric pressure. As a result, external venting is not required.

The HeartSaver VAD can be remotely powered, monitored and controlled using patented transcutaneous Energy Transfer (TET) and proprietary Biotelemetry technologies. To obtain the goal of total implantability, Heartsaver is remotely powered without wires or cables perforating the body by the TET system utilizing electromagnetic induction between two wire coils. The TET system consists of an external wire coil, a wire coil implanted under the skin and associated electronic modules on internal and external controllers. The TET system is used to transfer electrical energy through the user's intact skin and tissue to directly power the implanted device and the implanted, internal back-up battery. In addition to being remotely powered, the HeartSaver LVAD can be remotely monitored and controlled by the Biotelemetry data transfer system. The Biotelemetry system transfers data bidirectionally through intact skin and tissue using an infrared transmitter/receiver module. These modules are embedded in the TET system's two energy transfer coils and associated electronic modules on the internal and external controllers.

The HeartSaver LVAD is presently in pre-clinical *in vivo* and *in vitro* trials. Early prototypes have performed failure-free since 1992 *in vitro*. Following approval by Health Canada, clinical trials in humans are expected this year.

Patient selection for implantable mechanical support

Left ventricular assist devices are of benefit in three patient populations:

- those awaiting transplantation
- those with myocardial recovery over time following an acute insult
- as a long-term therapeutic modality for end-stage heart failure.

Bridging to transplantation

Consideration for insertion of an LVAD is warranted when specific conditions are present despite maximal pharmacological interventions. These include systemic hypotension, a cardiac index <2.0, a pulmonary capillary wedge pressure >20 mm Hg, and urine output <20 mL/h. In general, patients selected to receive LVADs are cardiac transplant candidates with end-stage heart disease without irreversible end-organ failure. Bridging is particularly valuable in heart transplant candidates unlikely to survive a 3-4 month wait for a donor organ. In addition, large patients or those with type O blood, for whom UNOS data indicate the average transplant waiting time is 595 days,[17] would also benefit from bridging. Both the HeartMate and Novocor devices have been approved by the FDA in the United States for use as a bridge to transplantation. The Novacor device is the only implantable LVAD approved for bridging to transplantation in Canada.

Thus far, the clinical experience with LVADs as a bridge to transplantation has shown dramatic improvements in cardiac output,[18,19] New York Heart Association functional class,[19,20] 6-minute walk endurance,[21] and peak oxygen consumption.[22] After implantation of an LVAD, patients can often return to work and engage in their usual activities of daily living.[23] With respect to mortality, the only controlled study of the effects of left ventricular assist support in bridge-to-transplant patients was performed with the HeartMate IP LVAD. The FDA approved a clinical study in which 116 HeartMate VAD bridge-to-transplant patients were compared to 46 control patients who met all the criteria for support, but who did not receive a device as a result of logistical problems.[24] The survival benefit in the device-supported patients was significantly compared to the control group (71% vs 36%) 90 days post-transplantation. Hepatic, renal, and neurohormonal parameters were normal in the VAD group at the time of transplantation.

Relative contraindications to use of an LVAD as a bridge to transplantation include recent pulmonary embolism, recent gastrointestinal bleeding, marked peripheral vascular disease, severe chronic obstructive lung disease, irreversible major neurologic deficits, or any other condition that might limit long-term survival after cardiac transplantation.[25]

Finally, assist devices may also be used as a bridge to transplantation in patients who cannot be weaned from cardiopulmonary bypass, patients who are in cardiogenic shock following a myocardial infarction or post-myocarditis, and in those with acute rejection following heart transplantation. Under these circumstances, however, *external devices* are employed in order to evaluate the potential for patient recovery prior to proceeding with the insertion of an implantable device.

Bridging to recovery

Some centres have reported sufficient clinical improvements in selected patients to permit device removal. This patient outcome has defined another potential role for the use of LVADs, namely, as a "bridge to myocardial recovery." Mechanical unloading by an LVAD has been shown to attenuate the histological changes caused by chronic heart failure. These include normalization of fibre orientation,[26] regression of myocyte hypertrophy,[27] a reduction in myocyte wavy fibres,[28] and reduced contraction band necrosis.[28] These histologic changes have been shown to to be accompanied by favourable changes in LV chamber geometry, wall thickness, and volume.[29] Prolonged ventricular unloading has been shown to result in reversal of ventricular dilatation, improved ejection fraction, a lower wedge pressure, improved myocyte mitochondria efficiency, and a reduction in neuroendocrine perturbations.[30-32]

Unfortunately, only anecdotal reports of successful explantation have been reported.[33,34] The majority of those cases involved patients with idiopathic dilated cardiomyopathy.

Destination therapy

For those patients with end-stage heart disease who do not meet cardiac transplantation eligibility, permanent LVAD support may offer a survival benefit with a substantial improvement in quality of life.[23] Implantable LVADs in Canada and the United States have been designated only for use as a bridge to transplantation. In Europe, however, LVADs have been used as an alternative therapy for end-

stage heart failure since 1994. Since no prospective randomized data exists to support this therapeutic approach, the REMATCH trial was undertaken.[35] The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart failure (REMATCH), was initiated in order to determine if LVAD support is a reasonable alternative to medical therapy alone. Twenty clinical centres throughout the United States are engaged in this multicentre, non-blinded, randomized, controlled trial. The investigators hope to determine whether patients who require, but are ineligible, for heart transplantation can live longer and/or better lives after surgical implantation of a Heartmate LVAD, as compared to optimal medical management. Enrollment should be complete this year.

Complications

Common causes of morbidity and mortality following the placement of an LVAD include:

• Hemorrhage is the most common complication associated with the placement of a device. Initially, approximately 50% of patients required re-operation secondary to excessive bleeding.[36] Currently, only 30% require re-operation with the use of the serine protease inhibitor aprotonin.[37] The etiologies for excessive bleeding include postoperative bleeding due to the duration and complexity of the surgery which includes a median sternotomy, cardiac mobilization, dissection of the abdominal wall (for the non-fully implantable devices), and cannulation of the heart and great vessels. In addition, coagulopathies secondary to hepatic dysfunction, nutritional deficiencies, and antibiotic therapy may lead to excessive bleeding. Qualitative and quantitative platelet deficiencies, as a result of cardiopulmonary bypass, can also be problematic. A mild amount of hemolysis may occur in patients who have long-term treatment with pulsatile devices.[25]

• Right-sided heart failure was the leading cause of perioperative death following placement of an LVAD.[36] Initially, nearly 20% of LVAD recipients required right ventricular support as a result of increased venous return to the right ventricle and a transient increase in pulmonary artery pressures due to transfusions and cardiopulmonary bypass.[38] A reduction in pump flow to 5-6 L/min initially, with a gradual increase over time, has reduced the need for temporary right-sided mechanical support. In addition, the use of nitric oxide has also greatly reduced the need for right-sided mechanical support.[39] Today, hemodynamic stability can be achieved with isolated left ventricular support in more than 90% of patients.[40]

• Another common complication of mechanical circulatory support is thromboembolism. Turbulent flow, platelet damage, thrombogenicity, and device design put patients at risk for thrombus formation.[41] A 20% thromboembolic event rate was associated with VAD insertion initially.[42] Currently, among patients with a HeartMate VAD, the total thromboembolic event rate is 0.01 per patient-month of device use among 223 patients supported over 531 patient-months.[43] The low incidence is attributed to the textured blood-contacting surfaces of the HeartMate.

• Intraoperative symptomatic air embolisms are rare. Asymptomatic cerebral microemboli, however, have been documented in 34-67 % of LVAD recipients.[44,45] The prevalence of device-related neurological events in patients treated with VADs is now less than 5% with minimal or no anticoagulant therapy.[44]

• The most common infections in device recipients are those relating to the drive line. They are usually confined to the exit site and are easily treated. The HeartSaver device should eliminate this cause of morbidity given its fully implantable features. Infections of the abdominal pocket require more aggressive therapy including open drainage, debridement, and re-siting the drive line through a new exit site. Only rarely has infection necessitated removal of a device. In fact, it has been suggested that transplantation not be delayed in patients with infected VADs since acceptable results can be achieved in the presence of bacterial or fungal VAD infections.[46,47] In a review of more than 2000 recipients, clinically important infections occurred in 25% of LVAD recipients.[48]

• Device malfunctions are rare, and of those cases that have been reported, none have threatened the ability of the device to provide adequate blood flow.[11,23]

Conclusion

A host of technical advances in the last 5 years has facilitated the design of lightweight, portable LVADS that improve patient autonomy and quality of life. The devices are useful for bridging to transplantation, bridging to recovery, and possibly as a destination therapy. With respect to the latter, the efficacy of long-term mechanical support in patients with end-stage heart disease is being explored in the REMATCH trial. Should mechanical therapy prove to be more beneficial than medical therapy poses a dilemma for Canadian cardiologists and our healthcare system. A Canadian perspective regarding the cost-effectiveness of this therapy is the subject of a recent

review.[49] It is estimated that the cost of bridging 50 transplant patients per year would be $7 - $13 million, while the cost of permanently supporting 7000 heart failure patients would be in excess of $2.6 billion per year.[49] Device efficacy, the growing burden of disease, a decreased transplantation rate, and public opinion may make utilization of mechanical assist devices as a long-term therapy inevitable.

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Abstracts of Interest

Age Related Outcome for Patients Bridged to Heart Transplantation with HeartMate Left Ventricular Assist Devices

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Background: Chronic immunosuppression, allograft coronary disease and decreasing availability of the donor hearts continue to limit the benefits of the heart transplantation (HT) in patients with the end stage of heart failure in whom HT is deemed the only hope for survival. At the same time, there is a growing number of successfully supported left ventricular assist devices (LVAD) patients surviving and awaiting HT necessitating longer LVAD implant times. We hypothesized that older patients may not be able to withstand LVAD surgery and prolonged implant times pre and post FIT as well as younger patients. We would like to predict which age group would benefit the most from the LVAD bridge to HT.

Methods: We reviewed our experience with the pneumatic and vented electric HeartMate LVADs left ventricular assist devices (LVAD) implanted in our institution between 6/1/92 to 3/31/99. Twenty-seven patients were implanted with pneumatic LVADs and twenty-eight patients were implanted with electric HeartMate LVADs, of whom one is still waiting for donor heart. The younger LVAD recipients between 14-50 years old comprised Group I and the older LVAD recipients comprised Group II.

Results:

	Group I (N = 22)	Group II (N = 32)
Mortality on LVADs prior to HT	2/22 (9.1%)	11/32 (34.4%)*
1 Year survival after HT	18/20 (90%)	16/22 (81.8%)
Overall survival after HT	15/20 (75%)	12/22 (54.5%)

*$p<0.05$

Conclusions: The above data demonstrates that older patients had a statistically significant higher mortality while on LVADs. Even if they were fortunate enough to receive a donor heart and undergone HT, older patients were seen to do worse than younger patients. Especially at the time of the REMATCH trial, there should be special emphasis on careful patient selection for implantation of LVAD and special caution and restrained enthusiasm for LVAD as hope for permanent cardiac support in older patients.

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