Implantable Left Ventricular Assist System

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The first clinical application of the first-generation pulsatile implantable left ventricular assist system (LVAS) was in the mid 1980s as a bridge to transplantation and contributed to an advancement of this field from a clinical experiment to an established therapeutic option for treating advanced heart failure patients. However, there have been technological limitations that have surfaced as longer-term experience has been gained. These include a high incidence of thromboembolic complications, infection, mechanical failures associated with moving parts, and the large size of both implantable pump and percutaneous cable. In order to overcome the limitations of the first-generation pulsatile LVAS, a smaller rotary blood pump LVAS emerged as a possible alternative in the 1990’s and these new generation LVAS are in various stages of development and clinical application. This article reviews the history and current status of the implantable LVAS. (Circ J 2009; Suppl A: A-48–A-54)

Key Words: Chronic heart failure; Congestive heart failure; Dilated cardiomyopathy; Heart-assist device

Heart failure (HF) is a major cause of death throughout the world and is associated with a high rate of morbidity and a lower quality of life than that of patients suffering from any other chronic disease. More than 22 million people suffer from HF worldwide; in the United States alone, approximately 5.7 million people (2.5%) suffer from HF, with new diagnoses of more than 670,000 cases each year. The estimated direct and indirect cost of HF in the United States is $37.2 billion for 2009. The number of HF patients older than 45 years increases exponentially with age, and the incidence of HF for the population older than 65 years is as high as 10/1,000. The mortality rate of HF increased by 28% over the past 10 years and nearly 20% of the total patients have advanced HF, with a mortality rate of 20–50% at 1 year.

For patients with advanced HF, the treatment options are very limited. Heart transplant is the “gold standard” or preferred option for treatment and 60,000 patients with advanced HF would be potential candidates except that the number of transplant candidates far exceeds the donor pool. According to the International Society for Heart and Lung Transplantation Registry Report–2008, the number of heart transplant procedures continues to decrease worldwide and approximately 3,000 transplants were reported in 2006, a 35% reduction as compared with the peak number at of 4,429 in 1994. In the United States alone, more than 5,000 people are added to the registration list for heart transplant each year; however, fewer than 2,000 heart transplant procedures are currently performed. According to the Organ Procurement and Transplantation Network database, 25–30% of patients listed for the United Network for Organ Sharing Status 1A and 1B were unable to receive donor hearts even after 6 months of listing. Currently, 44% of listed patients receive intravenous inotropes and 23% are supported by left ventricular support devices while waiting for heart transplant, showing a significant increase in the necessity of pre-transplant support as compared with several years ago. Furthermore, many HF patients are not eligible for heart transplantation because of their age and other health limiting factors. Approximately 50% of patients who need a transplant are disqualified because of age. In addition, opportunistic infection, rejection, malignancy and graft coronary artery disease continue to be limitations of this treatment. These limitations have generated continued interest in the development of an “artificial heart” that can help patients survive until donor hearts become available, or as an alternative to heart transplantation.

In early development, the concept of an “artificial heart” was a mechanical device implanted in the body to replace a natural heart. Later, the “artificial heart” was divided into 2 major categories: “total artificial heart” (TAH) and “ventricular assist system” (VAS). TAH is the same as the original concept (ie, a mechanical device replacing the natural heart), whereas the VAS is defined as a mechanical device that assists the failing heart without replacing it. The device can be implanted in the body (implantable VAS) or placed outside the body (para-corporeal VAS). This article reviews the history of the “artificial heart” and the current status of the implantable VAS.

History of the Artificial Heart

The concept of an artificial heart was first described by Fuki Kozakai, a Japanese novelist and physician, in his novel entitled Artificial Heart published in 1921. In 1930, the world’s first concept model of an artificial heart was made by Charles Augustus Lindbergh II, an American aviator/explorer who emerged to world fame with his solo non-stop flight from New York City to Paris in 1927. The world’s first artificial heart was fabricated and implanted in a dog model by Willem J Kolff and Tetsuzo Akutsu at the Cleveland Clinic Foundation in 1957. The dog lived for 90min. In 1964, the National Institutes of Health (NIH) started an artificial heart program, a US National Project promoted by President Lyndon B Johnson, following the “Apollo” space program (1961–1975) initiated by President Lyndon B Johnson.
Since then, the NIH has almost continuously supported the development programs for TAH and VAS until recently. The most recent NIH national program is the “Interagency Registry for Mechanically Assisted Circulatory Support”, a 5-year program from 2005 to 2010.

**Early Development**

Early development focused on the TAH, using 2 volume-displacement (or pulsatile) blood pumps made of elastic polymers and driven by pneumatic power. In 1969, the world’s first clinical application of a pneumatically driven TAH (Liotta Heart) was performed by Dr Denton A. Cooley at the Texas Heart Institute as a “staged transplantation” (bridge to transplant (BTT)). The patient received a donor heart after 55 h of TAH support. A staged transplantation was performed by Dr Cooley and Dr Akutsu using the Akutsu Heart III TAH at the Texas Heart Institute in 1981, and the patient was successfully transplanted after 54 h of support. The research group lead by Willem J. Kolff at the University of Utah developed the Jarvik 7, a pneumatic TAH invented by Clifford Kwan-Gett, designed for permanent use in the late 1970s. In 1982, Dr William DeVries implanted the Jarvik 7 in Barney Clark as the world’s first permanent TAH. After 5 Jarvik 7 implants in the US, the Food and Drug Administration (FDA) banned its permanent use in 1984 because of the high complication rates of thromboembolism, infection, and bleeding associated with anticoagulation. The FDA allowed its use only as a BTT. The Jarvik 7 (currently CardioWest™) temporarily driven LVAS began in 1984 with the Novacor®, an electrically driven LVAS, followed by the pneumatically driven HeartMate IP in 1986 and the electrically driven HeartMate-VE in 1991–10. These devices are currently referred to as first-generation pulsatile LVASs. The FDA approved the HeartMate IP in 1994 and the Novacor and the HeartMate VE in 1998 as a BTT.

**First-Generation Implantable LVAS**

The first successful clinical application of a LVAS was performed by Dr Michael DeBakey and Dr Domingo Liotta at the Methodist Hospital in Houston, Texas as early as 1966. The LVAS was implanted paracorporeally in a patient with postcardiotomy shock as a bridge to recovery. The patient recovered well after 10 days of LVAS support and was discharged home.

Approximately 20 years later, the clinical application of an implantable LVAS with a wearable or portable controller began as a BTT. The first clinical application of an implantable LVAS began in 1984 with the Novacor®, an electrically driven LVAS, followed by the pneumatically driven HeartMate IP in 1986 and the electrically driven HeartMate-VE in 1991–10. These devices are currently referred to as first-generation pulsatile LVASs. The FDA approved the HeartMate IP in 1994 and the Novacor and the HeartMate VE in 1998 as a BTT.

The successful use of LVAS as a BTT for extended periods of time has led to consideration of the permanent use of LVAS (currently referred to as destination therapy (DT)), as originally envisioned when the artificial heart development program started in 1964. The landmark REMATCH (Randomized Evaluation of Mechanical Assistance in Treatment of Congestive Heart Failure) began in 1998 using the HeartMate VE LVAS as a DT for advanced HF patients who were ineligible for cardiac transplantation. This trial was partially supported by the NIH. A total of 129 patients were assigned in a 1:1 randomization to receive either LVAS (68 patients) or optimal medical therapy.
(OMM, 61 patients). The LVAS group demonstrated significantly improved survival benefit over the OMM group at 1 year (52% vs 28%) and 2 years (29% vs 13%) and improved quality of life, despite a high incidence of device failure and infection. Based on the REMATCH trial results, the FDA approved the HeartMate VE as a DT application for the first time in the history of the artificial heart.

New Generation LVAS

Over the past 20 years, first-generation LVASs, which used a pulsatile pump, were implanted in more than 10,000 patients worldwide and greatly contributed to the advancement of this field from a clinical experiment to an established therapeutic option for treating advanced HF. However, technological limitations have surfaced as we gained longer-term experience and include a high incidence of thromboembolic complications, infection, mechanical failure associated with moving parts, and the large size of both the implantable pump and percutaneous cable. In the REMATCH trial (HeartMate VE), sepsis and device failure were the most common causes of death. A total of 29 device replacements were performed in 23 (34%) patients. The major causes of device replacement were device failure (62%) and sepsis (19%). Freedom from device replacement was 87% at 1 year and 37% at 2 years. Despite the improvements in survival and quality of life, more reliable and safer devices need to be realized for widespread use of LVAS.

A smaller rotary blood pump emerged in 1990s as a possible alternative to the large pulsatile pump, eliminating the need for prosthetic valves and the external venting required for implantable pulsatile pumps. The advantages of rotary blood pumps as compared with pulsatile pumps include (1) small pump size: less invasive surgery and lower infection rate; (2) small percutaneous cable: lower infection rate; (3) low noise: better quality of life; (4) single moving part: extended mechanical durability and longevity; and (5) wide range of flow capacity despite small pump size.

The rotary blood pumps are categorized into second- and third-generation LVASs based on their technological aspects (Figure 1). The system configuration is similar to that of the first-generation wearable LVAS (ie, the system consists of an implantable pump with a percutaneous cable, inflow/outflow conduits, a wearable controller, 1 or 2 wearable batteries, a battery charger, and a system monitor or console). Some systems have a remote home-monitoring device. Figure 2 shows the system configuration of a wearable implantable LVAS.

The following sections review the systems and the current status of the clinical development of commercially available new generation LVASs.

Second-Generation LVAS

The second-generation LVASs include the DeBakey VAD, Jarvik 2000, and HeartMate II, which are based on miniaturized axial flow pump technology with a blood-immersed bearing or a pivot bearing (Figure 3a).

DeBakey VAD® This is an axial flow pump with a blood-immersed mechanical bearing that is 72 mm in length and 30 mm in diameter, and 92 g in weight. The titanium pump chamber contains the flow-straightener, inducer/impeller and diffuser. Nominal pump speed is 10,000–12,000 rpm. The ultrasonic flow probe is placed over the outflow graft for direct flow measurement. The pump is placed in the pericardial space above the diaphragm. The development of the DeBakey VAD began in 1984 in collaboration between Dr Michael DeBakey and NASA engineers. In 1995, MicroMed Technology, Inc (Houston, TX, USA) was formed for commercialization of the DeBakey VAD. A European multicenter clinical trial for BTT began in 1998 and CE-mark was granted in 2001. During the trial, the Carmeda™ heparin coating was introduced as a surface modification of the blood path (CBAS™), which also received CE-mark in 2002, although CBAS was later withdrawn. The US trial was started in 2001 for BTT, followed by DT in 2003. The trials are still underway. Over the past 10 years, several improvements have been made to the device that have resulted in the current model, HeartAssist 5.

Jarvik 2000 FlowMaker® The Jarvik 2000 (Jarvik Heart, Inc, New York, NY, USA) is another miniaturized axial flow pump with a blood-immersed mechanical bearing developed by Dr Robert Jarvik, a pioneer in mechanical circulatory support. The titanium pump comprises a direct-current motor, a rotor supported by 2 ceramic bearings, and an impeller. The pump is 55 mm in length, 25 mm in diameter, and 85 g in weight. The pump speed can be manually adjusted from 8,000 to 12,000 RPM in increments of 1,000. The pump can generate flow rates up to 6L/min under optimal conditions. Neither direct nor indirect pump flow measurement is implemented in the system. A unique feature of this pump is that the pump is directly placed in the left ventricular apex. The pump can be implanted either by left thoracotomy or median sternotomy. For DT patients, the power can be delivered by a skull-mounted pedestal. The pump is not designed to provide full support to take over LV function, but rather augment the failing heart to help restore normal cardiac output. The Jarvik 2000 received CE-mark in 2005 for both BTT and DT. Two BTT trials are currently ongoing in the US and Japan. To date, the Jarvik 2000 has been implanted in more than 200 patients.

Figure 2. Anatomical configuration of an implantable wearable left ventricular assist system.
Implantable LVAS

HeartMate® II

The HeartMate II (Thoratec Corp, Pleasanton, CA, USA) is an axial flow pump with a pivot mechanical bearing. The concept of the pump design was based on the Hemopump (Nimbus Inc, Rancho Cordova, CA, USA) developed by Dr Richard Wampler in 1982. The development project of the HeartMate II LVAS began in 1992 with a research partnership between Nimbus Corp and the University of Pittsburgh. The bearing design has

Figure 3. (a) Second-generation rotary pump left ventricular assist system (LVAS) based on an axial flow pump technology (from the left, DeBakey VAD®, Jarvik 2000 FlowMaker®, HeartMate® II). (b) Third-generation rotary pump LVAS using an active magnetic bearing (Left: INCOR™, Right: DuraHeart™). (c) Third-generation rotary pump LVAS using a hydrodynamic bearing (Left: VentrAssist™, Right: HeartWare HVAD™).

in the US, Europe, and Asia, with the longest duration of support being 7.5 years in the DT trial.
evolved from the purge system used in the Hemopump to journal bearings, then to the current pivot bearing (or ball-and-cup bearing) over time from 1991 to 1997. In 1998, Nimbus Corp. was acquired by ThermoCardiosystems, Inc., which was then acquired by Thoratec Corp in 2000. The pump comprises a rotor with pivot bearing at both inlet and outlet, and a motor inside the pump housing. The pump is 81 mm in length, 43 mm in diameter, and 281 g in weight. It is placed in the preperitoneal pocket parallel to the diaphragm. Pump speed ranges from 6,000 to 15,000 rpm and the pump can generate up to 10L/min of flow. The system integrates indirect flow estimation and automatic suction detection algorithms. Initially, the inlet/outlet stators and the intraventricular inlet conduit tip were textured with a titanium microsphere coating, the same textured surfaces as used in the pulsatile HeartMate pumps. However, in the first clinical trial in 2000 thrombus occurred where the textured surfaces were applied and this unfavorable clinical outcome led to modification of the inlet and outlet stators to smooth surfaces, while keeping the intraventricular inlet conduit tip with a textured surface. The clinical trial was restarted in 2003 using the modified pump in both US and Europe. The HeartMate II received CE-mark in 2005 for both BTT and DT applications. In 2008, the FDA approved the HeartMate II for BTT. The US pivotal trial for DT is currently ongoing. To date, more than 1,600 patients have been implanted with the HeartMate II worldwide.

Third-Generation LVAS

The technical advancement that defined the third-generation LVAS was the elimination of all mechanical contact between the impeller and the drive mechanism. This was accomplished by using an active magnetic bearing or hydrodynamic bearing technology to levitate the impeller, which enables friction-free rotation of the impeller.

The key advantages of a friction-free drive are reduced hemolysis, minimized thrombogenesis, and increased mechanical durability, necessary for long-term ventricular support. Several manufacturers are in various stages of development and clinical application of third-generation rotary blood pumps.

The third-generation LVASs include the INCOR™, DuraHeart™ LVAS, VentriAssist™, and HeartWare HVAD™. Of these, INCOR and DuraHeart have an active magnetic bearing (Figure 3b), and the VentrAssist and HVAD have a hydrodynamic bearing (Figure 3c). All of the third-generation pumps were based on centrifugal pump technology, with the exception of the INCOR, which uses an axial flow pump.

INCOR™

This is the only axial flow pump among the third-generation rotary pump LVASs using an active magnetic bearing. The impeller position is actively controlled axially and passively controlled radially. The pump is made of titanium and the blood contacting surfaces are coated with the Carmeda® BioActive Surface. The pump is 120 mm in length, 30 mm in diameter, and 200 g in weight. The inflow and outflow conduits are made of silicone and connected to the pump using a snap-in connector. The system incorporates indirect flow estimation and suction detection with an automatic pump speed control algorithm. The pump is implanted above the diaphragm without a preperitoneal pocket. The INCOR received CE-Mark in March 2003, and is commercially available in European countries. In August 2008, a patient implanted with the INCOR reached 5 years of support and more than 400 patients have been supported by the INCOR at 41 centers in 16 European countries.

VentrAssist™

The VentrAssist LVAS (Ventricor Ltd, Chatswood, NSW, Australia) is a centrifugal pump featuring 8 hydrodynamic bearings to levitate an open-flow impeller with 4 blades. The pump is made of titanium with the blood-contacting surfaces of the pump and blood path coated with a diamond-like carbon to enhance blood compatibility. The pump is 60 mm in diameter and 296 g in weight. The pump speed is 1,800–3,000 rpm in a normal setting. The inflow conduit is a straight silicone tube with a bell-shaped end. The pump is placed in a preperitoneal pocket. The VentriAssist LVAS received CE-mark in December, 2007. The US feasibility study began in 2005 and the pivotal studies for BTT and DT were started in June and September 2007, respectively. In March 2009, the company completed its US BTT trial and is currently preparing its premarket approval application while the DT trial is still ongoing. As part of the product iteration, the Model LVA4 VentrAssist with a thinner percutaneous cable was released worldwide in 2007. However, the company recently issued a voluntary urgent field safety notice because of cable fracture in this model. The VentriAssist LVAS has been implanted in more than 420 patients worldwide.

HeartWare HVAD™

The HVAD (HeartWare International Inc, Sydney, NSW, Australia) is a centrifugal pump with a hybrid system for levitating the impeller. The impeller is suspended using a combination of passive magnets and a hydrodynamic thrust bearing. The displacement of the pump is 50 ml and the weight is 145 g. The pump, together with an integrated inflow conduit made of titanium, is placed in the pericardial space above the diaphragm. The pump speed is 2,000–3,000 rpm under normal conditions. In January, 2009, HVAD received CE-mark based on the data from the initial 25 patients implanted in Europe and Australia, with a total of 50 patients enrolled in the trial. The US BTT trial was initiated in August, 2008, which will enroll 150 patients at a maximum of 28 centers.

DuraHeart™ LVAS

The DuraHeart™ LVAS (Terumo Heart, Inc, Ann Arbor, MI, USA) is the world’s first third-generation implantable LVAS to obtain market approval (CE-mark) that combines centrifugal pump and active magnetic-levitation designed for long-term circulatory support. The impeller is rotated by a magnetic coupling between the impeller and the motor, and is suspended magnetically by 3 electromagnets. The electric current of each electromagnet is controlled by using 3 position sensors to precisely control the impeller position. DuraHeart is the only pump available that uses 3 degrees-of-freedom active control of the impeller’s magnetic levitation. The large stable gaps between the impeller (250 microns each) and the blood chamber walls, in combination with magnetic levitation and centrifugal pump design, translate into significantly reduced shear stress and a corresponding reduction in hemolysis. The large stable gap also provides for improved wash-out, preventing thrombus formation. The pump is housed in a titanium enclosure that hermetically seals the electrical components against any blood or tissue contact. The DuraHeart Pump has a diameter of 73 mm, thickness of 45 mm, and weights approximately 540 g. The displacement volume is 196 ml, which is 30–50% smaller than the first-generation pulsatile pumps. The pump is placed in a preperitoneal pocket. The DuraHeart pump is capable of providing 81/min of blood flow at 120 mmHg with no residual LV function and is able to generate a wide pressure range from 50 mmHg at 1.200 rpm to 180 mmHg at 2.400 rpm, a comparable capacity to the pulsatile pumps.
The blood-contacting surfaces of the pump and the inlet conduit and outflow conduit connector are made of titanium and are entirely modified with a stable covalently-bound heparin to enhance blood compatibility and reduce the risk of thrombus formation in low-flow areas.

An added feature of the DuraHeart is the integrated flow-estimation algorithm based on the very stable motor current required to maintain the set rotational speed and viscosity of the blood (as estimated from the measured hematocrit). The DuraHeart was also designed with additional safety features, such as a hydrodynamic bearing support for backup in case of failure of magnetic levitation (single-fault recovery mode).

The DuraHeart received CE-mark in February, 2007 and is commercially available in European countries.18 As of March 31, 2009, 8 patients had been supported with the DuraHeart for more than 2 years and 2 patients for more than 3 years, with the longest support being 3 years and 8 months. The US BTT pivotal trial was initiated in July 2008, and can enroll 140 patients at up to 40 study sites. The Japanese BTT study also began in October 2008 and completed enrollment of the 6 patients required for Japanese premarket approval.

**Comment**

After more than 50 years of painstaking development efforts, the newer generation rotary pump LVASs have been demonstrating better survival outcome, mechanical reliability, quality of life, and decreased adverse event rates of neurological dysfunction, infection and mechanical failure as compared with the first-generation pulsatile LVASs. The new generation rotary pump LVASs also demonstrated an improved survival comparable to cardiac transplantation when used as a BTT.15,17,18

**Table. Major Adverse Events Reported for Left Ventricular Assist Systems**

<table>
<thead>
<tr>
<th>Adverse event (per patient-year)</th>
<th>1st generation</th>
<th>2nd generation</th>
<th>3rd generation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HM VE (n=280)</td>
<td>HM II (n=133)</td>
<td>DuraHeart (n=33)</td>
</tr>
<tr>
<td></td>
<td>86 patient-years (mean 112 days)</td>
<td>62 patient-years (mean 168 days)</td>
<td>18 patient-years (mean 197 days)</td>
</tr>
<tr>
<td>Bleeding requiring surgery</td>
<td>1.47</td>
<td>0.78</td>
<td>0.28</td>
</tr>
<tr>
<td>Driveline/pocket infection</td>
<td>3.49</td>
<td>3.77</td>
<td>4.0</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.44</td>
<td>0.19</td>
<td>0.28 0*</td>
</tr>
<tr>
<td>Non-stroke neurologic</td>
<td>0.67</td>
<td>0.26</td>
<td>0.28 0.23*</td>
</tr>
<tr>
<td>RHF requiring RVAD</td>
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<td>0.08</td>
<td>0.06</td>
</tr>
<tr>
<td>Device thrombosis</td>
<td>NA</td>
<td>0.03</td>
<td>0</td>
</tr>
<tr>
<td>Pump mechanical failure</td>
<td>0.03</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hemolysis</td>
<td>0</td>
<td>0.06</td>
<td>0</td>
</tr>
</tbody>
</table>

*Event rate after implementing less intensive anticoagulation (n=22, 13 patient-years).

HM, HeartMate; RHF, right heart failure; RVAD, right ventricular assist device.

**Figure 4.** Comparison of Kaplan-Meier survival analysis at 1 year between cardiac transplantation (Registry of the International Heart and Lung Transplantation, 1999–2004) and the DuraHeart LVAS (European post-market study, as of October 31, 2008). For the LVAS group, the patients were censored when they underwent transplantation or device explant. LVAS, left ventricular assist system.
vs 3.49). The higher infection and bleeding rates of the pulsatile LVAS may be related to the large size of the pump and percutaneous cable. The rate of overall neurological dysfunction of the first-generation LVAS was 50–60% higher than that of the new generation LVASs (1.11 vs 0.45, 0.51). Stroke rate for the first-generation LVAS was 40–50% higher than that of the new generation LVASs (0.44 vs 0.19, 0.28). In the DuraHeart European trial, a high rate of fatal intracerebral bleeding was observed in the initial 11 patients, with the likely cause being excessive anticoagulation/antithrombotic regimen. The investigators agreed to follow a less-intensive regimen, which resulted in significantly improved result (ie, there was no incidence of hemorrhagic or embolic stroke in the remainder of the trial). Device thrombosis (0.03 per patient-year) and hemolysis (0.06 per patient-year) occurred with the second-generation LVASs, but there has been no incidence of device thrombosis, hemolysis or peripheral thromboembolism in the third-generation DuraHeart trial. Mechanical failure of the pump was only observed with the first-generation pulsatile LVASs (0.03 per patient-year).

At present, there are no reliable clinical data available for new generation LVASs as a DT application, as they are still going through clinical trials. Over the past years, the importance of patient selection on the clinical outcome of LVAS therapy has been discussed and it is now well recognized that appropriate patient selection and timing of LVAS implantation are critical factors for improved clinical outcomes of DT.20 A combination of new generation LVAS and better patient selection may result in an improved outcome for DT and LVAS therapy, and in the near future may become a more viable alternative to cardiac transplantation for advanced HF patients. In order to achieve a better quality of life for the patients, several manufacturers have been working on product iterations from the current wearable system to a totally implantable LVAS.

Disclosures

The author is an employee of Terumo Heart, Inc.

References


