Medical Device Innovation Workshop

LVADs

Images are from Thoratec and are used for educational purposes.
1. Background

Heart failure (HF) is a growing disease burden. Patients with severe HF, often become candidates to receive a Ventricular Assist Device (VAD). A VAD is a mechanical circulatory device that is implanted in people whose heart is too weak to pump blood on its own (HF, heart failure). It is also referred to as a heart pump, and partially or completely takes over the function of a failing heart. If a VAD is implanted to assist the right ventricle, it is referred to as the Right Ventricular Assist Device (RVAD); if it is implanted to assist the left ventricle, it is referred to as the Left Ventricular Assist Device (LVAD), if two devices are implanted to assist both ventricles, it is referred to as a Bi-Ventricular Assist Device (BiVAD).

2. Problem Statement

Patients with severe heart failure who are waiting to receive a heart transplant, or are not qualified to receive a heart transplant require a device to assist the pumping function of their heart. The figures below display the basic components of a ventricular assist device.
Heartmate VAD device

Overall HeartMate VAD system
HeartMate VAD system

Chest X-ray showing a HeartMate VAD device
1. The body's oxygen-poor blood flows into the right atrium (from which it normally goes into the right ventricle).

2. But because the right ventricle is not able to pump blood into the lungs, the blood goes into the Berlin Heart through tube A.

3. Blood is pumped from the device through tube B into the pulmonary artery and then to the lungs.

4. Then the oxygen-rich blood flows from the lungs into the heart's left atrium (from which it normally goes into the left ventricle).

5. But because the left ventricle is not able to pump the blood into the aorta, the blood passes from the left ventricle and reenters the Berlin Heart through tube C.

6. The device then pumps blood through tube D to the aorta and into the body.

The pumps are connected to the Berlin Heart controller, which uses a pneumatic system to pump the blood to the patient.
3. Current Solutions (see additional datasheets/articles)
   • Medgadget
   • HeartWare
   • HeartMate II
   • Berlin Heart

4. Review Papers (see attached papers)
   • Slaughter et al (2009) Advanced Heart Failure Treated with Continuous-Flow Left Ventricular Assist Device
   • Russel and Miller (2008) Advanced Heart Failure: A Call to Action

5. Related Patents
   • Smith et al (2010) Left Ventricular Assist Device
   • Downey et al (2001) Removable Left Ventricular Assist Device with an Aortic Support Apparatus
   • Young et al (1992) Drive System for artificial Hearts and Left Ventricular Assist Devices
A ventricular assist device (VAD) is a mechanical circulatory device that is used to partially or completely replace the function of a failing heart. Some VADs are intended for short term use, typically for patients recovering from heart attacks or heart surgery, while others are intended for long-term use (months to years and in some cases for life), typically for patients suffering from advanced congestive heart failure.

VADs are distinct from artificial hearts, which are designed to completely take over cardiac function and generally require the removal of the patient's heart. VADs are designed to assist either the right (RVAD) or left (LVAD) ventricle, or both at once (BiVAD). The type that is used depends primarily on the underlying heart disease and the pulmonary arterial resistance that determines the load on the right ventricle.

LVADs are most commonly used, but when pulmonary arterial resistance is high, right ventricular assistance may become necessary. Long term VADs are normally used to keep patients alive with a good quality of life while they wait for a heart transplantation (known as a "bridge to transplantation"). However, LVADs are sometimes used as destination therapy, meaning they will never undergo heart transplant, and sometimes as a bridge to recovery.\[2\]

In the last few years, VADs have improved significantly in terms of providing survival and quality of life among recipients.
Design

Pumps

The pumps used in VADs can be divided into two main categories – pulsatile pumps, that mimic the natural pulsing action of the heart, and continuous flow pumps. Pulsatile VADs use positive displacement pumps. In some of these pumps, the volume occupied by blood varies during the pumping cycle, and if the pump is contained inside the body then a vent tube to the outside air is required.

Continuous flow VADs are smaller and have proven to be more durable than pulsatile VADs. They normally use either a centrifugal pump or an axial flow pump. Both types have a central rotor containing permanent magnets. Controlled electric currents running through coils contained in the pump housing apply forces to the magnets, which in turn cause the rotors to spin. In the centrifugal pumps, the rotors are shaped to accelerate the blood circumferentially and thereby cause it to move toward the outer rim of the pump, whereas in the axial flow pumps the rotors are more or less cylindrical with blades that are helical, causing the blood to be accelerated in the direction of the rotor's axis.

An important issue with continuous flow pumps is the method used to suspend the rotor. Early versions used solid bearings; however, newer pumps, some of which are approved for use in the EU, use either electromagnetic suspension (“maglev”) or hydrodynamic suspension. These pumps contain only one moving part.

History

The early VADs emulated the heart by using a “pulsatile” action where blood is alternately sucked into the pump from the left ventricle then forced out into the aorta. Devices of this kind include the HeartMate IP LVAS, which was approved for use in the US by the Food and Drug Administration in October 1994. These devices are commonly referred to as first generation VADs.

More recent work has concentrated on continuous flow pumps, which can be roughly categorized as either centrifugal pumps or axial flow impeller driven pumps. These pumps have the advantage of greater simplicity resulting in smaller size and greater reliability. These devices are referred to as second generation VADs. A side effect is that the user will not have a pulse, or that the pulse intensity will be seriously reduced.

Third generation VADs suspend the impeller in the pump using either hydrodynamic or electromagnetic suspension, thus removing the need for bearings and reducing the number of moving parts to one.

Another technology undergoing clinical trials is the use of trans cutaneous induction to power and control the device rather than using percutaneous cables. Apart from the obvious cosmetic advantage this reduces the risk of infection and the consequent need to take preventative action. A pulsatile pump using this technology has CE Mark approval and is in clinical trials for US FDA approval.

A very different approach in the early stages of development is the use of an inflatable cuff around the aorta. Inflating the cuff contracts the aorta and deflating the cuff allows the aorta to expand – in effect the aorta becomes a second left ventricle. A proposed refinement is to use the patient's skeletal muscle, driven by a pacemaker, to power this device which would make it truly self-contained. However a similar operation (cardiomyoplasty) was tried in the 1990s with disappointing results. In any case, it has substantial potential advantages in avoiding the need to operate on the heart itself and in avoiding any contact between blood and the device. This approach involves a return to a
Ventricular assist device

[pulsatile flow][citation needed]

Peter Houghton was the longest surviving recipient of a VAD for permanent use. He received an experimental Jarvik 2000 LVAD in June 2000. Since then, he completed a 91-mile charity walk, published two books, lectured widely, hiked in the Swiss Alps and the American West, flew in an ultra-light aircraft, and traveled extensively around the world. He died of acute renal failure in 2007 at the age of 69.[5]

Studies and outcomes

Recent developments

- In July 2009 in England, surgeons removed a donor heart that had been implanted in a toddler next to her native heart, after her native heart had recovered. This technique suggests mechanical assist device, such as an LVAD, can take some or all the work away from the native heart and allow it time to heal.
- In July 2009, 18-month follow-up results from the HeartMate II Clinical Trial concluded that continuous-flow LVAD provides effective hemodynamic support for at least 18 months in patients awaiting transplantation, with improved functional status and quality of life. (see below).
- Heidelberg University Hospital reported in July 2009 that the first HeartAssist5, known as the modern version of the DeBakey VAD, was implanted there. The HeartAssist5 weighs 92 grams, is made of titanium and plastic, and serves to pump blood from the left ventricle into the aorta.
- A phase 1 clinical trial is underway (as of August 2009), consisting of patients with coronary artery bypass grafting and patients in end-stage heart failure who have a left ventricular assist device. The trial involves testing a patch, called Anginera(TM) that contains cells that secrete hormone-like growth factors that stimulate other cells to grow. The patches are seeded with heart muscle cells and then implanted onto the heart with the goal of getting the muscle cells to start communicating with native tissues in a way that allows for regular contractions.
- In September 2009, a New Zealand news outlet, Stuff, reported that in another 18 months to two years, a new wireless device will be ready for clinical trial that will power VADs without direct contact. If successful, this may reduce the chance of infection as a result of the power cable through the skin.
- The National Institutes of Health (NIH) awarded a $2.8 million grant to develop a "pulse-less" total artificial heart using two VADS by Micromed, initially created by Michael DeBakey and George Noon. The grant was renewed for a second year of research in August 2009. The Total Artificial Heart was created using two HeartAssist5 VADs, whereby one VAD pumps blood throughout the body and the other circulates blood to and from the lungs.
- HeartWare International announced in August 2009 that it had surpassed 50 implants of their HeartWare Ventricular Assist System in their ADVANCE Clinical Trial, an FDA-approved IDE study. The study is to assess the system as bridge-to-transplantation system for patients with end-stage heart failure. The study, Evaluation of the HeartWare LVAD System for the Treatment of Advance Heart Failure, is a multi-center study that started in May 2009.

The majority of VADs on the market today are somewhat bulky. The smallest device approved by the FDA, the HeartMate II, weighs about 1 pound (0.45 kg) and measures 3 inches (7.6 cm). This has proven particularly important for women and children, for whom alternatives would have been too large.

One device gained CE Mark approval for use in the EU and began clinical trials in the US (VentrAssist). As of June 2007 these pumps had been implanted in over 100 patients. In 2009, Ventracor was placed into the hands of Administrators due to financial problems and was later that year liquidated. No other companies purchased the technology, so as a result the VentrAssist device was essentially defunct. Around 30–50 patients worldwide remain supported on VentrAssist devices as of January 2010.[citation needed]

The Heartware HVAD works similarly to the VentrAssist — albeit much smaller and not requiring an abdominal pocket to be implanted into. The device has obtained CE Mark in Europe and is currently in clinical trials in the USA. Recently, it was shown that the Heartware HVAD can be implanted through limited access without
Ventricular assist device

In a small number of cases left ventricular assist devices, combined with drug therapy, have enabled the heart to recover sufficiently for the device to be able to be removed (explanted).

**HeartMate II LVAD pivotal study**

A series of studies involving the use of the of HeartMate II LVAD have proven useful in establishing the viability and risks of using LVADs for bridge-to-transplantation and destination therapy.

- The pilot trial for the HeartMate II LVAS began in November 2003 and consisted of 46 study patients at 15 centers. Results included 11 patients supported for more than one year and three patients supported for more than two years.
- The HeartMate II pivotal trial began in 2005 and included the evaluation of HeartMate II for two indications: Bridge to transplantation (BTT) and destination therapy (DT), or long-term, permanent support. Thoratec Corp. announced that this was the first time the FDA had approved a clinical trial to include both indications in one protocol.
- A multicenter study in the United States from 2005 to 2007 with 113 patients (of which 100 reported principal outcomes) showed that significant improvements in function were prevalent after three months, and a survival rate of 68% after twelve months.
- Based on one-year follow up data from the first 194 patients enrolled in the trial, the FDA approved HeartMate II for bridge-to-transplantation. The trial provided clinical evidence of improved survival rates and quality of life for a broad range of patients.
- Eighteen-month follow up data on 281 patients who had either reached the study end-point or completed 18 months of post-operative follow-up showed improved survival, less frequent adverse events and greater reliability with continuous flow LVADS compared to pulsatile flow devices. Of the 281 patients, 157 patients had undergone transplant, 58 patients were continuing with LVADs in their body and seven patients had the LVAD removed because their heart recovered; the remaining 56 had died. The results showed that the NYHA Class of heart failure the patients had been designated had significantly improved after six months of LVAD support compared to the pre-LVAD baseline. Although this trial involved bridge-to-transplant indication, the results provide early evidence that continuous flow LVADs have advantages in terms of durability and reliability for patients receiving mechanical support for destination therapy.
- Following the FDA approval of HeartMate II LVAD for bridge-to-transplantation purposes, a post-approval ("registry") study was undertaken to assess the efficacy of the device in a commercial setting. The study found that the device improved outcomes, both compared to other LVAD treatments and baseline patients. Specifically, HeartMate II patients showed lower creatinine levels, 30-day survival rates were considerably higher at 96%, and 93% reached successful outcomes (transplant, cardiac recovery, or long-term LVAD).

**HARPS**

The Harefield Recovery Protocol Study (HARPS) is a clinical trial to evaluate whether advanced heart failure patients requiring VAD support can recover sufficient myocardial function to allow device removal (known as explantation). HARPS combines an LVAD (the HeartMate XVE) with conventional oral heart failure medications, followed by the novel β2 agonist clenbuterol. This opens the possibility that some advanced heart failure patients may forgo heart transplantation.

To date, 73% (11 of 15) of patients who underwent the combination therapy regimen demonstrated sufficient recovery to allow explantation and avoid heart transplantation; freedom from recurrent heart failure in surviving patients was 100% and 89% at one and four years after explantation, respectively; average ejection fraction was 64% at 59 months after explantation – all patients were NYHA Class I; and no significant adverse effects were reported with clenbuterol therapy.
REMATCH

The REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) clinical trial began in May 1998 and ran through July 2001 in 20 cardiac transplant centers around the USA. The trial was designed to compare long-term implantation of left ventricular assist devices with optimal medical management for patients with end-stage heart failure who require, but do not qualify to receive cardiac transplantation. As a result of the clinical outcomes, the device received FDA approval for both indications, in 2001 and 2003, respectively. The trial demonstrated an 81% improvement in two-year survival among patients receiving HeartMate XVE compared to optimal medical management. In addition, a destination therapy study following the REMATCH trial demonstrated an additional 17% improvement (61% vs. 52%) in one-year survival of patients that were implanted with a VAD (HeartMate XVE), with an implication for the appropriate selection of candidates and timing of VAD implantation.

A test carried out in 2001 by Dr. Eric A. Rose and REMATCH study group with patients with congestive heart failure that were ineligible for a transplant showed a survival at two years of 23% for those implanted with an LVAD compared with 8% for those who were treated with drugs. The two major complications of VAD implantation were infection and mechanical failure (see below).

According to a retrospective cohort study comparing patients treated with a left ventricular assist device versus inotrope therapy while awaiting heart transplantation, the group treated with LVAD had improved clinical and metabolic function at the time of transplant with better blood pressure, sodium, blood urea nitrogen, and creatinine. After transplant, 57.7% of the inotrope group had renal failure versus 16.6% in the LVAD group; 31.6% of the inotrope group had right heart failure versus 5.6% in the LVAD group; and event-free survival was 15.8% in the inotrope group versus 55.6% in the LVAD group.

Complications and side effects

Early postoperative bleeding complications are a major cause of morbidity and reoperation in LVAD patients. Bleeding is the most common postoperative early complication after implantation or explantation of LVADs, necessitating reoperation in up to 60% of recipients. The implications of massive blood transfusions are great and include infection, pulmonary insufficiency, increased costs, right heart failure, allosensitization, and viral transmission, some of which can prove fatal or preclude transplantation. When bleeding occurs, it impacts the one year Kaplan-Meier mortality. In addition to complexity of the patient population and the complexity of these procedures contributing to bleeding, the devices themselves may contribute to the severe coagulopathy that can ensue when these devices are implanted. Critical in the management of bleeding in the early hours after implantation or explantation is to adequately evacuate the post-surgical blood from around the heart and lungs to prevent retained blood from contributing to the need for reoperation to wash out clot that can compress the device features and contribute to post operative shock. Preventing chest tube clogging during this period is critical to recovery.

Because the devices generally result in blood flowing over a non-biologic surface, predisposing the blood to clotting, there is need for anticoagulation measures. One device, the HeartMate XVE, is designed with a biologic surface derived from fibrin and does not require long term anticoagulation (except aspirin); unfortunately, this biologic surface may also predispose the patient to infection through selective reduction of certain types of leukocytes.

New VAD designs which are now approved for use in the European Community and are undergoing trials for FDA approval have all but eliminated mechanical failure. [citation needed]

VAD-related infection can be caused by a large number of different organisms:

- Gram positive bacteria (*Staphylococci*, especially *Staph. aureus, Enterococci*)
- Gram negative bacteria (*Pseudomonas aeruginosa, Enterobacter species, Klebsiella species*)
- Fungi, especially *Candida* species
Treatment of VAD-related infection is exceedingly difficult and many patients die of infection despite optimal treatment. Initial treatment should be with broad spectrum antibiotics, but every effort must be made to obtain appropriate samples for culture. A final decision regarding antibiotic therapy must be based on the results of microbiological cultures. [citation needed]

Other problems include immunosuppression, clotting with resultant stroke, and bleeding secondary to anticoagulation. Some of the polyurethane components used in the devices cause the deletion of a subset of immune cells when blood comes in contact with them. This predisposes the patient to fungal and some viral infections necessitating appropriate prophylactic therapy.

### List of implantable VAD devices

*This is a partial list and may never be complete

*Referenced additions are welcome*

<table>
<thead>
<tr>
<th>Device</th>
<th>Manufacturer</th>
<th>Type</th>
<th>Approval Status as of July 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novacor</td>
<td>World Heart</td>
<td>Pulsatile</td>
<td>Was approved for use in North America, European Union and Japan. Now defunct and no longer supported by the manufacturer. (Heartware completed acquisition August 2012)</td>
</tr>
<tr>
<td>HeartMate XVE</td>
<td>Thoratec</td>
<td>Pulsatile</td>
<td>FDA approval for BTT in 2001 and DT in 2003. CE Mark Authorized. Rarely used anymore due to reliability concerns.</td>
</tr>
<tr>
<td>HeartMate II</td>
<td>Thoratec</td>
<td>Rotor driven continuous axial flow, ball and cup bearings.</td>
<td>Approved for use in North America and EU. CE Mark Authorized. FDA approval for BTT in April 2008. Recently approved by FDA in the US for Destination Therapy (as at January 2010).</td>
</tr>
<tr>
<td>HeartMate III</td>
<td>Thoratec</td>
<td>Continuous flow driven by a magnetically suspended axial flow rotor.</td>
<td>Pivotal trials for HeartMate III expected 2013.</td>
</tr>
<tr>
<td>Incor</td>
<td>Berlin Heart</td>
<td>Continuous flow driven by a magnetically suspended axial flow rotor.</td>
<td>Approved for use in European Union. Used on humanitarian approvals on case by case basis in the US. Entered clinical trials in the US in 2009.</td>
</tr>
<tr>
<td>Jarvik 2000</td>
<td>Jarvik Heart</td>
<td>Continuous flow, axial rotor supported by ceramic bearings.</td>
<td>Currently used in the United States as a bridge to heart transplant under an FDA-approved clinical investigation. In Europe, the Jarvik 2000 has earned CE Mark certification for both bridge-to-transplant and lifetime use. Child version currently being developed.</td>
</tr>
<tr>
<td>MicroMed DeBakey VAD</td>
<td>MicroMed</td>
<td>Continuous flow driven by axial rotor supported by ceramic bearings.</td>
<td>Approved for use in the European Union. The child version is approved by the FDA for use in children in USA. Undergoing clinical trials in USA for FDA approval.</td>
</tr>
<tr>
<td>VentrAssist</td>
<td>Ventracor</td>
<td>Continuous flow driven by a hydrodynamically suspended centrifugal rotor.</td>
<td>Approved for use in European Union and Australia. Company declared bankrupt while clinical trials for FDA approval were underway in 2009. Company now dissolved and intellectual property sold to Thoratec.</td>
</tr>
<tr>
<td>MTIHeartLVAD</td>
<td>MiTiHeart Corporation</td>
<td>Continuous flow driven by a magnetically suspended centrifugal rotor.</td>
<td>Yet to start clinical trials.</td>
</tr>
<tr>
<td>C-Pulse</td>
<td>Sunshine Heart</td>
<td>Pulsatile, driven by an inflatable cuff around the aorta.</td>
<td>Currently in clinical trials in the US and Australia.</td>
</tr>
<tr>
<td>Device</td>
<td>Pulsatile system</td>
<td>Power source</td>
<td>Status/Notes</td>
</tr>
<tr>
<td>-----------------</td>
<td>------------------</td>
<td>--------------</td>
<td>------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>MVAD [20]</td>
<td>HeartWare's MVAD Pump is a development-stage miniature ventricular assist device, approximately one-third the size of HeartWare's HVAD pump.</td>
<td>HeartWare Completed GLP Studies (September 2011).</td>
<td></td>
</tr>
<tr>
<td>Thoratec PVAD</td>
<td>Pulsatile system includes three major components: Blood pump, cannulae and pneumatic driver (dual drive console or portable VAD driver).</td>
<td>CE Mark Authorized. Received FDA approval for BTT in 1995 and for post-cardiotomy recovery (open heart surgery) in 1998.</td>
<td></td>
</tr>
<tr>
<td>(Paracorporeal Ventricular Assist Device) [22]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVAD – Implantable Ventricular Assist Device [23]</td>
<td>Pulsatile system includes three major components: Blood pump, cannulae and pneumatic driver (dual drive console or portable VAD driver).</td>
<td>CE Mark Authorized. Received FDA approval for BTT in 2004. Authorized only for internal implant, not for paracorporeal implant due to reliability issues.</td>
<td></td>
</tr>
</tbody>
</table>

References

[15] Ventracor was put into liquidation on 3 July 2009, whereby the company's assets including its intellectual property, data from clinical trials, plant and equipment and residual assets will be put up for sale
External links

- LifeFlow LVAD at the University of Virginia (http://lifeflow.mae.virginia.edu/)
- Nader Moazami, Patrick M. McCarthy Temporary Circulatory Support (http://cardiacsurgery.ctsnetbooks.org/cgi/content/full/2/2003/495)
- Eugene L. Kukuy, Mehmet C. Oz, Yoshifumi Naka Long-Term Mechanical Circulatory Support (http://cardiacsurgery.ctsnetbooks.org/cgi/content/full/2/2003/1491?ck=nck) — a review of the subject as at 2003.
- Mechanical Circulatory Support Resource Center (http://www.mcsresourcecenter.com)
- Health Center Online VAD (http://heart.healthcентroline.com/heartfailure/ventricularassistdevice.cfm)
- Mayo Clinic VAD (http://www.mayoclinic.org/heart-transplant/vad.html)
- Life without a pulse (http://www.cbc.ca/canada/ottawa/story/2006/12/13/mechanical-heart.html) — news story about Canadian man with VAD
- Heart pump improves quality of life in congestive heart failure patients (http://www.news-medical.net/?id=4104) A rapid review of the medical literature and specialist opinion as at December 2005
- NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE (UK) Interventional procedures overview — short-term circulatory support with left ventricular assist devices as a bridge to cardiac transplantation or recovery (http://guidance.nice.org.uk/download.aspx?o=ip059overview) A rapid review of the medical literature and specialist opinion as at December 2005
- MyLVAD.com (http://mylvad.com) Non branded site with video, news, and community discussions on VAD's.
- Ventricular Assist Device (VAD) (http://www.nmh.org/nm/heart-failure-ventricular-assist-devices) Center for Heart Failure — Northwestern Memorial Hospital
HeartMate II® Left Ventricular Assist System

The New Era Begins

The HeartMate II is Thoratec's first-line intermediate-to-chronic left ventricular assist device. Designed to dramatically improve survival and quality of life, the HeartMate II was developed with the goal of providing several years of circulatory support for a broad range of advanced heart failure patients. Its small size and quiet operation make the HeartMate II suitable for a wider range of patients, including women and those of smaller stature*. With product attributes specifically developed to minimize the risk of complications, the HeartMate II is exceptionally durable, dependable, and thromboresistant.

It offers a range of features and benefits:

- Implantation requires a less invasive surgical procedure
- Relative ease of management; completely wearable system
- Low-dose anticoagulation regimen
- Improvement of hemodynamics prior to cardiac transplantation can help optimize long-term outcomes

*The safety and effectiveness of Thoratec VADs in the pediatric population has not been established.

The HeartMate II LVAS has been tested and approved for air transport, including commercial aircraft. The HeartMate II LVAS is compliant with all related FAA safety requirements and will not interfere with aviation electronics, per Section 21, Category M of the RTCA document number RTCA/DO-160D, as specified in "Use of Portable Electronic Devices Aboard Aircraft" AC number 91.21-1A, Section 7C.

Click here to download a letter template that can be used to notify airline and security personnel that one of your patients has a HeartMate II LVAS and therefore has special needs with respect to air travel.

Watch animation
HeartWare® Ventricular Assist System
Product Data Sheet

HeartWare System Implantables

HVAD® PUMP

General Characteristics
- Continuous flow
- Displaced volume = 50cc, Weight = 160g
- Device size and integrated inflow cannula allow for pericardial placement, which eliminates the need for abdominal surgery and device pockets
- Can provide up to 10L/min of flow*

Impeller
- Magnetically and hydrodynamically suspended
- Wide-bladed
- Operates at speeds ranging from 1800 to 4000 rpm
- Provides multiple blood flow paths

Market Approvals
European Commercial approval in January 2009.
US ADVANCE Bridge-to-Transplant (BTT) approval in November 2012.

DRIVELINE

- Percutaneously connects the HVAD pump to an external controller
- Length = 119cm
- Diameter up to 4.8 mm
- Constructed with conductor wires similar to those used in pacemakers
- Six individually insulated, fatigue-resistant cables each encased within a silicon lumen with an outer sheathing
- Contains a portion that is wrapped with woven polyester fabric to encourage tissue in-growth at the skin exit site
HeartWare System Implantables (continued)

OUTFLOW GRAFT WITH STRAIN RELIEF

- 10mm gel impregnated polyester
- Articulating strain relief designed to prevent kinking

SEWING RING

- Designed to secure the HVAD pump to the myocardium
- Composed of titanium and polyester

HeartWare System Peripherals

PATIENT PACK

- Designed to support an ambulatory lifestyle
- Patient-worn controller and batteries weigh about 2.5 pounds (1.1 kg)

HEARTWARE® BATTERIES AND CHARGER

- Lithium ion battery pack
- Each battery allows up to 6 hours of operation when fully charged*
- Battery charger has capacity to charge 4 batteries simultaneously

HEARTWARE® CONTROLLER

- Microprocessor unit that regulates pump function and monitors the system
- Contains 2-line LCD screen that displays parameters, alarms and recommended troubleshooting
- Each alarm has a unique sound, color coded prioritization, visual display and message
- Requires power from 2 sources at all times
  - Two batteries OR one battery and electricity from the wall (AC) or car outlet (DC)

HEARTWARE® MONITOR

- Used by clinicians to set system parameters
- Touchscreen tablet PC computer
- Uses proprietary software to display real-time pump information, historical pump information and alarm conditions

*Bench test on file with HeartWare, Inc.

HEARTWARE, HVAD and the HEARTWARE logo are registered trademarks of HeartWare, Inc.

CAUTION: Federal Law (USA) restricts this device to sale by or on the order of a physician. Refer to the “Instructions For Use” for complete Indications for Use, Contraindications, Warnings, Precautions, Adverse Events and Instructions prior to using this device.
Berlin Heart EXCOR® Pediatric Ventricular Assist Device (VAD) - H100004

Product Name: EXCOR® Pediatric Ventricular Assist Device (VAD)
PMA Applicant: Berlin Heart, GmbH
Address: 200 Valleywood Suite A500, The Woodlands, TX 77382
Approval Date: December 16, 2011

What is it? The EXCOR® Pediatric VAD is a blood pump that vibrates rhythmically and is designed to assist patients who cannot pump enough blood with their own natural heart. The device can be used in patients who cannot effectively pump blood with their left and/or right ventricle. The VAD device consists of one or two air-driven blood pumps (depending on single-ventricle or double-ventricle support), small tubes inserted into the body that are used to connect the blood pumps to the atrium or ventricle and to the great arteries, and the IKUS driving unit. The IKUS provides air pulses that drive the rhythm of the pumps and also has computer controls to be used by hospital staff.

How does it work? The EXCOR® Pediatric VAD does not entirely replace the natural function of the heart. Instead, it works along with the patient’s own heart to pump blood. In a healthy heart, the left ventricle pumps blood rich with oxygen (oxygenated) to the vital organs and the right ventricle pumps non-oxygenated blood to the lungs to obtain oxygen. In a heart weakened by heart failure, the left and/or right ventricles are not strong enough to pump blood sufficiently. The EXCOR® Pediatric VAD helps the heart by supporting the weak ventricles.

The blood pump interior is divided into an air chamber and a blood chamber by a flexible membrane. Air pressure provided by the IKUS driving unit causes the membrane inside the pump to inflate and deflate. The air pulse moves the membrane, thus allowing blood to enter and exit the device. Valves are located at the blood pump connection branches to ensure one-way directional blood flow. The pulse rate and pump pressures can all be monitored and adjusted on the IKUS driving unit by hospital staff.

When is it used? The EXCOR® Pediatric VAD is used when the natural heart is unable to maintain normal blood flows and/or pressure or if it cannot adequately provide oxygenated blood to the vital organs. It is intended to provide support to the heart while these pediatric patients await a heart transplant.

What will it accomplish? In the U.S clinical trial of a total of 48 patients, 43 out of the 48 patients (approximately 90%) survived to cardiac transplantation or were successfully taken off the device (because their hearts recovered). Of these 43 patients, 35 out of the 43 patients (greater than 70%) received a heart transplant or were taken off the device with either: a) no neurologic events (such as a clot blocking a blood vessel in the brain) or; b) neurologic events that resulted in good neurologic outcomes (no apparent effect on normal brain function as a result of an event such as a clot blocking a blood vessel in the brain).

When should it not be used? The device should not be implanted in patients who may undergo an MRI (magnetic resonance imaging). Additionally, patients who cannot take medicines that stop blood from clotting should not be implanted with the EXCOR® Pediatric VAD.

Additional information: The Summary of Safety and Probable Benefit and labeling are available online.

Other Resources:
- FDA News Release – Berlin Heart EXCOR
- NIH – MedlinePlus – Heart Failure
Heart failure (HF) affects more than 5 million patients in the United States and is associated with high morbidity and mortality rates.\(^1\) Despite improvements in medical therapy with the use of angiotensin-converting enzyme (ACE) inhibitors, aldosterone antagonists, \(\beta\)-blockers, and cardiac defibrillators, more than 250,000 people die of HF each year.\(^1\) Although some of these patients die suddenly with few symptoms of HF, it is estimated that between 300,000 and 800,000 patients have “advanced HF.” This is defined as patients with left ventricular systolic dysfunction who experience symptoms that limit daily activity with poor exercise capacity despite maximal therapy.\(^5\) Recommended therapies for these patients, in addition to optimal medical management, include biventricular pacing, cardiac transplant, and mechanical circulatory support.\(^2\)\(^-\)\(^4\) When patients do not respond to these therapies, or cannot tolerate them, hospice and palliative care become the only option.

While there is significant clinical evidence demonstrating that advanced HF patients benefit from the recommended therapies, it is often quite difficult to determine when a patient with stable New York Heart Association (NYHA) functional class III will progress to advanced-stage HF. As shown in Figure 1, there is a continuum across which patients with HF progress. Recently, the American College of Cardiology (ACC) and the American Heart Association (AHA) developed a stage classification system for describing HF.\(^6\) Many patients, despite having left ventricular dysfunction, are completely asymptomatic and are classified as having stage BHF. Some of these patients, regardless of their evolution of disease will not seek or receive medical care. Others will be treated with optimal medical management and will remain stable for a period of time. Eventually, most patients progress to developing symptoms of HF and are classified as having stage CHF. Presentation will vary among patients. With time, as the left ventricle dilates further, patients will progress to advanced HF with symptoms at rest or with mild exertion, known as stage D. Patients may have periods of decompensation that require hospitalization but will then temporarily improve and become less symptomatic, fluctuating between NYHA functional class III and IV and ACC/AHA stages C and DHF. The ideal time for referral for advanced HF therapies is when the patient progresses from having stable HF to having advanced HF. Often, this referral doesn’t happen until the patient is moribund or doesn’t happen at all. This may occur for many reasons. Physicians may not be convinced that the advanced HF therapies available provide superior outcomes to those they can provide without making a referral to a tertiary care center. The referring physician may not have an established referral.
pathway that allows the partnership required to provide care for these complex patients. Most common, progression of HF is often quite difficult to predict and, when the progression occurs, it may happen so quickly that the patient is soon not a viable candidate for any of the advanced-stage therapies.

In this article, we have 3 goals:
- Define the current field in terms of available therapies.
- Provide guidance to referring physicians who wish to identify patient progression.
- Propose further study to validate our model/theory.

We will begin with a review of the current therapies and the corresponding outcomes available for advanced-stage HF patients. Also, based on published predictors of mortality, we offer a simple prognostic model to assist referring physicians in determining when their patients have progressed to the point at which referral for advanced-stage therapies are necessary. Finally, we propose a study to validate this model.

**Therapies for Advanced HF**

The ACC/AHA 2005 update for the diagnosis and management of HF approaches the treatment of HF by dividing therapies based on the patient’s clinical stage of HF.\(^4\) Therapies vary depending on the severity of the patient’s disease, as outlined in Table 1. For the stage D refractory patient, optimal medical and device management includes salt and fluid restriction; use of ACE inhibitors or angiotensin receptor blockers, \(\beta\)-blockers, diuretics, and implantable cardioverter-defibrillators (ICDs); and, in select patients, use of aldosterone antagonists, digitalis, hydralazine/nitrates, and biventricular pacers. In addition, other therapies that should be considered include heart transplant, chronic inotropes, permanent mechanical support, and experimental surgery or medications, depending on the patient presentation and appropriateness of these options for the particular patient.

**Heart Transplant.** Cardiac transplant is considered a preferred therapy for appropriately selected patients with advanced-stage HF. Transplant provides strong outcomes, with a 50% survival rate at 9.9 years for all patients and a 50% survival rate of 13 years for patients who survive the initial posttransplant year.\(^2\) Patients return to a near-normal quality of life and functional capacity. Due to limitations in the supply of donor organs, however, only 2000 patients a year receive transplants in the United States, and it is clearly not an option for the vast majority of patients with advanced-stage HF. In addition, due to long waiting times for donor organs, more than 10% of the waiting-list patients die each year. Better therapeutic options must be sought to improve outcomes and avoid mortality for these patients.

**Chronic Inotropes.** Inotropes are known for their ability to increase contractility and improve symptoms in the short term but are frequently associated with a mixture of negative side effects. All inotropes can induce arrhythmias and tachycardia and activate the renin-angiotensin-aldosterone system. Despite the routine and accepted use of inotropes in patients with refractory HF, inotropes have not been extensively evaluated in this patient population. The Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study\(^8\) evaluated the use of milrinone in addition to routine medical therapy in patients admitted with HF. Patients with predominantly NYHA III and IV symptoms were randomized to either a 48-hour infusion of milrinone or placebo. There were no differences in the number of days hospitalized within 60 days of randomization, in hospital or 60-day mortality, or the incidence of death or readmission. However, 35% of the patients were readmitted or had died within the next 60 days. This study revealed that despite an improvement in clinical status, inpatient therapy with milrinone for routine exacerbations of HF is not clinically useful. In addition, the study demonstrated that HF hospitalization is a marker of disease progression, with 8.9% of the placebo patients and 10.3% of the milrinone patients dying within the next 60 days.

This study was followed by the Continuous Outpatient Support With Inotropes (COSI) study.\(^9\) Thirty-six inotrope-dependent patients (defined as worsening of clinical status with attempted withdrawal) were discharged to home on long-term inotrope therapy. These patients had truly advanced-stage HF, with an ejection fraction of 19.9%, systolic blood pressure of 97 mm Hg, serum creatinine of 1.6 mg/dL, and serum sodium of 132 mEq/L. The median survival rate postdischarge was 3.4 months, and 12-month survival was 6%. Truly inotrope-dependent patients do not do well with inotropic therapy. Similar results were found from a retrospective analysis of the outcomes of patients taking inotropes in the Randomized Evaluation of Mechanical

<table>
<thead>
<tr>
<th>Table 1. ACC/AHA–Recommended Therapy for Heart Failure Patients by Stage(^6)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage A</strong></td>
</tr>
<tr>
<td><strong>Stage B</strong></td>
</tr>
<tr>
<td><strong>Stage C</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Stage D</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ACC, American College of Cardiology; ACE, angiotensin-converting enzyme; AHA, American Heart Association; ARB, angiotensin receptor blocker.
Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial. In this trial that evaluated the use of ventricular assist devices as permanent therapy for patients with advanced-stage HF, 91 of 129 patients were taking inotropic therapy at the time of randomization. The survival rates in the group that received medical therapy was 24% at 1 year and 11% at 2 years.

Bridging patients to transplant on inotropes is also a commonly accepted, although minimally documented, practice. In fact, there is a mounting body of evidence that suggests that other advanced HF therapies, such as ventricular assist devices (VADs), offer better outcomes and decreased mortality. Aaronsen and colleagues reported in a cohort of 102 patients awaiting heart transplant, overall survival of the VAD patients was superior to the inotropic group. Bhat found that in 16 of 39 patients treated with an inotrope, a VAD was still needed to successfully bridge the patients to transplant. Clearly, inotropes alone should not be considered the only option for bridge to transplant and, in fact, may negatively impact outcomes if used inappropriately.

Ventricular Assist Devices. Left VADs (LVADs) have been used for nearly 30 years to support patients awaiting cardiac transplant until a suitable donor becomes available. Until recently, however, they were limited to this small group of patients. The REMATCH trial was designed to evaluate the use of an LVAD as a long-term permanent therapy for patients not eligible for a transplant. In the trial, 129 patients not eligible for cardiac transplant were randomized to either continued medical therapy or surgery with placement of an LVAD. The survival rate at 1 year was 52% in the LVAD group and only 25% in the medical therapy group. Similar improvements in survival were present at year 2. Although quality-of-life measurements all showed improvements in the LVAD arm, LVAD therapy was associated with a longer total and initial hospital stay, more infections, and more neurologic events. However, a follow-up study demonstrated that many of these outcomes improve with improved surgical experience. Long and colleagues reported results in 42 patients that had an LVAD placed after the REMATCH trial, and survival at 1 year had improved to 61%. Despite this improvement, “destination” therapy has still not been widely accepted by the medical community, except in relatively isolated circumstances. In addition, a recently presented study has shown that refined patient selection is required to improve outcomes, noting that some patients receive VAD therapy at a point when they are too ill to experience an optimal outcome. Based on a multivariate analysis of clinical predictors of poor outcomes after placement of an LVAD, a group of very high-risk patients were identified with a greater than 90% chance of in-hospital mortality. This study demonstrates that there is a group of patients that are simply too ill for a positive outcome, thus negatively impacting the perception of destination therapy. Although there is not a limit to the number of VADs that can be implanted, as there is with transplant, there is still a need for appropriate and timely application of the technology. This validates the need for development of a simple clinical risk model to identify patients for referral to an advanced HF center when these advanced, proven therapies still have the potential for clinical benefit.

Risk Factors for Mortality in Patients Evaluated for Cardiac Transplant

There are a large number of biochemical-, structural-, physiologic-, and medical-based risk factors that have been associated with mortality in patients with HF. The landmark Studies of Left Ventricular Dysfunction (SOLVD) trial was the first major study in HF to evaluate clinical predictors of mortality. From this trial, retrospective analyses have shown that elevated plasma norepinephrine levels, atrial fibrillation, renal insufficiency, reduced ejection fractions, enlarged diastolic dimensions, and diuretic use have all been shown to be associated with an increased risk of mortality.

Similarly, others have developed risk models for predicting mortality in patients evaluated for cardiac transplant. Mancini and colleagues first evaluated the use of the metabolic exercise test to determine whether the use of peak oxygen consumption can help to predict mortality. They found a direct relationship between lower peak oxygen consumption values and mortality. In addition, they found that patients with peak oxygen consumption ≤14 mL/kg/min had a survival advantage with cardiac transplant compared with continued medical therapy. Since that landmark paper in 1992, peak oxygen consumption has been used to determine whether patients should be listed for transplant. This work was later advanced by the Heart Failure Survival Score (HFSS). Aaronson and colleagues developed a risk model for HF patients and identified low-, medium-, and high-risk groups. Risk factors for mortality included an ischemic etiology, higher heart rates, lower ejection fraction and mean blood pressure, presence of an intraventricular conduction delay, peak oxygen consumption, hyponatremia, and elevated pulmonary capillary wedge pressures. While simple, variables such as oxygen consumption and pulmonary capillary wedge pressures are rarely obtained unless a patient is being evaluated for cardiac transplant and therefore rarely assist in determining when someone is ready for referral. There is still a need for help in determining when patients should be referred for advanced therapies.

Risk Factors for Mortality in Patients With HF

Table II outlines a number of studies that have been performed in both the inpatient and outpatient settings to assist in determining prognosis in patients with HF. Although the modeling methods that were performed, the exact variables evaluated, and length of follow-up varies from study to study, a consistent pattern of results are
reported. Evidence of poor perfusion to end organs manifested by decreased renal function, neuro-hormonal upregulation manifested by hyponatremia, poor exercise tolerance manifested by both NYHA functional class and 6-minute walk distance, hypotension, high diuretic doses, inability to tolerate either an ACE inhibitor or a β-blocker, and recent hospitalizations are repeatedly demonstrated to be markers of poor patient outcomes. Many of these studies have developed sophisticated models using risk scores or dividing patients into risk groups based on scores that are quite beneficial academically but, similar to the HFSS, are not used practically. Furthermore, a proven, reliable, simple clinical risk score classification that can be calculated from memory to predict mortality during the next year has never been developed, especially in the outpatient setting, despite multiple studies that have examined various risk factors for mortality.

As shown in Table III, we propose a simple group of clinical markers that, when present in patients, should predict poor outcomes during the next year, and their presence should trigger consideration for a referral to an advanced HF center for advanced medical and surgical therapies not available in the community. All of these indicators are noted during a routine clinical visit and laboratory evaluation and would not require additional testing. Although no prognostic studies have been performed to evaluate the predictive value of these variables, based on the studies in Table II, it is quite clear that all of these variables have been shown to predict survival in large patient populations. Furthermore, a prospective trial evaluating a number of similar risk factors should be performed. Despite multiple retrospective studies of predictors, a prospective study specifically designed to evaluate risk factors for mortality in patients with HF has never been performed. The following factors should be included in such a study.

**Exercise Tolerance.** Bouvy,28 Felker,31 Mahon,15 Greenberg,37 Levy,38 and colleagues all included either 6-minute walk distance or NYHA functional class in their prognostic models. We believe that the clinically relevant “how far can you walk before becoming short of breath” question reflects this evaluation in a practical manner. In addition, Stewart and colleagues30 presented a study at the 2006 AHA Annual Meeting in which they asked patients at what point

<table>
<thead>
<tr>
<th>AUTHORS</th>
<th>PATIENT TYPE</th>
<th>NO.</th>
<th>MARKERS</th>
<th>1-YEAR SURVIVAL RATE, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chin et al24</td>
<td>In</td>
<td>257</td>
<td>BP &lt; 100 mm Hg, DM, nonsinus rhythm</td>
<td>N/A</td>
</tr>
<tr>
<td>Alla et al25</td>
<td>In</td>
<td>301</td>
<td>HR &gt; 100 beats per minute, Na &lt; 134 mEq/L, Creat &gt; 2.0 mg/dL, age &gt; 70 y, prior hosp</td>
<td>57.6</td>
</tr>
<tr>
<td>Cowie et al26</td>
<td>In</td>
<td>220</td>
<td>Age, crackles on examination, low BP, high Creat</td>
<td>62</td>
</tr>
<tr>
<td>Jong et al27</td>
<td>In</td>
<td>38,702</td>
<td>Male; age; malignancy; dementia; renal, cerebrovascular, rheumatologic, peripheral vascular, or pulmonary disease; ischemic etiology, DM</td>
<td>66.9</td>
</tr>
<tr>
<td>Bouvy et al28</td>
<td>In</td>
<td>152</td>
<td>DM, high Creat, NYHA III/IV, low BMI, low BP, edema</td>
<td>N/A</td>
</tr>
<tr>
<td>Lee et al29</td>
<td>In</td>
<td>4031</td>
<td>Age, low BP, high RR, high BUN, low Na</td>
<td>69.5</td>
</tr>
<tr>
<td>Kittleson et al30</td>
<td>In</td>
<td>259</td>
<td>No ACE, low BP, low Na, high Creat</td>
<td>N/A</td>
</tr>
<tr>
<td>Felker et al31</td>
<td>In</td>
<td>949</td>
<td>Age, low BP, NYHA IV, high BUN, low Na</td>
<td>N/A</td>
</tr>
<tr>
<td>Fonarow et al32</td>
<td>In</td>
<td>37,772</td>
<td>BUN &gt; 43 mg/dL, systolic BP &lt; 115 mm Hg, Creat &gt; 2.75 mg/dL</td>
<td>N/A</td>
</tr>
<tr>
<td>Rector et al33</td>
<td>In</td>
<td>769</td>
<td>Age, low BP, low Hgb, low Na, high BUN</td>
<td>50% (high risk)</td>
</tr>
<tr>
<td>Rohde et al34</td>
<td>In</td>
<td>779</td>
<td>Cancer, systolic BP &lt; 124 mm Hg, Creat &gt; 1.4 mg/dL, BUN &gt; 37 mg/dL, Na &lt; 136 mEq/L, age &gt; 70 y</td>
<td>N/A</td>
</tr>
<tr>
<td>Mahon et al35</td>
<td>Out</td>
<td>585</td>
<td>Low Creat cl, 6 MW &lt; 262 m, low EF, recent hosp, diuretic dose</td>
<td>N/A</td>
</tr>
<tr>
<td>Eshaghian et al36</td>
<td>In</td>
<td>1354</td>
<td>Low EF, low Na, low Hgb, high BUN, high Creat, diuretic dose</td>
<td>N/A</td>
</tr>
<tr>
<td>Greenberg et al37</td>
<td>Out</td>
<td>4280</td>
<td>NYHA III/IV, HF hosp, angina</td>
<td>N/A</td>
</tr>
<tr>
<td>Levy et al38</td>
<td>Out</td>
<td>1125</td>
<td>Diuretic dose, low BP, % lymph, Hgb &lt; 16 g/dL, ischemic etiology, EF, low cholesterol, high uric acid/albumin use, Na &lt; 138 mEq/L, NYHA, age, male sex</td>
<td>N/A</td>
</tr>
<tr>
<td>Teuteberg et al39</td>
<td>Out</td>
<td>160</td>
<td>High BUN, Creat, low Na, low Hct, recent hosp, no ACE/BB</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, angiotensin-converting enzyme inhibitor; BB, β-blocker; BMI, body mass index; BP, blood pressure; BUN, serum urea nitrogen; Creat, serum creatinine; Creat cl, creatinine clearance; DM, diabetes mellitus; EF, ejection fraction; HF, heart failure; Hct, hematocrit; Hgb, hemoglobin; hosp, hospitalization; HR, heart rate; lymph, lymphocytes; Na, serum sodium; N/A, not available; NYHA, New York Heart Association; RR, respiratory rate; 6 MW, 6-minute walk.
would they consider an LVAD. Just over 40% stated that they would consider such a therapy when they couldn’t walk a block. Clearly, using exercise tolerance as a marker of functional status identifies a patient group that is willing to undergo the therapies provided at an advanced HF center and defines a group that would also benefit from the therapy.

Laboratory Evaluation. Numerous studies have included either low sodium and hematocrit values or high creatinine and serum urea nitrogen values in their prognostic values.20,21,25,26,28–30,32,36,38 The majority of these studies used the absolute value of these numbers in their model, which makes it difficult to choose a simple value. The numbers chosen in this model, however, reflect abnormal values that fall within a range that has been shown to be predictive of events.

Medication. The inability to tolerate medications appears to be a very significant marker for predicting poor outcomes. Thirty-five percent of the patients who died in the Teuteberg experience could not tolerate an ACE inhibitor and only 38% were on a β-blocker.39 Similarly, the Seattle Heart Failure Model (SHFM) demonstrates the effects of intolerance of these medications.38 Conversely, the presence of a diuretic and the absolute dose of a diuretic have also been shown to be predictive of worse outcomes.21,35,36,38 Based on data from the SHFM, we decided on a furosemide equivalent dose of 1.5 mg/kg/d as a marker of high-dose diuretic use.

HF Admissions. Admission to the hospital for HF exacerbation has a 30% to 50% mortality rate during the next year.35,37,39 Clearly this is a very important marker of progression of disease and reflects a group of patients with worse outcomes.

CRT Therapy. Cardiac resynchronization therapy (CRT) improves quality of life and survival in patients with NYHA functional class III and IV symptoms and is now indicated as a therapy in patients who have a QRS width >0.12.5 Recently, Saxon and colleagues’ evaluated predictors of sudden cardiac death and appropriate shock in patients who had both an ICD and CRT. They found that NYHA functional class IV patients and worsening renal function predicted appropriate ICD therapy. In addition, appropriate ICD therapy was associated with the risk of death or all-cause hospitalization. Patients who do not clinically respond to this therapy and continue to be very symptomatic should be thought of as having a high risk for poor outcomes.

Call to Action

Despite significant improvements in current HF therapies, HF continues to be the number one discharge diagnosis in the United States each year and is associated with significant mortality. A number of risk models have been developed to predict patients with poor outcomes, but they are rarely used because of their complexity. A simple prognostic model that includes variables routinely obtained at clinical visits is required so that practitioners can quickly identify and refer patients with advanced HF symptoms before they decompensate to the point that only desperation therapies are available. Risk factors such as those shown in Table III should be used to determine whether a patient with NYHA functional class III or IV symptoms should be referred for evaluation to an advanced HF center. Using the flow chart shown in Figure 2, those patients can then be directed to the appropriate therapy. In addition, a prospective validation study using simple risk factors that can be easily obtained and used in daily practice is necessary to further advance the care of these patients.

Disclosures: Dr Russell is a consultant and receives research support from Thoratec Corporation. Dr Miller receives research support from Thoratec Corporation.

REFERENCES


Prospective Trial of a Pediatric Ventricular Assist Device

Charles D. Fraser, Jr., M.D., Robert D.B. Jaquiss, M.D., David N. Rosenthal, M.D., Tilman Humpl, M.D., Ph.D., Charles E. Canter, M.D., Eugene H. Blackstone, M.D., David C. Naftel, Ph.D., Rebecca N. Ichord, M.D., Lisa Bomgaars, M.D., James S. Tweddell, M.D., M. Patricia Massicotte, M.D., Mark W. Turrentine, M.D., Gordon A. Cohen, M.D., Ph.D., Eric J. Devaney, M.D., F. Bennett Pearce, M.D., Kathleen E. Carberry, R.N., M.P.H., Robert Kroslowitz, B.S., and Christopher S. Almond, M.D., M.P.H., for the Berlin Heart Study Investigators

From Texas Children’s Hospital (C.D.F., L.B., K.E.C.) and Baylor College of Medicine (C.D.F., L.B.), Houston, and Berlin Heart, The Woodlands (R.K.) — all in Texas; Duke Children’s Hospital and Health Center, Duke University School of Medicine, Durham, NC (R.D.B.J.); Lucile Packard Children’s Hospital, Stanford University School of Medicine, Stanford, CA (D.N.R.); the Hospital for Sick Children, University of Toronto, Toronto (T.H.), and Stollery Children’s Hospital, University of Alberta School of Medicine, Edmonton (M.P.M.) — both in Canada; St. Louis Children’s Hospital, Washington University School of Medicine, St. Louis (C.E.C.); Heart and Vascular Institute and Department of Quantitative Health Sciences, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland (E.H.B.); University of Alabama School of Medicine, Birmingham (D.C.N., F.B.P.); Children’s Hospital of Philadelphia, Perelman School of Medicine of the University of Pennsylvania School of Medicine, Philadelphia (R.N.I.); Children’s Hospital of Wisconsin, Medical College of Wisconsin, Milwaukee (J.S.T.); Riley Hospital for Children, Indiana University School of Medicine, Indianapolis (M.W.T.); Seattle Children’s Hospital, University of Washington School of Medicine, Seattle (G.A.C.); C.S. Mott Children’s Hospital, University of Michigan Health System, Ann Arbor (E.J.D.); and Children’s Hospital of Boston, Harvard Medical School, Boston (C.S.A.). Address reprint requests to Dr. Fraser at Texas Children’s Hospital, Baylor College of Medicine, 5621 Fannin St., WT 19345H, Houston, TX 77030, or at cdfraser@texaschildrens.org.

ABSTRACT

BACKGROUND
Options for mechanical circulatory support as a bridge to heart transplantation in children with severe heart failure are limited.

METHODS
We conducted a prospective, single-group trial of a ventricular assist device designed specifically for children as a bridge to heart transplantation. Patients 16 years of age or younger were divided into two cohorts according to body-surface area (cohort 1, <0.7 m²; cohort 2, 0.7 to <1.5 m²), with 24 patients in each group. Survival in the two cohorts receiving mechanical support (with data censored at the time of transplantation or weaning from the device owing to recovery) was compared with survival in two propensity-score–matched historical control groups (one for each cohort) undergoing extracorporeal membrane oxygenation (ECMO).

RESULTS
For participants in cohort 1, the median survival time had not been reached at 174 days, whereas in the matched ECMO group, the median survival was 13 days (P<0.001 by the log-rank test). For participants in cohort 2 and the matched ECMO group, the median survival was 144 days and 10 days, respectively (P<0.001 by the log-rank test). Serious adverse events in cohort 1 and cohort 2 included major bleeding (in 42% and 50% of patients, respectively), infection (in 63% and 50%), and stroke (in 29% and 29%).

CONCLUSIONS
Our trial showed that survival rates were significantly higher with the ventricular assist device than with ECMO. Serious adverse events, including infection, stroke, and bleeding, occurred in a majority of study participants. (Funded by Berlin Heart and the Food and Drug Administration Office of Orphan Product Development; ClinicalTrials.gov number, NCT00583661.)
Systolic heart failure causes 280,000 deaths in adults annually in the United States.¹ Heart failure is much less common among children than among adults, but it is highly lethal, with 46% of children with heart failure dying or undergoing transplantation within 5 years after diagnosis, according to one estimate.² The survival rate among children after heart transplantation is estimated at 83% at 3 years,³,⁴ but the limited availability of donor hearts for children prolongs the waiting period,⁵ resulting in a high rate of death among children on waiting lists.⁶⁻⁸

Options for mechanical circulatory support as a bridge to transplantation are limited for children. The mainstay of support for small children has been extracorporeal membrane oxygenation (ECMO). The effective period of support with ECMO is typically limited to only 10 to 20 days before serious complications ensue, such as bleeding and major organ-system failure, which often preclude transplantation. The short duration of support afforded by ECMO is often inadequate, considering the current waiting times (a median of 119 days for all infants in 2008⁸). As a result, only 40 to 60% of children requiring support with ECMO survive long enough to undergo heart transplantation.⁹

The Excor Pediatric ventricular assist device (Berlin Heart) is a paracorporeal, pneumatically driven, pulsatile-flow mechanical circulatory-support device available in a wide range of sizes. We conducted a prospective study to evaluate this device as bridge therapy in children who were on waiting lists for orthotopic heart transplantation.

**Methods**

**Study Design**

In this prospective, multicenter, single-group cohort study,¹⁰ we compared children who underwent implantation of the Excor Pediatric ventricular assist device as a bridge to transplantation with a historical control group of children who received circulatory support with ECMO. Seventeen pediatric cardiac centers in the United States and Canada participated in the trial (see the Supplementary Appendix, available with the full text of this article at NEJM.org, for a list of study sites and investigators).

The study was designed by the principal investigators and by clinical experts in pediatric trial design, hematology, and neurology in collaboration with the sponsor, Berlin Heart, and the Food and Drug Administration. Data were gathered by study coordinators at each site and were analyzed by the sponsor and independent academic statisticians in collaboration with the study investigators. The investigators had full access to the data. Data monitoring was performed by a contract research organization (Alquest). Data confidentiality was required by contractual agreement between each study site and the sponsor. The decision to submit the manuscript for publication was made by members of the publication committee (see the Supplementary Appendix) and the sponsor. All authors participated in writing, revising, and reviewing the manuscript. The academic authors and the authors who are employees of the sponsor vouch for the accuracy and completeness of the data and analysis and the fidelity of the study to the trial protocol. The study protocol (available at NEJM.org) was approved by the institutional review board at each participating center, and written informed consent was provided by a parent or legal guardian for all study participants.

**Participant Selection**

Children were eligible for the study if they were 16 years of age or younger, weighed between 3 and 60 kg, had two-ventricle circulation, had severe heart failure despite optimized medical treatment, and were on a waiting list for cardiac transplantation. Children who had already been receiving another form of mechanical circulatory support were allowed to participate, except for those who had received circulatory support with ECMO for 10 days or more (see Table S1 in the Supplementary Appendix for a complete list of inclusion and exclusion criteria). After enrollment, participants were stratified according to body-surface area. Cohort 1 included all participants with a body-surface area of less than 0.7 m², and cohort 2 all participants with a body-surface area of at least 0.7 m² but less than 1.5 m².

**Study Protocol**

Each participant underwent surgical implantation of an Excor Pediatric ventricular assist device, the size of which was chosen on the basis of age and body weight. Devices with stroke volumes of 10, 25, 30, 50, and 60 ml were available (Fig. S1 and S2 in the Supplementary Appendix).¹¹ Par-
ticipants underwent implantation of one device in the left ventricle only (left ventricular assist) or of devices in both left and right ventricles (biventricular assist) on the basis of an algorithm developed to predict right-heart performance at the time of surgery and at the clinical discretion of the surgeon performing the implantation. Standardized antithrombotic therapy was recommended (Fig. S3 in the Supplementary Appendix). After postoperative recovery, patients in stable condition were typically treated with aspirin, dipyridamole, and either warfarin or enoxaparin.

Study data were collected within 48 hours before device implantation; at implantation; at 1, 2, 4, and 6 weeks; at 3 and 6 months; and every 3 months thereafter while the child received circulatory support with the ventricular assist device. Participants who were deemed to be acceptable candidates for a heart transplant after implantation of the device underwent transplantation if and when a suitable donor organ became available. Participants with signs of substantial ventricular recovery were weaned from the ventricular assist device, meaning that support with the device was gradually discontinued, and the pump surgically explanted.

### Table 1. Characteristics of the Study Participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>VAD Cohort 1 (N = 24)</th>
<th>ECMO Matched Group for Cohort 1 (N = 48)†</th>
<th>P Value‡</th>
<th>VAD Cohort 2 (N = 24)</th>
<th>ECMO Matched Group for Cohort 2 (N = 48)†</th>
<th>P Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — mo§</td>
<td>11.7</td>
<td>10.6</td>
<td>0.53</td>
<td>111.2</td>
<td>138.7</td>
<td>0.96</td>
</tr>
<tr>
<td>Range</td>
<td>2.6–45.6</td>
<td>0.1–112.3</td>
<td></td>
<td>50.8–191.8</td>
<td>1.8–188.6</td>
<td></td>
</tr>
<tr>
<td>Weight — kg§</td>
<td>9.2</td>
<td>8.8</td>
<td>0.79</td>
<td>30.7</td>
<td>36.0</td>
<td>0.96</td>
</tr>
<tr>
<td>Range</td>
<td>3.6–13.6</td>
<td>3.1–27.0</td>
<td></td>
<td>16.0–58.1</td>
<td>4.0–59.0</td>
<td></td>
</tr>
<tr>
<td>Primary diagnosis — no. (%)§</td>
<td></td>
<td></td>
<td>0.32</td>
<td></td>
<td></td>
<td>0.51</td>
</tr>
<tr>
<td>Congenital heart disease</td>
<td>3 (12)</td>
<td>8 (17)</td>
<td></td>
<td>6 (25)</td>
<td>15 (31)</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>0</td>
<td>0</td>
<td></td>
<td>0</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Dilated cardiomyopathy or myocarditis</td>
<td>19 (79)</td>
<td>39 (81)</td>
<td></td>
<td>17 (71)</td>
<td>31 (65)</td>
<td></td>
</tr>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>1 (4)</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Restrictive cardiomyopathy</td>
<td>1 (4)</td>
<td>0</td>
<td></td>
<td>1 (4)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>0</td>
<td>1 (2)</td>
<td></td>
<td>0</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Preoperative mechanical ventilation — no. (%)§</td>
<td>20 (83)</td>
<td>36 (75)</td>
<td>0.42</td>
<td>11 (46)</td>
<td>26 (54)</td>
<td>0.50</td>
</tr>
<tr>
<td>Preoperative inotrope infusion — no. (%)§</td>
<td>22 (92)</td>
<td>43 (90)</td>
<td>0.78</td>
<td>21 (88)</td>
<td>40 (83)</td>
<td>0.64</td>
</tr>
<tr>
<td>Preoperative cardiac arrest — no. (%)§</td>
<td>7 (29)</td>
<td>14 (29)</td>
<td>1.00</td>
<td>5 (21)</td>
<td>13 (27)</td>
<td>0.56</td>
</tr>
<tr>
<td>Body-surface area — m²</td>
<td>0.44</td>
<td></td>
<td></td>
<td>1.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0.23–0.62</td>
<td></td>
<td>0.71–1.66</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>12 (50)</td>
<td></td>
<td></td>
<td>13 (54)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INTERMACS profile status at implantation — no. (%)¶</td>
<td>1</td>
<td>11 (46)</td>
<td></td>
<td>13 (54)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>13 (54)</td>
<td></td>
<td>11 (46)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Proposed Trial of a Pediatric Ventricular Assist Device

The New England Journal of Medicine

Table 1. (Continued.)

<table>
<thead>
<tr>
<th>Variable</th>
<th>VAD Cohort 1 (N = 24)</th>
<th>VAD Cohort 2 (N = 24)</th>
<th>ECMO Matched Group for Cohort 1 (N = 48)†</th>
<th>P Value‡</th>
<th>ECMO Matched Group for Cohort 2 (N = 48)†</th>
<th>P Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative ECMO — no. (%)</td>
<td>6 (25)</td>
<td>8 (33)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative centrifugal VAD — no. (%)</td>
<td>2 (8)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of implant — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVAD</td>
<td>17 (71)</td>
<td>14 (58)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIVAD</td>
<td>7 (29)</td>
<td>10 (42)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Closure of intracardiac shunt at implantation — no. (%)</td>
<td>7 (29)</td>
<td>3 (12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valve repair or replacement at implantation — no. (%)</td>
<td>2 (8)</td>
<td>4 (17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time required for cardiopulmonary bypass — min</td>
<td>185±49</td>
<td>176±52</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. BIVAD denotes biventricular assist device, ECMO extracorporeal membrane oxygenation, LVAD left ventricular assist device, and VAD ventricular assist device.
† The correlation coefficient for the matched propensity scores was 0.97 for cohort 1 (P<0.001) and 0.96 for cohort 2 (P<0.001).
‡ P values for comparison of the ventricular-assist cohorts with the propensity-score–matched ECMO groups were obtained with the t-test or chi-square test.
§ These variables were used in the propensity-score analysis to match historical control groups from the Extracorporeal Life Support Organization (ELSO) database with the ventricular-assist cohorts.
¶ According to the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), a profile status of 1 indicates critical cardiogenic shock, and 2 progressive decline.
‖ One participant had a body-surface area of 1.66 m², which was outside the eligibility-criteria specifications; a protocol deviation was documented for this occurrence.

A voluntary database that enrolls patients who receive ECMO support. A propensity-score analysis was used to match each participant who received a ventricular assist device to two children who had received support with ECMO (selected from the ELSO database). The propensity-score matching was performed separately and independently for each of the two cohorts. Details regarding the ELSO database and the propensity-score matching are provided in the Supplementary Appendix.

STUDY OUTCOMES

The primary efficacy end point was defined differently for the ventricular-assist and ECMO groups. For the ventricular-assist group, the primary end point was the time to death or weaning from the device with an unacceptable neurologic outcome. Death was defined as any death occurring while the child required support with the device or death within 30 days after weaning from the device or before hospital discharge, whichever was longer. An unacceptable neurologic outcome was defined as either coma or the presence of profound sensory, motor, language, or cognitive impairment as assessed with the Pediatric Stroke Outcome Measure (see the Supplementary Appendix for details of the neurologic assessments and the Pediatric Stroke Outcome Measure). Data from participants who underwent heart transplantation or who had ventricular recovery with uneventful weaning from the device were censored at the time of transplantation or weaning.

For the ECMO group, the primary end point was only the time to death (as defined above), because data on neurologic status were not available in the ELSO database. Data from patients who underwent device explantation and survived for at least 30 days were censored; the ELSO database does not specify whether such explants were due to recovery or transplantation.

In a secondary outcome assessment, outcome events were classified for a competing-risk analysis. For the ventricular-assist group, four mutually exclusive outcome events were tracked: death during receipt of circulatory support with the device; heart transplantation; failure of weaning (defined
as death or an unacceptable neurologic outcome, as defined above, within 30 days after weaning or before discharge from the hospital, whichever was longer; and successful weaning (defined as weaning from the device without death or an unacceptable neurologic outcome within 30 days after weaning or before discharge from the hospital). For the ECMO group, three mutually exclusive outcome events were tracked: death during receipt of support with ECMO, death within 30 days after weaning from the device, and removal of the device (without death within 30 days after device removal). For both groups, children who had not yet had any of these specific outcome events were classified as being alive and receiving support with the device.

Additional data were collected for the ventricular-assist group. Data on device performance (e.g., function of the driver system and the drivelines, system failures, systolic and diastolic pressures, and stroke rate) were recorded routinely while participants receiving circulatory support with the device. Functional status was assessed at each time point by determining whether the participant was sedated, intubated, eating, or ambulating. Information about functional status is provided in the Supplementary Appendix. Adverse events were documented throughout the study according to standardized definitions from the Interagency Registry for Mechanically Assisted Circulatory Support13 (Table S3 in the Supplementary Appendix).

A clinical events committee adjudicated all adverse events, the neurologic status of patients who were considered to be weaned from the device owing to recovery, and deaths. A data and safety monitoring committee evaluated the study data every 6 months to ensure the safety of the participants and the integrity of the study (see the Supplementary Appendix).

STATISTICAL ANALYSIS
We estimated that the median time to the primary end point for participants with the ventricular assist device would be 100 days, and the median time to the primary end point for the propensity-score-matched control group of children receiving support with ECMO would be 5 days. On the basis of these assumptions, we calculated that the inclusion of 24 participants in each ventricular-assist cohort would provide more than 99% power, with a two-sided alpha level of 0.05, to test the hypothesis that survival with the ventricular assist device would be significantly longer than survival with ECMO.

All comparisons between the ventricular-assist and ECMO groups were performed on an intention-to-treat basis. Cumulative event rates were calculated according to the Kaplan–Meier method. For the ventricular-assist group, the time to an event was measured from the time of implantation of the ventricular assist device, regardless of whether another form of mechanical support had been in use before implantation. For the ECMO group, the time to an event was measured from the time of implantation of the ECMO device. The between-group difference in the time to the occurrence of the primary end point was assessed by means of the log-rank test within each of the two study cohorts. The duration of support with the device was compared with the use of the Wilcoxon median two-sample test.

The primary safety end point was also evaluated with the use of a competing-risk analysis. The proportion of participants having each of the competing outcomes at each time point was plotted. Outcomes at 30 days and at the end of device support for the participant who received support for the longest time were compared between groups with the use of chi-square tests.

The primary safety end point was calculated as the number of serious adverse events per day during circulatory support with the ventricular assist device. A Poisson exact confidence interval was calculated, and the critical-value method was used for significance testing. Success was prospectively defined as less than 0.25 events per day for the upper bound of the 95% Poisson exact confidence interval. A two-tailed Fisher’s exact test was used to compare the proportion of participants in each functional-status category at each time point with the proportion in each category before the devices were implanted.

All reported P values are two-sided. A P value of less than 0.05 was considered to indicate statistical significance, without adjustment for multiple comparisons.

RESULTS

STUDY PARTICIPANTS
We enrolled 48 children, 24 in each cohort, in the trial between May 2007 and December 2010. In cohort 1, the median age was 1 year and the median weight was 9 kg. In cohort 2, the median age
was 9 years and the median weight was 31 kg. In both cohorts, the cause of cardiac failure in most participants was cardiomyopathy or myocarditis, with a much smaller proportion having congenital heart disease (Table 1). The propensity-score–matching process resulted in statistically well-matched control groups (Table 1, and Table S2 in the Supplementary Appendix).

**DEVICE EFFICACY AND SUPPORT OUTCOMES**

For children in cohort 1, the median duration of support with the ventricular assist device was 28 days, as compared with 5 days for the matched ECMO group (P<0.001 by the Wilcoxon median two-sample test). The longest duration of support with the device in each of these two groups was 174 days and 21 days, respectively. For children in cohort 2, the median duration of support with the device was 43 days, as compared with 5 days for the matched ECMO group (P<0.001 by the Wilcoxon median two-sample test). The longest duration of support with the device in each of these two groups was 192 days and 28 days, respectively.

Among participants in cohort 1, the median time to the primary end point had not yet been reached at 174 days. In contrast, the median time to the primary end point in the matched ECMO group was 13 days (P<0.001 by the log-rank test) (Fig. 1A). Among participants in cohort 2, the median time to the primary end point was 144 days, as compared with 10 days in the matched ECMO group (P<0.001 by the log-rank test) (Fig. 1B).

Competing-outcome analyses are shown in Figures 2 and 3. In the ECMO group for cohort 1, at 21 days, 25% of the patients had died, and none were alive and still receiving support with ECMO (Fig. 2A). In the ECMO group for cohort 2, at 30 days, 33% of the patients had died, and none were alive and still receiving support with ECMO (Fig. 2B). In contrast, in cohort 1, at 174 days, 88% of the patients had undergone successful transplantation and 12% had died or had an unacceptable neurologic outcome after weaning from the device (Fig. 3A). In cohort 2, at 192 days, 92% of the patients had undergone successful transplantation or had been weaned from the device, and 8% had died (Fig. 3B). Overall, 88% of the participants in cohort 1 and 92% of those in cohort 2 survived to undergo either heart transplantation or weaning from the device (Table 2).
The rate of serious adverse events in cohort 1 was 0.07 events per patient-day (95% confidence interval [CI], 0.06 to 0.08), and in cohort 2, the rate was 0.08 events per patient-day (95% CI, 0.06 to 0.09). The upper bounds of the 95% confidence intervals were both below the prospectively set criterion for success of 0.25.

The most common serious adverse events were major bleeding (in 42% of participants in cohort 1 and in 50% of those in cohort 2), infection (in 63% and 50%, respectively), stroke (in 29% and 29%), and hypertension (in 50% and 33%). More details regarding deaths and adverse neurologic outcomes, as well as a table of adverse events (Table S7 in the Supplementary Appendix), are provided in the Supplementary Appendix.

Forty-six pump changes occurred in cohorts 1 and 2 combined. Thrombus formation in the device was identified as the reason for 43 of these pump changes. Pump changes were required in three participants for whom no thrombus in the device was identified: one participant had multiple infarcts on computed tomography of the head, one had a neurologic event, and one had positive fungal blood cultures.

**ADVERSE EVENTS**

Three mutually exclusive outcome events were tracked for this analysis: death occurring while the child was receiving circulatory support with ECMO, death within 30 days after weaning from the device, and device removal (without death within 30 days). Children who had not yet had any of these specific outcome events were classified as being alive and receiving circulatory support.

The most common serious adverse events were major bleeding (in 42% of participants in cohort 1 and in 50% of those in cohort 2), infection (in 63% and 50%, respectively), stroke (in 29% and 29%), and hypertension (in 50% and 33%). More details regarding deaths and adverse neurologic outcomes, as well as a table of adverse events (Table S7 in the Supplementary Appendix), are provided in the Supplementary Appendix.

Four mutually exclusive outcome events were tracked for this analysis: death occurring while the child was receiving circulatory support with the ventricular assist device, heart transplantation, weaning from the device but either dying or having an unacceptable neurologic outcome within 30 days after weaning or before discharge from the hospital (whichever was longer), and weaning from the device without death or an unacceptable neurologic outcome in the period defined above. Children who had not yet had any of these specific outcome events were classified as being alive and receiving circulatory support.
Table 2. Efficacy Outcomes.*

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of Children</th>
<th>Outcome at 30 Days</th>
<th>Success at 30 Days†</th>
<th>P Value</th>
<th>Outcome at End of Circulatory Support</th>
<th>Success at End of Circulatory Support‡</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of children</td>
<td>No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Receiving Circulatory Support</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Received Transplant</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weaned with Recovery</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weaned with Poor Outcome§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Died</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAD cohort 1</td>
<td>24</td>
<td>12</td>
<td>11</td>
<td>0</td>
<td>1</td>
<td>23 (96)</td>
<td>0.048</td>
</tr>
<tr>
<td></td>
<td>23 (96)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECMO matched group</td>
<td>48</td>
<td>0</td>
<td>NA</td>
<td>36¶</td>
<td>2</td>
<td>36 (75)</td>
<td>0.048</td>
</tr>
<tr>
<td>for cohort 1</td>
<td>0</td>
<td>36 (75)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VAD cohort 2</td>
<td>24</td>
<td>17</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>23 (96)</td>
</tr>
<tr>
<td></td>
<td>22 (92)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECMO matched group</td>
<td>48</td>
<td>0</td>
<td>NA</td>
<td>32¶</td>
<td>6</td>
<td>32 (67)</td>
<td>0.059</td>
</tr>
<tr>
<td>for cohort 2</td>
<td>0</td>
<td>32 (67)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* The days by which no participants were still alive and receiving circulatory support were as follows: 174 days in cohort 1, 21 days in the ECMO group for cohort 1, 192 days in cohort 2, and 28 days in the ECMO group for cohort 2. NA denotes not available.
† Success at 30 days in the ventricular-assist group was defined as being alive and receiving circulatory support with the device, having undergone transplantation, or having been weaned from the device with an acceptable neurologic outcome within 30 days after device removal. Success at 30 days in the ECMO group was defined as being alive and receiving circulatory support with ECMO or having been successfully weaned from ECMO, either owing to transplantation or weaning without death within 30 days after device removal.
‡ Success at the end of device support in the ventricular-assist group was defined as having undergone transplantation or having been weaned from the device with an acceptable neurologic outcome within 30 days after device removal. Success at the end of device support in the ECMO group was defined as weaning from ECMO because of transplantation or recovery.
§ A poor outcome in the ventricular-assist group was defined as death or an unacceptable neurologic outcome within 30 days after weaning or before discharge from the hospital, whichever was longer. A poor outcome in the ECMO group was defined as death within 30 days after weaning from the device; data on neurologic outcomes were unavailable from the ELSO database.
¶ Data from patients who underwent device explantation and survived for at least 30 days were censored; the ELSO database does not specify whether such explants are due to recovery or transplantation.
DISCUSSION

Adults with severe heart failure have benefited from a series of technological advances in the use of ventricular assist devices as a bridge to heart transplantation. Progress in developing pediatric devices has been much slower because of the proportionately greater variation in size among children. Other reasons for the slow progress include biologic differences in the response to anticoagulant medicines, low levels of interest in the medical industry, and in particular, the size constraints in very small babies.

In this trial, we evaluated the use of the Excor Pediatric ventricular assist device as a bridging therapy in children who were on waiting lists for orthotopic heart transplantation. This device is available in several sizes, so that its use may be feasible in children of various ages. We compared outcomes in participants who had received a ventricular assist device to those in propensity-score–matched, historical control groups of children who received support with ECMO, the only other option for mechanical circulatory support that is currently available for small children. We found that the rate of survival to device explantation (owing to either transplantation or recovery) was markedly higher with the ventricular assist device than with ECMO. The outcome comparison was particularly stringent because a successful outcome in the ventricular-assist group included an acceptable neurologic outcome, which could not be systematically analyzed in the ECMO group.

As with the use of a ventricular assist device for circulatory support in adults, serious adverse events, including bleeding, infection, and stroke, occurred in a majority of the study participants. Although the occurrence of stroke is troubling, the stroke rate in this cohort is similar to that reported during the use of ventricular assist devices in children who had a body-surface area greater than 1.2 m² and who were treated with adult-sized ventricular assist devices. The sequelae of stroke in this trial did not preclude eligibility for transplantation in the majority of participants, and the stroke-related deficits were generally mild.

An important limitation of this trial is the lack of randomization. A randomized design was contemplated, but equipoise in the medical community was lacking. The propensity-score–matching process resulted in an ECMO group that was statistically similar to the ventricular-assist group. However, it is plausible that despite propensity-score matching, the children in the ECMO group were in some respects more ill than those in the ventricular-assist group. Given that no other mechanical support device exists for these patients, we believe that children receiving support with ECMO represent the best comparison group.

In conclusion, we found that a ventricular assist device available in several sizes for use in children as a bridge to heart transplantation was associated with a significantly higher rate of survival, as compared with ECMO. Serious adverse events, including infection, stroke, and bleeding, occurred in a majority of the study participants.

The views expressed in this article are those of the authors and do not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. government.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Mary Beth Kepler and Christine Tjossem for assistance with the data analysis; all the study coordinators for their efforts in executing a very detailed study protocol; and Lucy Thuita, M.S., at the Cleveland Clinic for providing statistical assistance with the competing-risk analysis.

REFERENCES


Copyright © 2012 Massachusetts Medical Society.
Advanced Heart Failure Treated with Continuous-Flow Left Ventricular Assist Device

Mark S. Slaughter, M.D., Joseph G. Rogers, M.D., Carmelo A. Milano, M.D., Stuart D. Russell, M.D., John V. Conte, M.D., David Feldman, M.D., Ph.D., Benjamin Sun, M.D., Antone J. Tatooles, M.D., Reynolds M. Delgado, III, M.D., James W. Long, M.D., Ph.D., Thomas C. Wozniak, M.D., Waqas Ghumman, M.D., David J. Farrar, Ph.D., and O. Howard Frazier, M.D., for the HeartMate II Investigators*

From Advocate Christ Medical Center, Oak Lawn, IL (M.S.S., A.J.T.); Duke University Medical Center, Durham, NC (J.G.R., C.A.M.); Johns Hopkins Hospital, Baltimore (S.D.R., J.V.C.); Ohio State University, Columbus (D.F., B.S.); Texas Heart Institute, Houston (R.M.D., O.H.F.); Intermountain Medical Center, Salt Lake City (J.W.L.); Clarian Methodist Hospital, Indianapolis (T.C.W., W.G.); and Thoratec, Pleasanton, CA (D.J.F.). Address reprint requests to Dr. Slaughter at the Division of Thoracic and Cardiovascular Surgery, University of Louisville, 201 Abraham Flexner Way, Suite 1200, Louisville, KY 40202, or at mark.slaughter@louisville.edu.

Drs. Slaughter, Rogers, and Milano contributed equally to this article.

*The HeartMate II investigators are listed in the Appendix.

This article (10.1056/NEJMoa0909938) was published on November 17, 2009, at NEJM.org.


Copyright © 2009 Massachusetts Medical Society.

Abstract

Background
Patients with advanced heart failure have improved survival rates and quality of life when treated with implanted pulsatile-flow left ventricular assist devices as compared with medical therapy. New continuous-flow devices are smaller and may be more durable than the pulsatile-flow devices.

Methods
In this randomized trial, we enrolled patients with advanced heart failure who were ineligible for transplantation, in a 2:1 ratio, to undergo implantation of a continuous-flow device (134 patients) or the currently approved pulsatile-flow device (66 patients). The primary composite end point was, at 2 years, survival free from disabling stroke and reoperation to repair or replace the device. Secondary end points included survival, frequency of adverse events, the quality of life, and functional capacity.

Results
Preoperative characteristics were similar in the two treatment groups, with a median age of 64 years (range, 26 to 81), a mean left ventricular ejection fraction of 17%, and nearly 80% of patients receiving intravenous inotropic agents. The primary composite end point was achieved in more patients with continuous-flow devices than with pulsatile-flow devices (62 of 134 [46%] vs. 7 of 66 [11%]; P<0.001; hazard ratio, 0.38; 95% confidence interval, 0.27 to 0.54; P<0.001), and patients with continuous-flow devices had superior actuarial survival rates at 2 years (58% vs. 24%, P=0.008). Adverse events and device replacements were less frequent in patients with the continuous-flow device. The quality of life and functional capacity improved significantly in both groups.

Conclusions
Treatment with a continuous-flow left ventricular assist device in patients with advanced heart failure significantly improved the probability of survival free from stroke and device failure at 2 years as compared with a pulsatile device. Both devices significantly improved the quality of life and functional capacity. (ClinicalTrials.gov number, NCT00121485.)
MEDICAL AND ELECTRICAL THERAPIES for systolic heart failure have improved outcomes and altered the natural history of the disease. However, heart failure commonly progresses and becomes refractory to current treatments. Continuous intravenous inotropic support may improve clinical status in the short term but results in a survival rate at 1 year of only 10 to 30%.1-11 Cardiac transplantation is available for only a minority of patients, because of a lack of suitable donor hearts. The paucity of effective therapies for advanced heart failure led to the evaluation of mechanical circulatory-support devices as permanent therapy.

To date, only two completed trials, one randomized12 and one nonrandomized,13 have evaluated patients with advanced heart failure who were ineligible for transplantation and compared optimal medical therapy with the use of a pulsatile left ventricular assist device. The survival status, functional capacity, and quality of life were superior in the patients treated with the pulsatile left ventricular assist devices. However, the 2-year survival rate among patients with a left ventricular assist device in the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial (ClinicalTrials.gov number, NCT00000607) was only 23%, as compared with 8% among patients receiving medical therapy.12 Despite these substantial improvements in outcomes, broader application of left ventricular assist devices for advanced heart failure has been limited by the large size of the pump and drive line, clinically significant adverse events, and limited device durability.

Newer designs of left ventricular assist devices, involving rotary-pump technology to provide blood flow with reduced pulsatility, have undergone clinical investigation. These continuous-flow left ventricular assist devices have improved the hemodynamics, end-organ function, quality of life, and functional capacity of patients awaiting transplantation.14,15 They are also smaller, quieter, and more durable than pulsatile-flow devices, making them potentially better suited for long-term support.

This study reports the results of a randomized trial comparing outcomes in patients with advanced heart failure who were ineligible for transplantation and received either a pulsatile-flow left ventricular assist device or a continuous-flow left ventricular assist device.

STUDY ORGANIZATION
The study was conducted at 38 centers in the United States. Data were collected by study coordinators at participating centers, analyzed by the sponsor (Thoratec, Pleasanton, CA), and audited by the sponsor. The authors vouch for the completeness and accuracy of the data and analyses. An independent data and safety monitoring board monitored the study and reviewed the protocol compliance and outcome data. An independent clinical events committee adjudicated the causes of death and adverse events. The protocol was approved by each participating center’s institutional review board.

STUDY PATIENTS
Patients with advanced heart failure who were ineligible for heart transplantation and whose heart failure was refractory to optimal medical management were considered for study enrollment. Detailed inclusion and exclusion criteria are listed in the Supplementary Appendix (available with the full text of this article at NEJM.org). Enrolled patients met the following criteria: a left ventricular ejection fraction of less than 25%; a peak oxygen consumption of less than 14 ml per kilogram of body weight per minute, or less than 50% of the predicted value; and New York Heart Association (NYHA) class IIIb or IV symptoms for at least 45 of the 60 days before enrollment or dependence on an intraaortic balloon pump for a period of 7 days or inotropes for a period of at least 14 days before enrollment. Exclusion criteria included irreversible, severe renal, pulmonary, or hepatic dysfunction or active infection. All patients or an authorized representative provided written informed consent.

STUDY DESIGN
Patients were randomly assigned, in a 2:1 ratio, to receive either a continuous-flow left ventricular assist device or a pulsatile-flow left ventricular assist device. Randomization was stratified according to study center and with the use of permuted blocks to maintain the 2:1 ratio over time. Baseline data — including demographic characteristics, concomitant use of medications, health history, responses on the Minnesota Living with Heart Failure and Kansas City Cardiomyopathy questionnaires, and clinical laboratory values —
were collected for all patients. After implantation of the left ventricular assist device, device performance, laboratory results, and medication use were initially recorded at daily to weekly intervals and after hospital discharge were recorded monthly. Quality-of-life assessments and the 6-minute walk tests were completed at baseline, 1 month, 3 months, 6 months, and then every 6 months until study completion at 24 months. Adverse events were recorded throughout the study, with the use of standardized definitions (see the Supplementary Appendix). All causes of death were determined by means of autopsy or through examination of medical records, with final adjudication by the clinical events committee.

LEFT VENTRICULAR ASSIST DEVICES
The two left ventricular assist devices used in this study were the pulsatile-flow HeartMate XVE and the continuous-flow HeartMate II (both from Thoratec). These implanted pumps draw blood from the apex of the left ventricle and deliver it to the ascending aorta. Both are electrically driven by means of a percutaneous lead that connects the pump to an external system controller and power source (Fig. 1, and the animation available with the full text of this article at NEJM.org). The continuous-flow left ventricular assist device has a volume of 63 ml and a weight of 390 g, as compared with 450 ml and 1250 g for the pulsatile-flow left ventricular assist device. Both devices are capable of a flow rate up to 10 liters per minute at a mean pressure of 100 mm Hg. Antithrombotic management included aspirin for all patients and warfarin (with a targeted international normalized ratio of 2.0 to 3.0) only for those with the continuous-flow device.

STATISTICAL ANALYSIS
The primary end point was a composite of survival at 2 years, free of disabling stroke (stroke with a Rankin score >3) or reoperation to replace the device. The percentage of patients in whom the primary composite end point was reached was compared between the two treatment groups with the use of Fisher’s exact test. Cox proportional-hazards analyses, with the data stratified on the basis of the treatment assignment, were used to calculate hazards ratios and 95% confidence intervals for the primary end point and component events. Analysis of the primary composite end point was conducted on the basis of the intention-to-treat principle. Patients who had undergone randomization but not implantation of a device were considered to have had treatment failure, as were patients who had device failure requiring either device explantation or urgent heart transplantation.

Secondary study end points included actuarial survival, frequency of adverse events, functional status, and the quality of life. The secondary end points were evaluated with the use of an as-treated analysis of all data until use of the treatment device was discontinued. Data on the categorical variables were compared with the use of Fisher’s exact test. Longitudinal changes in functional status and quality of life were analyzed by means of linear mixed-effects modeling. Adverse-event rates and relative risks were compared between the two treatment groups with the use of Poisson regression. Actuarial-survival analysis was performed by means of the Kaplan–Meier method and the results were compared between the two groups with the use of log-rank analysis. P values of less than 0.05 were considered to indicate statistical significance. All reported P values are two-sided and were not adjusted for multiple testing.

RESULTS
STUDY PATIENTS
A total of 200 patients were randomly assigned to undergo implantation of a continuous-flow left ventricular assist device (134 patients) or a pulsatile-flow left ventricular assist device (66 patients) between March 2005 and May 2007. The baseline characteristics of each of the two treatment groups were similar, except more women were in the continuous-flow device group (Table 1). Resynchronization therapy had failed in more than 60% of patients, nearly 80% were receiving intravenous inotropic agents, and over 20% had an intraaortic balloon pump at the time of enrollment. There was no significant difference between the two groups in the destination therapy risk score.17

CLINICAL COURSE
Five patients randomly assigned to receive a pulsatile-flow left ventricular assist device and three
patients randomly assigned to receive a continuous-flow device did not undergo implantation with a device; however, these patients were counted as having treatment failure (see the flow chart in the Supplementary Appendix). Three patients who had a small body size and who had been randomly assigned to the pulsatile-flow device group received the smaller continuous-flow device instead, because of difficulty with anatomical fitting. One patient randomly assigned to the continuous-flow device group received a pulsatile-flow left ventricular assist device instead, because the patient’s health insurance would only cover the pulsatile-flow device.

The remaining patients, whose data were included in the as-treated analyses, consisted of 133 who underwent implantation of a continuous-flow left ventricular assist device and 59 who underwent implantation of a pulsatile-flow left ventricular assist device. The median duration of support

---

**Figure 1.** Pulsatile-Flow (Panel A) and Continuous-Flow (Panel B) Left Ventricular Assist Devices (LVADs).
was 1.7 years (range, 0.0 to 3.7) and 0.6 years (range, 0.0 to 2.1) for the continuous-flow left ventricular assist device and the pulsatile-flow device, respectively, with a cumulative follow-up of 211 and 41 patient-years, respectively. Cardiac transplantation was performed in 17 patients randomly assigned to the continuous-flow left ventricular assist device and 9 patients randomly assigned to the pulsatile-flow left ventricular assist device, after contraindications to transplantation resolved while the device was providing support.

The mean (±SD) cardiac index increased from 2.0±0.6 liters per minute per square meter of body-surface area preoperatively to 2.9±0.7 liters per minute by 24 hours after implantation of the continuous-flow left ventricular as-

---

**Table 1. Baseline Characteristics of the Study Patients, According to Treatment Group.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Continuous-Flow LVAD (N=134)</th>
<th>Pulsatile-Flow LVAD (N=66)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td></td>
<td></td>
<td>0.81</td>
</tr>
<tr>
<td>Mean 62±12</td>
<td>63±12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range) 64 (26–79)</td>
<td>65 (29–81)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex — no. (%) 108 (81)</td>
<td>61 (92)</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Body-surface area — m² 2.0±0.3</td>
<td>2.1±0.3</td>
<td>0.54</td>
<td></td>
</tr>
<tr>
<td>Ischemic cause of heart failure — no. (%) 88 (66)</td>
<td>45 (68)</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>Left ventricular ejection fraction — % 17.0±5.5</td>
<td>16.8±5.4</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>Arterial blood pressure — mm Hg Systolic 104±14</td>
<td>104±18</td>
<td>0.93</td>
<td></td>
</tr>
<tr>
<td>Diastolic 61±13</td>
<td>61±12</td>
<td>0.94</td>
<td></td>
</tr>
<tr>
<td>Pulmonary-capillary wedge pressure — mm Hg 24±8</td>
<td>24±9</td>
<td>0.82</td>
<td></td>
</tr>
<tr>
<td>Cardiac index — liters/min/m² of body-surface area 2.0±0.6</td>
<td>2.1±0.6</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>Pulmonary vascular resistance — dyn-sec-cm⁻⁵ 264±128</td>
<td>264±152</td>
<td>0.98</td>
<td></td>
</tr>
<tr>
<td>Central venous pressure — mm Hg 13±6</td>
<td>13±8</td>
<td>0.67</td>
<td></td>
</tr>
<tr>
<td>Serum sodium — mmol/liter 134.7±4.3</td>
<td>133.9±6.0</td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine — mg/dl 1.6±0.6</td>
<td>1.8±0.7</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>History of stroke — no. (%) 21 (16)</td>
<td>11 (17)</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>Concomitant medication or intervention — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous inotropic agent 103 (77)</td>
<td>55 (83)</td>
<td>0.36</td>
<td></td>
</tr>
<tr>
<td>Diuretic 123 (92)</td>
<td>57 (86)</td>
<td>0.32</td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor 43 (32)</td>
<td>22 (33)</td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>Angiotensin II–receptor antagonist 12 (9)</td>
<td>3 (5)</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td>Beta-blocker 71 (53)</td>
<td>38 (58)</td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td>Biventricular pacemaker 85 (63)</td>
<td>39 (59)</td>
<td>0.64</td>
<td></td>
</tr>
<tr>
<td>ICD 111 (83)</td>
<td>52 (79)</td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>IABP 30 (22)</td>
<td>15 (23)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation 9 (7)</td>
<td>6 (9)</td>
<td>0.57</td>
<td></td>
</tr>
<tr>
<td>Destination therapy risk score†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean 10.4±5.4</td>
<td>9.9±4.7</td>
<td>0.78</td>
<td></td>
</tr>
<tr>
<td>Score denoting high or very high risk — no. (%) 24 (18)</td>
<td>5 (8)</td>
<td>0.06</td>
<td></td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD. Additional data on baseline characteristics are given in the Supplementary Appendix.

To convert values for creatinine to micromoles per liter, multiply by 88.4. ACE denotes angiotensin-converting enzyme, IABP intraaortic balloon pump, ICD implantable cardioverter–defibrillator, and LVAD left ventricular assist device.

† The destination therapy risk score was calculated according to the methods of Lietz et al. Possible scores range from 0 to 31, with higher scores indicating an increased risk of death at 90 days.
sist device (P<0.001) and from 2.1±0.6 to 2.9±0.7 liters per minute per square meter after implanta-
tion of the pulsatile-flow left ventricular assist
device (P<0.001). At the same time points, the
pulmonary-capillary wedge pressure decreased
from 24±8 to 17±7 mm Hg (P<0.001) with the
continuous-flow left ventricular assist device
and from 24±9 to 16±6 mm Hg (P<0.001) with the
pulsatile-flow left ventricular assist device.

A total of 114 of the 133 patients (86%) with
the continuous-flow left ventricular assist
device and 45 of the 59 (76%) with the pulsatile-flow left
ventricular assist device were discharged from
the hospital with the device in place. The medi-
an length of stay after surgery was 27 days in the
continuous-flow device group and 28 days in the
pulsatile-flow device group. The percentage of
total time spent out of the hospital after device
implantation was 88% with the continuous-flow
left ventricular assist device, as compared with
74% with the pulsatile-flow device (P=0.02).

### PRIMARY END POINT

All 200 patients were followed for at least 2 years
or until death, transplantation, or device explan-
tation. The primary composite end point was
achieved in more patients assigned to receive a
continuous-flow left ventricular assist device than
in those assigned to receive a pulsatile-flow left
ventricular assist device (46% vs. 11%; hazard ra-
tio, 0.38; 95% confidence interval [CI], 0.27 to 0.54;
P<0.001) (Table 2). Failure to reach the primary
end point was influenced by reoperation to repair
or replace the left ventricular assist device and
death within 2 years after device implantation,
the rates of which were reduced with the contin-
uous-flow device.

Of the 59 patients who underwent implanta-
tion with a pulsatile-flow left ventricular assist
device, 20 required 21 pump replacements (3 re-
placed with another pulsatile-flow device and 18
with a continuous-flow device) — and an addi-
tional 1 patient required urgent transplantation
— owing to bearing wear, valve malfunc-
tion, or infection. In the 133 patients who under-
went implantation with a continuous-flow left
ventricular assist device, 12 required 13 pump
replacements with a continuous-flow device ow-
ing to breakage of the percutaneous lead (in 10 of
the 13 replacements), pump thrombosis (in 2),
or outflow elbow disconnection (in 1). One addi-
tional patient required device explantation because
of a broken lead.

### ACTUARIAL SURVIVAL

On the basis of the as-treated analysis, the Ka-
plan–Meier estimate of actuarial survival was sig-
nificantly better for patients who had a contin-
uous-flow left ventricular assist device as compared
with those with a pulsatile-flow left ventricular
assist device (relative risk, 0.54; 95% CI, 0.34 to
0.86; P=0.008) (Fig. 2). Estimates of the 1- and
2-year survival rates were 68% (95% CI, 60 to 76)
and 58% (95% CI, 49 to 67), respectively, with the
continuous-flow device and 55% (95% CI, 42 to 69)

---

**Table 2. Primary End Point and Hazard Ratios, According to Treatment Group.**

<table>
<thead>
<tr>
<th>End Point</th>
<th>Continuous-Flow LVAD (N=134)</th>
<th>Pulsatile-Flow LVAD (N=66)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival free from disabling stroke and reoperation to repair or replace LVAD at 2 yr (primary composite end point)</td>
<td>62 (46 [38–55])</td>
<td>7 (11 [3–18])</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

* Hazard ratios were calculated with the use of Cox regression, and the P value for the primary end point with the use of Fisher’s exact test. CI denotes confidence interval, and LVAD left ventricular assist device.
† Disabling stroke was defined as stroke with a Rankin score of more than 3.
‡ Reoperation to repair or replace pump included urgent heart transplantation or device explantation.
and 24% (95% CI, 1 to 46%) with the pulsatile-flow device. Eighteen of the pulsatile-flow left ventricular assist devices were replaced with a continuous-flow device during the follow-up period, leaving only two patients with a pulsatile-flow device (which had been replaced) at 2 years.

**FUNCTIONAL STATUS AND QUALITY OF LIFE**

Early and sustained improvements in functional capacity were seen in both groups. A total of 80% of patients with a continuous-flow left ventricular assist device had NYHA functional class I or II symptoms at 24 months, with a doubling of the mean distance on the 6-minute walk test (vs. the distance at baseline) (Table 3). Similar trends were seen with quality-of-life metrics. As compared with the baseline scores, scores on the Minnesota Living with Heart Failure questionnaire and the Kansas City Cardiomyopathy questionnaires improved by over 30 points in both groups at each time point (except the 24-month point in the single patient tested who had a pulsatile-flow device) (P<0.001).

**ADVERSE EVENTS**

The adverse-event data are shown in Figure 3 (with details in the Supplementary Appendix). As compared with patients with a pulsatile-flow left ventricular device, there were significant reductions in the rates of major adverse events among patients with a continuous-flow left ventricular assist device — including device-related infection (relating to the percutaneous lead, pump, or pump pocket), non–device-related infection, right heart failure, respiratory failure, renal failure, and cardiac arrhythmia. The incidence of stroke did not differ significantly between the continuous-flow group (which had 0.13 events per patient-year [stroke in 17% of patients]) and the pulsatile-flow group (which had 0.22 events per patient-year [stroke in 14% of patients]). There was a 38% relative reduction in the rate of rehospitalization among patients with a continuous-flow left ventricular assist device as compared with those with a pulsatile-flow device.

The leading causes of death among the patients with a continuous-flow left ventricular assist device were hemorrhagic stroke (in 10% who underwent device implantation), right heart failure (in 8%), multisystem organ failure (in 7%), and ischemic stroke (in 5%).

**DISCUSSION**

Our study shows that implantation of a continuous-flow left ventricular assist device, as compared with a pulsatile-flow device, significantly improved the probability of survival free of stroke and reoperation for device repair or replacement at 2 years in patients with advanced heart failure in whom current therapy had failed and who were ineligible for transplantation. In addition, the actuarial survival over a 2-year period of support by a left ventricular assist device was significantly better with the continuous-flow device than with the pulsatile-flow device in a population of patients whose 2-year survival rate while receiving medical therapy had been shown to be approximately 10%.12,13 The continuous-flow left ventricular assist device was also associated with significant reductions in the frequency of adverse events and the rate of repeat hospitalization, as well as...
Table 3. Functional Status and Quality-of-Life Secondary End Points, Based on the As-Treated Analysis, According to Time Point.∗

<table>
<thead>
<tr>
<th>End Point</th>
<th>Continuous-Flow LVAD</th>
<th>P Value for Treatment over Time†</th>
<th>P Value between Treatments at 12 mo</th>
<th>Pulsatile-Flow LVAD</th>
<th>P Value for Treatment over Time†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 3 Mo 12 Mo 24 Mo</td>
<td></td>
<td>*</td>
<td>Baseline 3 Mo 12 Mo 24 Mo</td>
<td></td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients tested</td>
<td>126 91 72 50</td>
<td></td>
<td>55 38 18 1</td>
<td>0 10 (26) 6 (33) 1 (100)</td>
<td></td>
</tr>
<tr>
<td>Class I — no. (%)</td>
<td>0 30 (33) 30 (42) 21 (42)</td>
<td></td>
<td></td>
<td>0 16 (42) 5 (28) 0</td>
<td></td>
</tr>
<tr>
<td>Class II — no. (%)</td>
<td>0 38 (42) 25 (35) 19 (38)</td>
<td></td>
<td></td>
<td>0 16 (42) 5 (28) 0</td>
<td></td>
</tr>
<tr>
<td>Class IIIA — no. (%)</td>
<td>4 (3) 16 (18) 13 (18) 6 (12)</td>
<td></td>
<td></td>
<td>1 (2) 10 (26) 4 (22) 0</td>
<td></td>
</tr>
<tr>
<td>Class IIIB — no. (%)</td>
<td>27 (21) 5 (5) 4 (6) 1 (2)</td>
<td></td>
<td></td>
<td>11 (20) 1 (3) 2 (11) 0</td>
<td></td>
</tr>
<tr>
<td>Class IV — no. (%)</td>
<td>95 (75) 2 (2) 0 3 (6)</td>
<td>43 (78) 1 (3) 1 (6) 0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with class I or II — no. (%)</td>
<td>0 68 (75) 55 (76) 40 (80)</td>
<td>&lt;0.001</td>
<td></td>
<td>0 26 (68) 11 (61) 1 (100)</td>
<td>&lt;0.001 0.22</td>
</tr>
<tr>
<td>6-Minute walk test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients tested</td>
<td>50 77 61 36</td>
<td>19 29 12 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distance walked — m</td>
<td>182±140 319±164 318±164 372±191</td>
<td>&lt;0.001</td>
<td></td>
<td>172±108 291±134 306±145 277</td>
<td>&lt;0.001 0.62</td>
</tr>
<tr>
<td>Minnesota Living with Heart Failure questionnaire</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients tested</td>
<td>116 89 76 44</td>
<td>49 36 19 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Score</td>
<td>75.4±17.7 37.4±22.2 34.1±22.4 29.6±22.4</td>
<td>&lt;0.001</td>
<td></td>
<td>76.1±18.0 42.1±23.3 44.4±23.2 61.0</td>
<td>&lt;0.001 0.03</td>
</tr>
<tr>
<td>Kansas City Cardiomyopathy questionnaire</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients tested</td>
<td>115 89 76 47</td>
<td>47 36 18 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall summary score</td>
<td>27.4±16.3 63.4±18.5 65.9±20.0 69.9±18.7</td>
<td>&lt;0.001</td>
<td></td>
<td>26.5±17.4 56.7±21.1 59.1±20.3 33.3</td>
<td>&lt;0.001 0.06</td>
</tr>
<tr>
<td>Clinical summary score</td>
<td>35.1±18.5 67.2±17.4 68.6±21.8 72.9±19.3</td>
<td>&lt;0.001</td>
<td></td>
<td>31.6±18.4 64.0±19.8 60.8±20.2 63.5</td>
<td>&lt;0.001 0.12</td>
</tr>
</tbody>
</table>

∗ Plus–minus values are means ±SD. Scores on the 21-question Minnesota Living with Heart Failure questionnaire range from 0 to 105, with higher scores indicating a worse quality of life. Scores on the Kansas City Cardiomyopathy questionnaire range from 0 to 100, with higher scores indicating a better quality of life. The number of patients tested at each time point varied as a result of ability to complete the test and unavailability owing to death or transplantation. LVAD denotes left ventricular assist device, and NYHA New York Heart Association.

† P values for the effect of the treatment over time were calculated with the use of linear mixed-effects modeling.
with an improved quality of life and functional capacity. The survival rate at 2 years among our patients with a pulsatile-flow left ventricular assist device was similar to that among patients with a left ventricular assist device in the REMATCH trial,\(^1\) whereas the survival rate among our patients with a continuous-flow device was more than twice the rate among the REMATCH patients.

Device durability is an important limitation to use of the currently approved pulsatile-flow left ventricular assist device as long-term therapy, because valve or bearing failures occurred routinely by 18 months. The need for pump replacement in the continuous-flow left ventricular assist device occurred at a rate of 6 events per 100 patient-years, almost one eighth the incidence seen with the pulsatile-flow device, and was mainly required because of damage to the percutaneous lead. There were no primary-pump or bearing failures in patients with a continuous-flow left ventricular assist device, with 62 patients having functioning devices for at least 2 years (and 1 patient with ongoing device support at 4 years). Redesign of the percutaneous lead and development of modular components may further reduce the infrequent need for replacement of the continuous-flow device.

Concerns persist that left ventricular assist devices may predispose patients to an undue burden of thromboembolic and infectious events. The rate of ischemic stroke among patients with a continuous-flow left ventricular assist device (6 events per 100 patient-years) is similar to that among patients with advanced heart failure who do not have device support and have other cardiovascular conditions such as atrial fibrillation.\(^1\) In our study, the rate of bleeding events associated with either type of left ventricular assist device were almost 10 times the rate of thromboembolic events. This finding was also noted in the HeartMate II bridge to transplant trial and has led many centers to reduce the targeted international normalized ratio to 1.5 to 2.5 for the continuous-flow left ventricular assist device. The smaller pump and

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Continuous-Flow LVAD (N=133) (211 patient-yr)</th>
<th>Pulsatile-Flow LVAD (N=59) (41 patient-yr)</th>
<th>Relative Risk (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. (%) no. of Events/Patient-Yr</td>
<td>no. (%) no. of Events/Patient-Yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pump replacement</td>
<td>12 (9) 0.06</td>
<td>20 (34) 0.51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>24 (18) 0.13</td>
<td>8 (14) 0.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>11 (8) 0.06</td>
<td>4 (7) 0.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>15 (11) 0.07</td>
<td>5 (8) 0.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVAD-related infection</td>
<td>47 (35) 0.48</td>
<td>21 (36) 0.90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local non-LVAD infection</td>
<td>65 (49) 0.76</td>
<td>27 (46) 1.33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>48 (36) 0.39</td>
<td>26 (44) 1.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding requiring PRBC</td>
<td>108 (81) 1.66</td>
<td>45 (76) 2.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding requiring surgery</td>
<td>40 (30) 0.23</td>
<td>9 (15) 0.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other neurologic event</td>
<td>29 (22) 0.17</td>
<td>10 (17) 0.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right heart failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Managed with extended use of inotropes</td>
<td>27 (20) 0.14</td>
<td>16 (27) 0.46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Managed with RVAD</td>
<td>5 (4) 0.02</td>
<td>3 (5) 0.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac arrhythmia</td>
<td>75 (56) 0.69</td>
<td>35 (59) 1.31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>50 (38) 0.31</td>
<td>24 (41) 0.80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal failure</td>
<td>21 (16) 0.10</td>
<td>14 (24) 0.34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic dysfunction</td>
<td>3 (2) 0.01</td>
<td>0 0.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVAD thrombosis</td>
<td>5 (4) 0.02</td>
<td>0 0.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rehospitalization</td>
<td>107 (94) 2.64</td>
<td>42 (96) 4.25</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 3. Adverse Events and Associated Relative Risks from the As-Treated Analysis, According to Treatment Group.**

The “other neurologic event” subcategory included transient ischemic attack and neurologic events other than stroke. For the “rehospitalization” subcategory, the rates were calculated on the basis of patient-years after initial hospital discharge. LVAD denotes left ventricular assist device, PRBC packed red cells, and RVAD right ventricular assist device.
percutaneous lead in the continuous-flow left ventricular assist device also requires less surgical dissection for implantation, which reduces the potential for infection, as compared with the pulsatile-flow device. Patients with a continuous-flow left ventricular assist device had a rate of device-related infection nearly 50% of that among patients with a pulsatile-flow device, which contributed to their reduced need for rehospitalization.

A critical therapeutic goal in treating patients with advanced heart failure is to enhance their quality of life and functional capabilities. There are few data from medical-therapy trials involving this population of patients that highlight exercise or quality-of-life benefits.1,8,9 A retrospective analysis of patients with NYHA class IV symptoms who were treated with cardiac-resynchronization therapy showed an increase of 45 m in the 6-minute-walk distance, a 25-point improvement in the Minnesota Living with Heart Failure score, and improvement in symptoms corresponding to a reduction by at least one NYHA functional class in 78% of the patients.21 The exercise and quality-of-life benefits with a continuous-flow left ventricular assist device in our trial consist of a doubling of the 6-minute-walk distance, an average improvement of 35 points in the quality-of-life scores, and an increase in the number of patients whose symptoms showed improvement, to NYHA functional class I or II. Patients in both groups in our study had significant early and sustained improvements in the 6-minute-walk distance and the functional class, suggesting that the exercise benefits are related to the reduction of cardiac filling pressures and improvement in cardiac output rather than being related to the characteristics of either pulsatile or continuous flow. The patient-reported symptom burden and heart-failure–related quality-of-life scores reflected similar improvements in the two groups over the duration of the study, with a trend toward greater improvement with the continuous-flow left ventricular assist device as compared with the pulsatile-flow device.

This study was a randomized, controlled clinical trial, but it was not possible to ensure that the patients and investigators were unaware of the treatment assignments. Thus, there is potential for bias, particularly regarding patient-reported outcomes such as functional abilities and the quality of life. Several sites had limited experience with the continuous-flow device before the study began, and several enrolled a small number of patients.

Previous studies have shown a link between the volume of implantations with a left ventricular assist device and outcomes.22 In addition, most participating centers had more experience with the pulsatile-flow left ventricular assist device used in this trial than with the particular continuous-flow device, potentially biasing the analysis against the study device. Finally, the trial was performed in a select patient population, and applicability to the broader population of patients with heart failure, including those with less hemodynamic and functional compromise than our patients, would be speculative.

In conclusion, this study shows improvements in the rate of survival, quality of life, functional capacity of patients, and device durability with the continuous-flow left ventricular assist device (HeartMate II) as compared with the pulsatile-flow left ventricular assist device (HeartMate XVE). Reductions in the frequencies of adverse events related to device characteristics and strategies of care for patients favorably affected the rate of rehospitalization. Our results support the use of continuous-flow, permanent left ventricular assist device therapy in selected patients as a means to provide long-term hemodynamic support that is linked to improvements in longevity and the quality of life.

Supported by Thoratec.

Dr. Slaughter reports receiving grant support from Thoratec and Heartware; Dr. Rogers, consulting fees and grant support from Thoratec; Dr. Milano, research and training grant support from Thoratec, Abiomed, and St. Jude and research grant support from Edwards Life Sciences and Sorin; Dr. Russell, training and consulting fees from Thoratec; Dr. Conte, training and consulting fees from Thoratec and grant support from Paracor; Dr. Feldman, grant support from Thoratec; and Dr. Sun, training grant support from Thoratec. Dr. Farrar reports being an employee of Thoratec with equity ownership in the company. Dr. Frazier reports receiving consulting and lecture fees from Thoratec, Terumo Heart, and Jarvik Heart. No other potential conflict of interest relevant to this article was reported.


HEART ASSIST DEVICES, SYSTEMS AND METHODS

Inventors: William Suttle Peters, Auckland (NZ); Peter Crispin Lawrence Marsh, Birehgrove (AU); Geoffrey Hamilton White, East Balmain (AU); Rolf Gunnar Unger, Kingsgrove (AU); Frederick Paget Milson, Auckland (NZ); Hans Hansforth Henrichsen, Shalvey (AU); Colin Edward Sullivan, Birehgrove (AU)

Assignee: Sunshine Heart Company Pty Ltd (AU)

Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 720 days.

This patent is subject to a terminal disclaimer.

Appl. No.: 12/035,247
Filed: Feb. 21, 2008

Prior Publication Data

Related U.S. Application Data
Continuation of application No. 10/786,699, filed on Feb. 24, 2004, now Pat. No. 7,357,771, which is a continuation of application No. 09/869,923, filed on Oct. 15, 2001, now Pat. No. 6,808,484.

Foreign Application Priority Data
Jun. 10, 1999 (AU) .............................. PQ0904

Int. Cl.
A61N 1/00 (2006.01)

ABSTRACT
An apparatus and method for use in assisting a human heart are disclosed. The apparatus comprises an aortic compression means which may be fully implantable, a fluid reservoir and a pump means adapted to pump a fluid from the reservoir to the aortic compression means so as to actuate the aortic compression means at least partly in counterpulsation with the patient’s heart. In addition, the device is adapted to be wholly positioned within the right chest cavity of the patient. The aortic compression means of the device may be curved along its length so as to substantially replicate the curve of the ascending aorta.

21 Claims, 10 Drawing Sheets
Hiroshi Odaguchi et al., “Experimental Study of Extraaortic Balloon Counterpulsation as a Bridge to Other Mechanical Assists” ASAIO Journal, pp. 190-194, vol. 42, No. 3, Lippincott Williams & Wilkins/ASAIO, Hagerstown, MD, May 1, 1996.


* cited by examiner
HEART ASSIST DEVICES, SYSTEMS AND METHODS

RELATED INFORMATION

This application is a continuation of application Ser. No. 10/786,699 filed on Feb. 24, 2004 now U.S. Pat. No. 7,357,771, which is a continuation of U.S. application Ser. No. 09/829,923 filed on Oct. 15, 2001 now U.S. Pat. No. 6,808,484. The priority of the prior application is expressly claimed, and the disclosure of this application is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to heart assist devices, systems and methods.

BACKGROUND OF THE INVENTION

Currently the only real options for improvement of end-stage heart failure are medical therapy, left ventricular assist devices (LVADs) and transplantation. ACE (Angiotensin Converting Enzyme) inhibitors unload the heart and prolong survival. LVADs pump blood and significantly improve life style and survival, but are complicated to implant, maintain and remove, with relatively high complications relating to bleeding, infection, thromboembolism, and device malfunction.

The transplant rate has stabilised at approximately 2,300 per year in the USA, being limited by organ availability. Transplantation achieves a 75% five year survival rate and a 65% ten year survival rate with significant improvements in functional class.

The number of people awaiting heart transplantation is steadily increasing and they are a sicker group, with increasing numbers requiring hospitalisation, intravenous inotropes, short-term percutaneous trans-femoral intra-aortic balloon pump and/or LVAD implantation.

The Institute of Medicine has estimated that by the year 2010, up to 70,000 patients will be candidates for permanent mechanical circulatory support systems.

Over the last ten years, LVADs have been well proven to save lives, acting as bridges to transplantation for critically ill patients. Recently, LVADs have been considered as alternatives to transplantation, and very recently, have been explanted in a few patients who have shown recovery. This latest realisation is starting to gather a lot of interest as researchers focus on recovery of the failing heart. LVADs totally unload the left ventricle and many believe that the heart will then recover. Moreover there is evidence beyond the few patients in whom devices have been removed that there is reversal in markers of heart failure. On the other hand, others have described an increase in myocardial fibrosis which raises a question of whether the heart is being unloaded too much.

The intra-aortic balloon pump (IABP) was first proposed in the 1960s as a method of partial support for the acutely failing heart, for example, after heart surgery or heart attack. It was built as a long thin catheter [10-14 Fr] with an elongated balloon at its tip [volume 30-40 ml]. The balloon was inserted via the femoral artery and inflated and deflated in counter-pulsation with the heart beat. Inflation in diastole causes a diastolic pressure augmentation and increases coronary artery blood flow and deflating in systole (triggered by the R wave of the ECG) reduces the afterload, or the pressure head against which the left ventricle has to eject blood. Early investigators determined that the best and most efficient balloon position was closest to the heart, i.e., in the ascending aorta. However, in recent times, the balloon is positioned via the femoral artery in the descending aorta for short term (1-10 days) use. There is substantial proof beyond doubt that counterpulsation works very well in the short-term to assist hearts to recover when drugs (inotropes etc.) are insufficient or inappropriate to support the cardiovascular system.

Intra-aortic balloon heart pumps operating in counterpulsation assist the heart function. When inflated, the balloon propels blood peripherally from within the aorta to improve blood circulation in the patient. Moreover, more blood is forced into the coronary arteries to help nourish and strengthen the heart muscle. However, the balloon comes into direct contact with the blood flowing into the aorta, which can cause damage to the blood cells and there is a risk of thromboembolism. In addition, current intra-aortic balloon pump systems are inflated by means of a tube passing through the body, the tube connecting the balloon to an external compressor. The opening for the tube to enter the body provides a possible site of infection or other injury. The tube is typically inserted into a groin vessel, the femoral artery, and there is a high risk of associated leg complications. Further, the patient is bedridden and cannot mobilize. Additionally, the use of a gas to inflate the balloon is not an entirely safe operation since any leakage of gas from the balloon into the blood stream could cause an air embolus.

Aortic compression (periaortic diastolic compression) has been described as a means to increase coronary blood flow. For example, U.S. Pat. No. 4,583,523 describes an implantable heart assist device including an elongated assembly extending transversely between the ribs of a patient from the rib cage to the aorta of the heart to be assisted. The assembly includes an aorta compressing device at the front end and a mounting device at the rear end thereof to support the device from the ribs of the patient. A motive device actuates and deactuates the compressing device alternatively to help pump blood through the aorta in a counterpulsation mode of operation. Although this device has advantages for many applications, it does require relatively complicated surgery to implant/explant the device, particularly in regard to the need to mount the device including its motive means, to the ribs of the patient. Moreover the mounting arrangement and motive means of the device have to be positioned outside the rib cage, making the presence of the device more noticeable to the patient. There is also substantial risk of infection With the device coming through the skin. Furthermore, because the device is attached/mounted to the ribs, there may be shear stresses on the aorta as the rib cage moves with inspiration/expiration. These stresses may cause untoward damage of the aorta.

U.S. Pat. No. 4,979,936 discloses an autologous biologic pump in the form of an apparatus using skeletal muscle formed into a pouch which then surrounds a collapsible, shape-retaining bladder. The bladder is connected to a second bladder enclosed in a sheath around a portion of the aorta. The bladders are filled with a fluid such that when the skeletal muscle contracts in response to an electrical stimulation, the fluid is forced from the first bladder into the second bladder sheathed around the aorta, expanding that second bladder and forcing the aorta to compress. Although this approach may be useful in some circumstances, it is doubtful that it is suitable for long term in that the muscle function would probably degrade over time. Furthermore, the muscle has to be "trained" for many weeks before the device can be relied on to assist blood circulation.
WO 99/04833 discloses a cardiac ventricle aid device which is implanted in the abdominal cavity with an aorta sleeve tube placed in it, or inserted in the descending aorta. A disadvantage of the disclosed device is that it has a separate actuator and compliance chamber and its implantation is thus complicated. Another disadvantage is that it is difficult to securely mount the device components to the structure in the abdominal cavity that is capable of supporting its weight. A further disadvantage is a number of vertebral arteries stem from the descending aorta which can be damaged during the implantation of the device.

It would be desirable to have a heart assist device that could be quickly and totally implanted in a relatively easy manner and with minimum trauma to the patient and to allow ambulation with low risk of complications. Also desirable would be a heart assist device that allows partial unloading of the heart long-term, augmenting the cardiac output of the native heart, and possibly allowing substantial recovery of the heart so that the device could be weaned. Moreover, it would be desirable for such a device to have no blood contacting surfaces, and not require cardiopulmonary bypass to implant the device. In a small proportion of patients however there will exist aortic disease making a periaortic device unsuitable. In these patients it would be desirable to be able to apply the same aortic counterpulsation, but with a device that replaces the ascending aorta. Such a device would require cardiopulmonary bypass and would be blood contacting, but has the same advantages of allowing partial unloading of the heart long-term, augmenting the cardiac output of the native heart, and possibly allowing substantial recovery of the heart so that the device could be weaned.

It is an object of the present invention to satisfy one or more of the above desirable criteria.

SUMMARY OF THE INVENTION

In a first aspect, the present invention provides a heart assist device adapted for implantation into a patient, the device including:

a) an aortic compression means adapted, when actuated, to compress an aorta of a patient;
b) a fluid reservoir; and
c) a pump means adapted to pump a fluid from the fluid reservoir to the aortic compression means so as to actuate the aortic compression means at least partly in counterpulsation with the patient’s heart,

wherein the fluid reservoir is adapted to be wholly positioned within the chest cavity of the patient.

In a second aspect, the present invention provides a heart assist device adapted for implantation into a patient the device including:

a) an aortic compression means adapted, when actuated, to compress the ascending aorta of a patient;
b) a liquid reservoir;
c) a pump means adapted to pump a liquid from the liquid reservoir to the aortic compression means so as to actuate the compression means, wherein the liquid reservoir and the aortic compression means are adapted to be positioned in close juxtaposition with one another within the chest cavity of the patient.

In a third aspect, the present invention provides an aortic compression means for use in a heart assist device, the aortic compression means including:

a) an elastic inflatable cuff adapted to be placed about the ascending aorta of a patient; and
b) a flexible, substantially inelastic, sheath adapted to extend around the cuff and at least assist in retaining it in position on the aorta.

In a fourth aspect the present invention provides a heart assist device including:

a) an aortic compression means adapted to be placed around the ascending aorta of a patient; and
b) an actuation means to periodically actuate the aortic compression means in at least partial counterpulsation with the heart,

wherein the aortic compression means and the actuation means are placed wholly within the chest cavity of the patient.

In a fifth aspect, the present invention provides a heart assist device adapted for implantation wholly into a bodily cavity of a patient the device including:

a) an aortic compression means adapted, when actuated, to compress an aorta of a patient;
b) a housing with an exterior surface;
c) a fluid reservoir in the housing, the fluid reservoir having a flexible exterior surface forming part of the housing exterior surface; and
d) a pump means adapted to pump a fluid from the fluid reservoir to the aortic compression means so as to actuate the aortic compression means at least partly in counterpulsation with the patient’s heart,

wherein the fluid reservoir flexible exterior surface is adapted to expand during aortic compression and constrict in the absence of aortic compression and is further adapted to be positioned substantially adjacent a flexible organ in the patient’s bodily cavity.

Preferably, the bodily cavity is the thoracic cavity and the organ is the lung.

In a sixth aspect the present invention provides a heart assist device adapted for implantation into a patient, the device including:

a) an elastic inflatable cuff adapted, when inflated, to compress an aorta of a patient;
b) a fluid reservoir;
c) a means for pumping a fluid from the fluid reservoir to the cuff so as to inflate the aortic compression means at least partly in counterpulsation with the patient’s heart; and
d) a means for adjusting the volume of fluid in the cuff in the absence of aortic compression.

In a seventh aspect, the present invention provides a human or animal having a heart assist device according to any one of the preceding aspects of the invention implanted therein.

In a further aspect, the present invention provides an implantable system for assisting the functioning of the heart of a subject, the system including:

an implantable device for assisting the functioning of the heart of a subject, including:

means for externally engaging and compressing the aorta; motive means responsive to control signal(s) for actuating and deactivating the compressing means cyclically to help blood pump through the aorta, wherein the compressing means and the motive means are fully implantable within the thoracic cavity of the subject and wherein the compressing means and/or motive means include means to adapt for attachment to the aorta and/or surrounding tissue within the thoracic cavity of the subject;
sensing means adapted for sensing the heart and generating sensing signals;
control means responsive to the sensing signals for generating the control signal(s); and
a power source for providing power to the motive means.
The device of the invention may operate in countersynchronisation to the heart (counterpulsation).

An advantage of the device and system of the present invention is that the risk of limb ischemia associated with conventional IAB systems is avoided because there is no blood contact with the device whatsoever. Patient ambulation is also possible. Additionally, the implantation technique used for the device of the invention is less invasive than those required for other devices. In particular, compared to the arrangement taught in U.S. Pat. No. 4,583,523, the device of the present invention provides a better outcome in terms of reduced risk of infection, cosmesis and ease of implant and explant. A further advantage of the device and system of the present invention is that there is little risk to die patient in the event of device failure. The device has the great advantage of being able to be weaned and turned off in the event of cardiac recovery, which is simply not possible with known LVADs. Furthermore if the heart shows signs of relapsing back into failure, the device can be switched back on.

The compressing means of the device of the present invention preferably includes a preshaped balloon cuff for wrapping around a portion of the aorta. Preferably, the balloon is configured longitudinally to fit the curve, that of a circular or oval arc, of the ascending aorta. In a particularly preferred form of the device of the present invention, the cross-section of the cuff is C-shaped, allowing wrapping of the cuff with some overlap around the aorta. Preferably, the cuff is shaped such that it does concentrically compress the length of enclosed aorta and spreads the compression forces evenly, reducing any wear or fatigue on any one part of the aorta. The balloon cuff is enclosed within a flexible and non-elastic outer sleeve. The sleeve has an elongated “tongue” on one arm of the C-shaped cuff and this is passed around the aorta to be secured by suturing or other means on the outer aspect of the other arm of the C-shaped cuff. This arrangement stops the balloon inflation force from going outwards. Furthermore, the preshaped cuff and flexible sleeve are particularly designed to create a snug fit and low profile on the aorta, to reduce damage to the aorta and surrounding structures, and to create maximum efficiency of the device.

In a preferred form of the invention, the device is adapted for compression of the ascending aorta. An upper mid-line sternotomy provides easy surgical access to the ascending aorta and has the further advantage of not being very painful for the patient. A minimum incision is required in this procedure. In this mode of use of the device of the invention, the compressing means is preferably adapted to squeeze approximately 15-25 ml of blood from the ascending aorta in each compression cycle.

The cuff has a single inlet/outlet port for the fluid to move to inflate/deflate the balloon. The fluid used is preferably liquid, such as water or saline, as this is noncompressible and less likely to leak compared to gas. Furthermore, using a liquid allows a fully implantable device so that the patient can mobilize easily. The port and connecting tube to the motive means is of sufficient diameter and length to allow rapid emptying and filling of the cuff without generating too high compression pressures. The fluid must move within 0.15 sec for effective counterpulsation action. The compressive force emptying the cuff is the force exerted by the compressed aorta. This approximately 100 mmHg. A tube lumen of approximately 1 to 1.5 cm with a length of 5 to 8 cm allows 17 to 25 ml fluid to pass down a gradient of 100 mmHg in less than 0.15 sec. The compressive force filling the cuff is generated by the motive means, and this pressure gradient is approximately the same i.e. the motive means generates approximately 200 mmHg to allow the fluid to shift into the cuff in less than 0.15 sec.

The port more preferably has a trumpet-shaped or flanged opening into the cuff to spread the fluid more evenly into the balloon during inflation and to assist more rapid deflation. There may be a diffuser mounted within the lumen of the port to reduce the fluid force on the balloon cuff during inflation.

Preferably, the motive means drives the fluid via a fluid filled sac contained within the motive means. The motive means of the device of the invention may be any means that is capable of cyclically compressing and decompressing the fluid sac. The motive means may be a mechanical or an electromechanical device. The motive means may be an electric motor/cam arrangement. The motive means may include spring mounted arms driven by a pulse of power to hinged solenoids or the like to drive the pressure plates towards each other and thereby compress the aorta. An example of a suitable motive means is an adaptation of the solenoid actuator described in U.S. Pat. No. 4,457,673, the relevant disclosure of which is incorporated herein by reference. The motive means may also be based on that used in the Novacor N100 Left Ventricular Assist System.

The motive means is preferably enclosed in an air-tight housing. The housing may have a flexible portion that allows for the fluid shift from the motive means—the flexible portion is presented toward the lung tissue and can thus move back and forth. More particularly the motive means is fully implanted within the thoracic cavity and a pressure compliance membrane “interfaces” with the lung surface. Alternatively the housing may be rigid and when the motive means is activated and the fluid sac compressed, a small vacuum is created within the housing. This vacuum has the advantage of increasing the pressure gradient for subsequent emptying of the cuff, to make emptying more rapid. The level of vacuum could be adjusted by accessing a transcutaneous gas reservoir linked to the housing. A final alternative is to have an external gas line from the motive means to allow gas exhaust, eliminating the need for a compliance chamber, but introducing a percutaneous line that has an increased risk of infection.

The motive means may be designed so that in the event of failure, it automatically goes into “off” with the fluid sac filled so that the aorta is not compressed, thus minimising risk to the patient.

The motive means may include or be associated with means for detecting speed and completeness of cuff filling and emptying, and of monitoring the fluid pressure within the connector tube, means for measuring arterial blood pressure or flow. The motive means may also act to record the ECG, having electrodes positioned on the housing or as separate wires attached to body tissues.

The means adapted for attachment to the aorta and/or surrounding tissue of the subject may be any suitable means. For example, the attachment means may be adapted for suturing and/or gluing the compressing means or motive means to the aorta or the surrounding tissue within the chest cavity. The attachment means may be suturing tabs. The attachment means may be apertures allowing ingrowth of tissue and/or surface portions adapted to promote tissue growth into or onto the compressing means and/or the motive means so as to hold the device in position relative to the aorta. For example, the cuff may have a plurality of holes through which the cuff may be sutured to the aorta. The cuff may also have hole or slits to accommodate coronary artery bypass grafts to the ascending aorta. The motive means will sit within the chest cavity, preferably the right thoracic cavity, between the mediastinum and the right lung.
The sensor means may be means detecting a selected physiological event associated with heartbeat. The sensor means may be any means for producing an ECG. Means for detecting the action potentials of the cardiac muscles, for example electrodes, are well known to those skilled in the art and will not be described in detail here.

The control means may be any means capable of providing an output to actuate the motive means in response to signal(s) providing the sensor means.

The control means may provide signals to the motor means to countersynchronise compression of the aorta with the heart beat to provide counterpulsation, for example, aorta compression may commence with aortic valve closure (ventricular diastole), whilst aorta release occurs just prior to contraction/ejection (ventricular systole).

The power means may be an internal and/or external battery or P.E.T (transcutaneous electronic transfer).

Deactivation of the compressing means may be timed to the R wave of the ECG and may be adapted for adjustment either manually or automatically. The diocrit notch on the arterial pressure wave may provide the signal for actuation of the compressing means.

In yet a further aspect, the present invention provides a method for improving blood circulation in a subject, the method including implanting a device in accordance with the invention fully within the thoracic cavity of a subject, actuating the compressing means periodically in synchrony with the diastolic period to compress the aorta; and alternating the period of actuation with periods of deactivation of the compressing means thereby allowing the aorta to return to its uncompressed shape.

The system and device of the invention allow relief/recovery from chronic heart failure whilst allowing the subject to move around freely without being constrained by a large external pumping device.

BRIEF DESCRIPTION OF THE DRAWINGS

Preferred embodiments of the invention will now be described, by way of examples only, with reference to the accompanying drawings in which:

FIG. 1a is a schematic drawing of a first embodiment of a heart assist device according to the invention implanted in the thoracic cavity of a subject;

FIG. 1b is an enlarged view of the device shown in FIG. 1a;

FIG. 2a is an enlarged perspective detailed view of the device shown in FIG. 1a;

FIG. 2b is a partial top view of the device shown in FIG. 1a;

FIG. 3 is top view of a second embodiment of a heart assist device according to the invention;

FIG. 4 is a top view of a third embodiment of a heart assist device according to the invention;

FIG. 5a is a top view of a fourth embodiment of a heart assist device according to the invention;

FIG. 5b is a perspective view of the device shown in FIG. 5a;

FIG. 6 is a block diagram of an embodiment of a cardiac assist system according to the invention;

FIG. 7 is a side view of an embodiment of an inflatable cuff;

FIG. 8 is a rear view of the cuff shown in FIG. 7;

FIG. 9a is a top view of the cuff shown in FIG. 7;

FIG. 9b is a top view of the cuff shown in FIG. 7 after application of an external sheath;

FIG. 10 is a front view of the cuff shown in FIG. 7;

FIG. 11 is a fifth embodiment of a heart assist device according to the invention;

FIG. 12 is a schematic side view of a sixth embodiment of a heart assist device according to the invention;

FIG. 13 is a schematic side view of a seventh embodiment of a heart assist device according to the invention;

FIG. 14 is an indication of an electrical cardiograph (ECG) readout, heart diastolic pressure (Pd) and power supply (Po) for the device shown in FIG. 13;

FIG. 15 is a schematic side view of an eighth embodiment of a heart assist device according to the invention;

FIG. 16 is an exploded view of the pump housing of the device shown in FIG. 15;

FIG. 17 is a schematic cross sectional view of a ninth embodiment of a heart assist device according to the invention; and

FIG. 18 is a schematic view of a tenth embodiment of a heart assist device according to the invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

FIG. 1a to 2b are schematic drawings showing a first embodiment of a heart assist device 10 in accordance with the invention. The device 10 is suitable for complete implantation in the thoracic cavity of a subject 99 adjacent the ascending portion of the aorta 15, as shown. The device 10 includes an aortic compression means in the form of a hinged solenoid 2 (see FIGS. 2a and 2b) in a housing 12. The solenoid 2 is driven by pulses of electrical power from a controller/battery 14 to actuate wedge-shaped compression plates 4 via arms 3. The wedge-shaped plates 4 surround the ascending portion of the aorta 15. When the plates 4 are actuated they approach each other and that part of the aorta 15 between the plates 4 is compressed. The plates 4 have a plurality of holes 6 that provide means for suturing the plates to the aorta 15 and permitting ingrowth of tissue therethrough.

FIGS. 2a and 2b are detailed schematic drawings of the solenoid 2 which show that it includes two arcuate plates 26 hinged at 8. The plates 26 are shown in the de-activated (resting) position in FIG. 2a and are shown in the actuated position in FIG. 2b compressing the aorta 15. The plates 26 are soft form moulded and are actuated by the hinged solenoid 4 via arms 23.

FIG. 3 to 5b are schematic drawings of second to fourth embodiments of heart assist devices in accordance with the present invention.

In the second embodiment shown in FIG. 3, the compression plates 34 are actuated via arms 33, with each of the arms 33 being actuated by a respective rod solenoid 38 acting through springs 37 between the rod solenoid 38 and the respective arm 33.

In the third embodiment shown in FIG. 4, solenoids 48 act on deformable nitinol plates 44 connected together at either end 47 to encircle the aorta 15.

In the fourth embodiment shown in FIGS. 5a and 5b, wedge-shaped plates 54 are connected together at one end 57 and each plate is actuated by solenoids 58 acting through arms 53. As best shown in FIG. 5b, the wedge-shaped plates 54 effectively conform to the shape of the ascending aorta 15.

FIG. 6 is a block diagram of an embodiment of a cardiac assist system constructed in accordance with the invention suitable for use with, for example, the cardiac assist device 10.

Initiation of the compression of the aorta 15 by the compression plates 4 is accomplished by energisation of the solenoid 2. This energisation is under the control of a control means 100 which activates the solenoid 2 of the motive means 1 in response to signals received from an ECG monitor 102 or
systemic arterial blood pressure 103 or the like. The ECG monitor 102 and/or the control means 1 are preferably implanted but may be on the body of the subject 99.

In operation, de-activation of the compression plates 4 draws them apart and effectively unloads the left ventricle by allowing the aorta 15 to return to its usual circular shape. The expansion of the aorta 15 between the de-activated plates causes a pressure drop in the aorta 15, facilitating left ventricle ejection (ie unloading of the heart). After the heart has finished ejecting blood into the aorta 15 and the aortic valve closes, the plates 4 are activated to move them towards each other and compress the aorta 15 and thereby squeeze blood out of the volume of the aorta 15 compressed by the compression plates 4 and augment the diastolic pressure. Coronary artery blood flow to the left ventricle occurs predominantly in diastole so compression of the aorta 11 also augments coronary blood flow.

FIGS. 7 to 10 show an aortic compression means in the form of a flexible hollow inflatable cuff 60. The cuff 60 is curved along its length so as to substantially replicate the curve of the aorta 15 adjacent thereto. The cuff 60 is shown in its de-activated (uninflated) state in FIG. 9a, and has two free ends 61 and 62 which are adapted to overlap when the cuff 60 is placed around the aorta. As best shown in FIG. 10, the cuff 60 is retained adjacent the aorta after implantation by suturing the two free ends together at 63. This also ensures that the cuff 60 is snugly around the aorta, when the aorta is in its usual circular shape.

Further, as best shown in FIG. 9b, a substantially inelastic, flexible sheath 65 is also preferably placed around the cuff 60. The sheath 65 assists in retaining the cuff 60 adjacent the aorta and inwardly concentrates the compression forces generated by inflation of the cuff 60, as indicated by arrows 66. The sheath 65 can also have free ends sutured together to retain it and the cuff 60 adjacent the aorta in addition to, or in place of, the cuff sutures 63. The sheath 65 is preferably made from Dacron (Trade Mark), kevlar (Trade Mark), teflon (Trade Mark), Gore-tex (Trade Mark), polyurethane or other flexible inelastic bio-compatible materials. The sheath 65 is preferably glued, fused or otherwise bonded to the cuff 60.

The cuff 60 also has a single inlet/outlet port 64 for the introduction of fluid to inflate the cuff 60 and thereby compress the aorta and the removal of fluid for the deflation of the cuff and relaxing of the aorta. The fluid is preferably water or an isotonic solution of salt or other low-viscosity, non-toxic liquid.

The fluid is actively pumped into the cuff 60 for inflation into the shape indicated in phantom in FIG. 9b. The cuff 60 can be actively deflated by suctioning the fluid from the cuff 60. Alternatively, the cuff 60 can be passively deflated by the blood pressure of the constricted aorta re-expanding and returning the cuff 60 to the state shown in FIG. 9a, which ejects the fluid from the cuff 60. It is preferable to actively deflate the cuff 60 as it gives better prestyptic unloading of the heart and counteracts any high intrathoracic pressures, such as when the subject coughs. In either case, the natural resilience of the cuff 60 also assists in deflation by biasing the cuff 60 to the shape shown in FIG. 9b.

In another embodiment of heart assist device (not shown), the compression plates 4 are used to squeeze the cuff 60. This embodiment can be configured to operate in two ways. Firstly, the plates 4 can provide a larger aortic compression and the cuff 60 a smaller aortic compression, either simultaneously or one after the other. This reduces the fluid requirements of the cuff 60. Secondly, the cuff 60 can be set at a fixed inflation and provide a cushion between the plates 4 and the aorta.

In other embodiments of cuff (not shown), the sheath is integrally formed with the cuff, preferably by moulding, or in the form of flexible, inelastic fibres embedded in the cuff.

FIGS. 11 to 18 are schematic drawings of fifth to tenth embodiments of heart assist devices in accordance with the present invention that utilise the cuff 60 shown in FIGS. 7 to 10.

In the fifth embodiment shown in FIG. 11, the cuff 60 is closely coupl ed to a fluid-filled air-tight housing 79 that has therein a pump, in the form of a rotatable impeller 71 and a pair of valves 72 and 73 for directing the flow of the impeller 71. The housing also includes an inlet/outlet 76 in fluid communication with the inlet/outlet port 64 of the cuff 60. A fluid reservoir is also provided in the housing 79 in the form of an internal portion 74 of the volume of the housing 70, as is a pressure compliance means, in the form of a substantially flexible portion 75 of the housing 70.

In operation, energisation of the impeller 71 with the valves 72 and 73 in the position shown in FIG. 11 causes fluid to be actively withdrawn from the cuff 60, which allow the aorta to return to its usual circular shape. This fluid is pumped into the internal portion 74 of the housing 70 and causes the flexible portion 75 to expand to the position shown in FIG. 11. When the valves 71 and 73 are in the positions shown in phantom in FIG. 11 and the impeller 71 is energised, the fluid in the portion 74 is pumped into the cuff 60 to expand same and to compress the aorta. The removal of fluid from the portion 74 causes the flexible portion 75 to retract to the position shown in the phantom in FIG. 11. As with earlier embodiments, the control of the impeller and valves is in response to signals received from an ECG monitor or systemic arterial blood pressure or the like.

In the sixth embodiment shown in FIG. 12, the device has only a single valve 76. The aorta is compressed by positioning the valve 76 as shown in FIG. 12 and energising the impeller 71. When the valve 76 is moved to the position shown in phantom in FIG. 2 and impeller is de-energised the expanding aorta passively ejects the fluid back into the portion 74 of the housing 71 and causes the flexible portion 75 to expand to the position shown in phantom.

In the seventh embodiment shown in FIG. 13, the impeller 71 is driven in one direction to cause fluid flow in the direction indicated by the arrow to deflate the cuff 60 and expand the flexible portion 75. Reversing the direction of the impeller 71 causes the flexible portion 75 to retract to the position shown in phantom as fluid is displaced into the cuff 60 to inflate same. This embodiment requires variable power control to the motor driving the impeller 71 and a plot of the motor power requirements (Po) relative to the subject’s electrocardiograph reading (ECG) and aortic pressure (Pr) are shown in FIG. 14.

In the eighth embodiment shown in FIGS. 15 and 16, the housing 71 has a rigid upper portion 71a and a partially rigid lower portion 71b that includes the flexible portion 75. A motor 77 is mounted in the lower portion 71b that drives a pair of rollers 78, each positioned on an end of a common shaft 79. The housing portion 71b also has a pair of upstanding guide posts 80 which are slidably received in corresponding holes in a swash plate 81. The swash plate 81 has a pair of cam formations 82 on its underside. A fluid-filled sac 83 is positioned between the swash plate 81 and the housing portion 71a. The interior of the sac 83 is in fluid communication with the interior of the cuff 60. Power is supplied to the motor 77 through line 84.
In operation, the motor 77 is energised to rotate the rollers 78, which ride along the cam formations 82 to drive the swash plate 81 upwards to compress the sac 83 and eject the fluid therein into the cuff 60 to inflate same. When the rollers 78 have passed the cam formations 82 the swash plate 81 returns to its original position and the expanding aorta passively ejects the fluid back into the sac 83. In an alternative embodiment (not shown), the rollers 78 are linked to the cam formations 82 to drive the swash plate 81 up and down and thereby actively inflate and actively deflate the cuff 60. As a further alternative, (not shown) a stepper motor(s) can be used to drive the swash plate.

In the ninth embodiment shown in FIG. 17, the housing 71 has a fluid filled sac 83 positioned between a pair of compression plates 84 which are hinged at 85 and driven by a solenoid 86. Energising the solenoid 86 brings the plates 84 together to squeeze the sac 83 and force the liquid therein into the cuff 60 to inflate same. De-energising the solenoid 86 draws the plates 84 apart and the expanding aorta passively ejects the fluid back into the sac 83. As with earlier embodiments as the sac 83 inflates the flexible portion 75 of the housing 71 expands to accommodate the increase in pressure in the housing 71.

In the tenth embodiment shown in FIG. 18, the heart assist device includes a liquid pressure adjustment means, in the form of remote reservoir 90, connected between the cuff 60 and the reservoir 74. Liquid can be added to the heart assist device, via the remote reservoir 90, to adjust the liquid retained in the (de-activated) cuff 60 and thereby adjust the pressure therein. This allows the size of the cuff 60 to be adjusted to compensate for changes in the size of the aorta and/or the amount of aortic compression to be adjusted to, for example, weir the patient from the heart assist device. When the reservoir is positioned near the skin, its volume can be adjusted by using a needle to inject or withdraw liquid. When the reservoir is positioned near the heart assist device, its volume can be adjusted by adding or withdrawing liquid via a transcutaneous tube. The pressure in the reservoir 90 can also be sensed and automatically adjusted so as to maintain a predetermined pressure.

It will be appreciated that the system and device of the present invention, in their preferred forms, are designed to be simple without blood contact and a much lower morbidity risk compared to LVADs. The device and system allows the heart to remain totally un-instrumented, and the device, by effective counterpulsation in the aorta, augments the cardiac output up to 15-20%. All natural blood pathways are maintained. Pulsatile blood flow is also maintained. The patient is able to ambulate and there is no risk of leg ischaemia.

The present invention provides for long term relief and/or stabilization of recovery from chronic heart failure. Moreover, the present invention may be a suitable bridging device for transplantation.

The device and system of the above-described embodiments improve cardiac work efficiency by reducing the afterload (pressure/resistance to flow which the heart has to overcome to eject blood) during systole (ejection phase), by augmenting diastolic aortic blood pressure to maintain a greater mean arterial pressure, and by increasing left ventricular coronary artery blood flow during diastole.

The preferred embodiments of the heart assist device compress the ascending aorta. This is advantageous as the ascending aorta is less prone to disease than the descending aorta and, being closer to the heart, provides improved pumping efficiency and thus a smaller heart assist device.

It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as shown in the specific embodiments without departing from the spirit or scope of the invention as broadly described. For example, although the invention has been described in specific reference to compression of the aorta, the devices, systems and methods of the present invention can equally be used for the compression of the pulmonary artery to effectively act as a right ventricular assist device, and the present invention extends to this alternative aspect. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

We claim:

1. An aortic compression device for use in a heart assist device, the aortic compression device comprising:
   a) a flexible inflatable cuff configured to be positioned adjacent to the ascending aorta of a patient; and
   b) a flexible, substantially inelastic sheath configured to extend around the cuff and at least assist in retaining the cuff adjacent to the aorta,
   wherein the flexible inflatable cuff is curved along its length so as to substantially replicate the curve of the ascending aorta adjacent to the flexible inflatable cuff.

2. The compression device of claim 1, wherein the sheath is positioned around the cuff in a snug fit.

3. The compression device of claim 1, wherein the cuff comprises a single inlet/outlet port.

4. The compression device of claim 3, wherein the sheath has an opening complimentary to the inlet/outlet port.

5. The compression device of claim 1, wherein the cuff is substantially C-shaped and further comprises two free ends extending from the cuff, wherein the two free ends are configured to overlap when the cuff is positioned adjacent to the aorta.

6. The compression device of claim 1, wherein the sheath comprises two free ends configured to be coupled together in an overlapping relationship.

7. A heart assist system comprising:
   a) an aortic compression device configured to be positioned adjacent to the ascending aorta of a patient, wherein the aortic compression device is curved along its length so as to substantially replicate the curve of the ascending aorta adjacent to the aortic compression device; and
   b) a pump in fluid communication with the aortic compression device, wherein the pump is configured to pump a fluid to the aortic compression device so as to actuate the aortic compression device.

8. The heart assist system of claim 7, wherein the aortic compression device further comprises:
   a) a flexible inflatable cuff; and
   b) a flexible, substantially inelastic sheath configured to extend around the cuff and at least assist in retaining the cuff adjacent to the aorta.

9. The heart assist system of claim 7, wherein the cuff is substantially C-shaped and further comprises two free ends extending from the cuff, wherein the two free ends are configured to overlap when the cuff is positioned adjacent to the aorta.

10. The heart assist system of claim 7, further comprising a fluid reservoir in fluid communication with the pump, wherein the pump is configured to pump the fluid from the fluid reservoir to the aortic compression device.

11. The heart assist system of claim 10, further comprising a fluid conduit in fluid communication with the fluid reservoir, the pump, and the aortic compression device.

12. The heart assist system of claim 7, further comprising a fluid pressure adjustment component in fluid communication with the aortic compression device.
13. The heart assist system of claim 12, wherein the fluid pressure adjustment component comprises a reservoir configured for the receiving or removal of fluid therein, thereby allowing for adjustment of fluid pressure in the system.

14. The heart assist system of claim 12, further comprising a pressure sensor operably coupled to the fluid pressure adjustment component, wherein the pressure sensor is configured to measure fluid pressure in the fluid pressure adjustment component.

15. The heart assist system of claim 14, wherein the pressure sensor is further configured to automatically adjust the fluid pressure in the fluid pressure adjustment component based on the fluid pressure in the component.

16. The device of claim 7, further comprising a pressure compliance component.

17. A heart assist system comprising:
   a) an aortic compression device configured to be positioned adjacent to the ascending aorta of a patient, wherein the aortic compression device is curved along its length so as to substantially replicate the curve of the ascending aorta adjacent to the aortic compression device, the aortic compression device comprising:
      (i) a flexible inflatable cuff; and
      (ii) a flexible, substantially inelastic sheath configured to extend around the cuff and at least assist in retaining the cuff adjacent to the aorta;
   b) a fluid reservoir; and
   c) a pump in fluid communication with the aortic compression device and the fluid reservoir, wherein the pump is configured to pump fluid from the fluid reservoir to the aortic compression device so as to actuate the aortic compression device.

18. The heart assist system of claim 17, further comprising a fluid pressure adjustment component in fluid communication with the aortic compression device and the fluid reservoir, wherein the fluid pressure adjustment component comprises a reservoir configured for the receiving or removal of fluid therein, thereby allowing for adjustment of fluid pressure in the system.

19. The heart assist system of claim 18, further comprising a pressure sensor operably coupled to the fluid pressure adjustment component, wherein the pressure sensor is configured to measure fluid pressure in the fluid pressure adjustment component.

20. The heart assist system of claim 19, wherein the pressure sensor is further configured to automatically adjust the fluid pressure in the fluid pressure adjustment component based on the fluid pressure in the component.

21. The heart assist system of claim 17, further comprising a pressure compliance component.
VENTRICULAR ASSIST DEVICE AND RELATED METHODS

Inventors: Brian K. Whisenant, Salt Lake City, UT (US); Scott D. Miles, Sandy, UT (US)

Assignee: CohereX Medical, Inc., Salt Lake City, UT (US)

Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 365 days.

Appl. No.: 12/436,056
Filed: May 5, 2009

Prior Publication Data

Related U.S. Application Data
Provisional application No. 61/050,568, filed on May 5, 2008.

Int. Cl.
A61M 1/12 (2006.01)

U.S. Cl. 600/16

Field of Classification Search 600/16

References Cited
U.S. PATENT DOCUMENTS
5,190,528 A 3/1993 Fonger et al.
5,928,132 A 7/1999 Leschinsky
6,306,116 B1 10/2001 Hancock
6,344,022 B1 2/2002 Jarvik
2005/0165344 A1 7/2005 Dobak, III

FOREIGN PATENT DOCUMENTS
WO WO 00/37139 6/2000

* cited by examiner

Primary Examiner — George Evanisko
Assistant Examiner — Philip Edwards
(74) Attorney, Agent, or Firm — David L. Stott

ABSTRACT

A method and system are provided for percutaneously gaining access to oxygenated blood with an anastomosis device and pumping such oxygenated blood to other arterial regions of the vascular system via an LVAD system. In one embodiment, a system may include an anastomosis device extending through an opening of the atrial septum. A filament may be coupled to the anastomosis device. A snare device may access the right atrium through the superior vena cava, grasp the filament, and withdraw the filament through the superior vena cava. The filament may then be used as a guide to direct a catheter, a conduit or some other structure into the right atrium of the heart via the superior vena cava. A flow path may be defined between the anastomosis device and an arterial location such as in the aorta, such that at least some oxygenated blood may by-pass the left ventricle and be discharged into the aorta.

7 Claims, 13 Drawing Sheets
ACCESS RIGHT ATRIUM THROUGH INFERIOR VENA CAVA

ACCESS OXYGENATED BLOOD IN LEFT ATRIUM THROUGH TRANSEPTAL PUNCTURE

PERFORM ANASTOMOSIS

LEAVE FILAMENT ATTACHED TO ANASTOMOSIS ACCESSIBLE IN RIGHT ATRIUM

ACCESS ANASTOMOSIS THROUGH SUPERIOR VENA CAVA

GUIDE SNARE DEVICE TO RIGHT ATRIUM THROUGH SUPERIOR VENA CAVA

SNARE FILAMENT AND PULL THROUGH SUPERIOR VENA CAVA

USE FILAMENT AS GUIDE FOR COUPLING FLOW DEVICE WITH ANASTOMOSIS

DIRECT FLOW THROUGH FLOW DEVICE AND BACK TO AORTA

**FIG. 15**
VENTRICULAR ASSIST DEVICE AND RELATED METHODS

CROSS-REFERENCE TO RELATED APPLICATION

The present application claims the benefit of U.S. Provisional Patent Application Ser. No. 61/050,568, filed May 5, 2008, entitled METHOD AND APPARATUS FOR CONNECTING A VENTRICULAR ASSIST DEVICE TO A HEART, the disclosure of which is incorporated by reference herein in its entirety.

TECHNICAL FIELD

The present invention relates generally to methods, apparatus and systems for connecting a ventricular assist device to a heart. More specifically, the present invention relates to methods and apparatus for percutaneously connecting a ventricular assist device to a heart.

BACKGROUND

There are several instances when it is desirable to provide assistance to the heart in performing its function of pumping blood through the body. For example, when the heart has been arrested to perform a surgical procedure and then started again after the procedure, the heart conventionally needs assistance for some period of time until it has developed sufficient strength and overcome the trauma of being arrested. In other examples, a patient may experience some form of cardiac failure such that the heart requires more permanent assistance.

One type of assist device is known as a ventricular assist device (VAD) which helps pump blood through the body when, for example, a ventricle lacks sufficient strength to perform this function. More specifically, left ventricular assist devices (LVADs) have been used for some time to assist in the flow of oxygenated blood through the body.

An LVAD may be implemented through a procedure so as to couple, either directly, or indirectly, the device to the left atrium or left ventricle of the heart. Many of such procedures require open-heart surgery and are, therefore, extremely invasive and are particularly burdensome on patients that are already experiencing extreme health problems. Other procedures may be performed, and devices implemented, in a less invasive manner, but they may still pose a considerable risk to a patient or may be impractical for longer term use.

As such, it would be advantageous for a less invasive and less life threatening methods for providing an LVAD system or apparatus to a patient experiencing circulatory challenges. Further, in many instances, it would be advantageous for such system, apparatus and method to be implanted for the long-term use and benefit of the patient.

BRIEF SUMMARY OF THE INVENTION

The present invention is directed to methods and systems for percutaneously connecting a ventricular assist device to a heart as well as to components used in such methods and systems.

In accordance with one embodiment of the present invention, a system to assist the left ventricle of a heart is provided. The system includes an anastomosis device coupled to an intra-atrial (or intra-ventricular) septum and providing a flow path between a left atrium and a right atrium of a heart (or from the left ventricle to the right ventricle of a heart). A flow path including at least one conduit is configured to flow oxygenated blood from the left atrium (or left ventricle), through the anastomosis device, through the superior vena cava and back to an artery such as the aorta, a brachial artery, axillary artery, carotid artery, subclavian artery or other artery. A pumping device is coupled with the at least one conduit to help effect the flow of oxygenated blood along the flow path. In one particular embodiment, a filament is coupled with the anastomosis device.

In accordance with another embodiment of the invention, a method for percutaneously connecting a ventricular assist device to a heart is provided. The method includes accessing a right atrium or a right ventricle of the heart with a catheter through an inferior vena cava. The atrial or ventricular septum of the heart is punctured to access oxygenated blood in a left atrium or a left ventricle of the heart and an anastomosis device is implanted in the septum. The catheter is withdrawn from the heart while leaving a filament attached to the anastomosis device. The snare device is guided into the heart through the superior vena cava. The filament is grasped or snared with the snare device and pulled back through superior vena cava. A conduit is guided to the anastomosis device through use of the filament. The conduit is coupled to the anastomosis device, oxygenated blood is flowed from the left atrium or left ventricle through the conduit and returned from the conduit to an artery. In one embodiment, access to the superior vena cava may be accomplished through a jugular vein or a subclavian vein. In another embodiment, access to the aorta may be accomplished via a brachial artery, a carotid artery, an axillary artery or a subclavian artery.

In accordance with another embodiment of the invention, a kit is provided for percutaneous connection of a left ventricular assist device to a heart. The kit includes an anastomosis device sized and configured to be installed in an opening of an atrial or ventricular septum. A filament is coupled to the anastomosis device. A snare device is sized and configured to access a right atrium or right ventricle through a superior vena cava, the snare device also being configured to grasp the filament and pull the filament through the superior vena cava.

In accordance with another embodiment of the present invention, a method of guiding a structure to a right atrium or right ventricle of a heart is provided. The method comprises accessing the right atrium or right ventricle through an inferior vena cava and attaching a filament to a wall of the atrium or a wall of the ventricle. The right atrium or right ventricle is accessed with a snare device through the superior vena cava and the filament is grasped with the snare device and withdrawn through the superior vena cava. The structure is then guided through the superior vena cava into the right atrium or right ventricle using the filament.

In accordance with another particular embodiment a method includes accessing a right atrium of the heart with a catheter through the femoral vein and inferior vena cava; puncturing the atrial septum of the heart to access oxygenated blood in a left atrium of the heart; implanting an anastomosis device to the right atrium side of the atrial septum to access blood in the left atrium; withdrawing the catheter from the right atrium and leaving a filament attached to the anastomosis device; accessing the anastomosis device percutaneously through a subclavian or jugular vein at a subclavian or jugular access point; guiding a snare device into right atrium from the subclavian or jugular access point; snaring the filament with the snare device and pulling the filament back through the subclavian or jugular access point; inserting an in-flow catheter of the ventricular assist device to the anastomosis device with the filament as a guide to access the oxygenated blood; and percutaneously attaching an out-flow catheter of the ven-
tricular assist device to, for example, a brachial or carotid artery, via another anastomosis device or another type of inter-connection.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

The foregoing and other advantages of the invention will become apparent upon reading the following detailed description and upon reference to the drawings in which:

FIG. 1 is a simplified, cross-sectional view of a human heart and certain blood vessels associated therewith;

FIGS. 2 through 11 are simplified, cross-sectional views of a human heart at different stages of a procedure according to embodiments of the present invention and utilizing various devices and components in accordance with certain embodiments of the present invention;

FIG. 12 is a component utilized in association with a ventricular assist device in accordance with an embodiment of the present invention;

FIG. 13 is a component utilized in association with a ventricular assist device in accordance with another embodiment of the present invention;

FIG. 14 is a component utilized in association with a ventricular assist device in accordance with an embodiment of the present invention; and

FIG. 15 is a block diagram showing various acts in one example of percutaneously gaining access to oxygenated blood and pumping such blood to other arterial regions of the vascular system via an LVAD, according to an embodiment of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

Embodiments of the present invention are directed to methods, apparatus and systems for percutaneously connecting a ventricular assist device to a heart. Referring first to FIG. 1, a simplified, cross-sectional view of a human heart 100 is shown for purposes of context in describing embodiments of the present invention.

The human heart 100 includes several chambers that effect blood flow through the human body. These chambers include the right atrium 102, the left atrium 104, the right ventricle 106 and the left ventricle 108. The right atrium 102 receives unoxgenated blood from veins including the superior vena cava 110 and the inferior vena cava 112. It will be appreciated by those of ordinary skill in the art that the superior vena cava 110 receives blood from various veins such as the jugular veins, the subclavian veins, and numerous others. Likewise, those of ordinary skill in the art will appreciate that the inferior vena cava 112 receives blood from various veins such as the femoral veins.

Blood passes from the right atrium 102 to the right ventricle 106 through a tricuspid valve 114. Upon contraction of the right ventricle 106, blood is passed through the pulmonary valve 116 and through the pulmonary artery 118 to the lungs (not shown). The lungs oxygenate the blood which then returns to the heart 100, via pulmonary veins 120, to the left atrium 104.

Oxygenated blood passes through the mitral valve 122 and into the left ventricle 108. Upon contraction of the left ventricle 108, oxygenated blood passes through the aortic valve 124 and into the aorta 126. The aorta passes the blood to a network of arteries including the brachiocephalic artery, subclavian arteries, axillary arteries, brachial arteries, the carotid arteries, the femoral arteries and many others as will be appreciated by those of skill in the art.

As noted above, there are various situations where the heart needs some assistance in pumping blood through its network of arteries and veins. One type of assist device is a ventricular assist device (VAD) wherein assistance is provided to one of the ventricles by helping to pump the blood normally pumped upon contraction of such ventricles. More specifically, a left ventricular assist device (LVAD) helps to pump oxygenated blood to the aorta or associated arteries. The following description is directed more particularly to examples of LVADs, although various acts and apparatus described herein will find use in other devices, systems and methods.

Referring to FIG. 2, a catheter 130 is directed to the right atrium 102 through the inferior vena cava 112, such as by a femoral vein. The catheter 130 may be guided using the assistance of fluoroscopic imaging, ultrasound imaging or both. Such access of the right atrium 102 via a femoral vein is well known to those of ordinary skill in the art and is not described in further detail herein. The catheter 130 may be used to perform a procedure such as puncturing the septum 132 separating the right atrium 102 from the left atrium 104. By puncturing the septum 132, access to oxygenated blood may be obtained through the right atrium 102.

As shown in FIG. 3, an anastomosis device 134 may be inserted through and coupled to the septum 132. In one embodiment, the anastomosis device 134 may be configured such that it extends into the right atrium 102 but does not substantially extend into the left atrium 104. For example, as seen in FIG. 12, the anastomosis device 134 may have a small shoulder 136 or other feature or structure that abuts the left atrial side of the septum 132 to create a relatively smooth or flush transition along the septum wall and into a passage or flow channel defined by the anastomosis device 134. By keeping the anastomosis device 134 substantially out of the left atrium 104, and by having a smooth transition from the septum wall into the passage of the anastomosis device 134, the potential of thrombosis formation is reduced, the amount of pressure required to draw oxygenated blood from the left atrium 104 is also reduced and there is less likelihood of hemolysis (red blood cell damage).

It is noted, briefly, that other configurations of an anastomosis device 134 may be utilized. For example, it is contemplated that a portion of the anastomosis device 134 may protrude into the left atrium such as shown in FIG. 13. In such a case, an opening on the end 138, as well as lateral openings 139 may be used to draw blood from the left atrium 104. Again, such a structure enables blood to be drawn from the left atrium 104 with a relatively reduced level of pressure as compared to what is known as a reentrant connection where, for example, the end of the device protrudes into the left atrium and blood is drawn only through the opening at the end 138. As shown in FIG. 14, coupling of the anastomosis device may include positioning a grommet or a biasing member 137 (such as a member made of foam, elastomer, or other resilient material) against a shoulder 136A positioned on the right atrial side of the septum 132, the biasing member 137 may be used to effect a tighter fit of the anastomosis device 134 within the septum 132.

In one embodiment, the anastomosis device grommet 137 may be configured of a porous material to promote tissue in-growth and more securely connect the anastomosis device 134 to the septal tissue. Such materials might include, for example, foam, sintered titanium, porous tantalum, porous polytetrafluoroethylene (PTFE) or other porous material.

Referring to both FIGS. 3 and 4, as the catheter 130 is withdrawn, a filament member 140 remains with an end attached to the anastomosis device 134. The filament member 140 may include, for example, a strand of fibrous material, a
braided member, a polymeric material a suturing material, or even a slender flexible wire. The filament member 140 may also be formed of a material, or include markers formed therein, that is (are) detectable by various imaging techniques to verify its position within the heart and veins. Examples of materials that may be used to form the filament that provide radio opacity include, but are not limited to, a wire made from tantalum, tantalum-tungsten alloy, platinum, platinum-iridium and stainless steel. Additionally, a wire may be coated with a polymer (e.g., nylon, urethane, PTFE, expanded PTFE or some polymer). When the catheter 130 is withdrawn, the filament member 140 remains attached to the anastomosis device 134 and may have a portion extending through the inferior vena cava 112 and, possibly, through other veins. In one embodiment, the filament may extend all the way through the access point, such as through an access point for a femoral vein.

Referring to FIG. 5, a snare device 142 may be introduced into the right atrium 102 through the superior vena cava 110, such as by way of a jugular vein or the subclavian vein. The snare device 142 may be used to snare or grasp a portion of the filament member 140 disposed within the right atrium 102. Once the snare device 142 has grasped a portion of the filament member 140, the snare device 142 may be withdrawn from the right atrium 102 and then back through the superior vena cava 110. While not specifically shown, it is noted that the tip 144 of the snare device 142 may be positionable relative to an associated catheter housing 146 such that, while the snare device 140 is being deployed and withdrawn, it does not damage the tissue of the heart or veins to which the snare device 140 is exposed. As shown in FIGS. 6 and 7, as the snare device 142 is withdrawn, the filament member 140 is pulled up through the superior vena cava 110 and through any other vein (e.g., the jugular vein or the subclavian vein) which was used by the snare device 142 in gaining access to the right atrium 102.

Referring to FIG. 8, a conduit 150 may be inserted into the right atrium 102, using the filament member 140 as a guide to follow the same path that was used by the snare device 142. FIG. 9 shows the conduit 150 coupled with the anastomosis device 134 creating a flow path for oxygenated blood from the left atrium 104, through the right atrium 102 (via the anastomosis device 134), through the superior vena cava 110 and through another vein such as the jugular or subclavian vein. The conduit 150 may include appropriately sized tubing or other material configured to be compatible with human tissue to provide a fluid flow path for oxygenated blood from the left atrium 104 of the heart 100.

Referring to FIG. 10, the conduit 150 is coupled to a pumping device 152 which, in one embodiment, may be located external to the patient’s body. A return conduit 154 is also coupled with the pumping device 152. The return conduit 154 is inserted into an artery to return the oxygenated blood to the circulatory system. For example, an outlet end of the return conduit 154 may be disposed in the aorta 126. The return conduit 154 may be routed, for example, through a brachial artery 156, although other appropriate routes may be utilized including a carotid artery. For example, the return conduit 154 may be routed to return flow to the left subclavian artery. In another embodiment, the return conduit 154 may be routed through the left subclavian artery and into the aortic arch, directing flow of blood downstream to prevent possible thrombi from entering, for example, the brachiocephalic artery or the left common carotid artery and traveling to the brain.

It is noted that, in some instances when the return conduit 154 is of a size that may obstruct or otherwise limit the flow of blood through the artery in which it is disposed (e.g., the brachial artery 156), one or more openings 158 may be formed within the return conduit 154 at upstream locations so that blood flow may be maintained within the associated artery hosting the return conduit 154.

In one example, the pumping device 152 may include a pump similar to a pump offered by Cardiac Assist, Inc. under the mark of TandemHeart®. The TandemHeart® pump is capable of pumping up to 5.0 liters per minute (lpm) when used percutaneously such as with the presently described system.

Referring briefly to FIG. 11, in another embodiment, the conduit 150 may extend from the right atrium 102 until it is returned into the aorta 126, such as through a brachial artery 156 or other route. A pumping device 160 is located within the right atrium 102 and coupled between the anastomosis device 134 and the conduit 150 effectively placing the pumping action at the septum 132. By locating pump at the septum 132, the oxygenated blood is subjected to less of a “vacuum” force and less head may be required. In other embodiments, the pumping device 160 may be located in the left atrium 104, the right ventricle 106 or the left ventricle 108. In such a case, wires or other transmission lines may also be fed through the superior vena cava 110 into the heart 100 to provide power to, and control of, the pumping device 160. In one embodiment, such wires may extend along side the conduit 150. In another embodiment, the wires may extend through a separate and distinct lumen formed within the conduit 150 or be contained within the wall of the conduit 150.

One example of a pump that may be placed in the right atrium (or even in on of the veins leading to the right atrium 102) is the pump utilized by Abiomed, Inc. with the product offered under the trademark Impella™. Of course, other suitable pumps, such as the above described TandemHeart® pump, may also be utilized.

In either of the embodiments shown in FIG. 10 or 11, oxygenated blood is drawn from the left atrium 104, through the anastomosis device 134, through the conduit 150 which passes through the superior vena cava 110 and other veins such as the jugular or the subclavian, and is then returned to the aorta 126 through the return conduit 154 (or via the conduit itself in FIG. 11) which passes through an artery such as a brachial artery or a carotid artery.

One advantage of the described systems and methods includes the placement of the conduits. By routing the conduits (e.g., 150 and 154) through the superior vena cava 110 and arteries such as a brachial artery or a carotid artery, the system is easier to maintain and infections are less likely to occur. Often, when conduits are routed through the femoral veins or arteries for ventricular assist devices, infection is a likely complication. Additionally, use of a filament to guide the conduit 150 to the septum 134 is advantageous as it is difficult to steer and access a structure to such a location via the superior vena cava independent of such a guide structure.

Referring now to FIG. 15, various acts of a method 200 according to the present invention are shown. As described above with respect to FIGS. 2-11, the method provides access to oxygenated blood with an anastomosis device and includes pumping such oxygenated blood to other arterial regions of the vascular system. Such access to oxygenated blood is first initiated by percutaneous access to the femoral vein. As depicted at 202, a catheter may be inserted through the femoral access point up into the inferior vena cava into the right atrium. As previously noted, the catheter may be guided with the assistance of, for example, fluoroscopic and/or ultrasound imaging. As depicted at 204, a trans-septal puncture may be performed at a location in the atrial septum accessing oxy-
generated blood contained in the left atrium. As shown at 206, anastomosis can be performed with a catheter-based device which, in one embodiment, attaches only to the right atrial side of the atrial septum preventing potential thrombus formation or securement issues of an in-flow cannula protruding through the septal wall, or into the left atrium. Further, by attaching an anastomosis device to the right atrial side of the atrial septum, there is far less resistance to flow of the blood from the left atrium than that of an in-flow cannula protruding through the septal wall and into the left atrium.

As set forth at 208, after the anastomosis is performed, the catheter system can be withdrawn from the right atrium, from which a filament remains connected to the anastomosis device. As shown at 210, the anastomosis device is accessed by percutaneous access through the venous system, such as the subclavian or jugular vein. An intra-vascular snare device can be inserted through this subclavian or jugular vein access point and guided into the right atrium, as set forth at 212. The snare device can then be used to snare the filament that is attached to the anastomosis device and to exteriorize it through the access point, as set forth at 214.

As set forth at 216, the filament can then be used as a guide to insert a conduit, such as the in-flow catheter of a VAD pump, through the access point and up to the anastomosis device where it is attached thus providing access to oxygenated blood to the VAD pump. As set forth at 218, a conduit, such as an out-flow catheter of the pump, is percutaneously attached to a brachial artery or a carotid artery or even the aorta via another anastomosis device or another type of connection. In one embodiment, this additional anastomosis device can be similar to that used for connection of the in-flow catheter to the atrial septum. Further, it is contemplated that the LVAD can be disposed externally or internally. In one embodiment, the LVAD can be disposed in the chest, external the ribs or thoracic cavity, in the soft tissue, similar to a pacemaker.

Having considered the above examples, it is further noted that a similar procedure may be performed in the ventricles 106 and 108 of the heart 100 rather than the atria 102 and 104. For example, access to the right ventricle 106 may be obtained by first accessing the right atrium 102, as described above, and then passing a catheter 130 or other device through the tricuspid valve 114 into the right ventricle 106. The septum between the right and left ventricles 106 and 108 may then be punctured to access oxygenated blood in the left ventricle 108. An anastomosis device 134 may then be positioned in the septum between the right and left ventricles and the procedure may follow as outlined above, except that access to oxygenated blood will be through the anastomosis device in the right ventricle 106 rather than in the right atrium 102.

Additionally, while the description above has been set forth as performing the anastomosis procedure by access through the inferior vena cava 112, it is noted that access to the right atrium 102 or right ventricle via the inferior vena cava 112 may simply be to attach a filament 140 to, for example, the septum (either between atria 102 and 104 or between ventricles 106 and 108). The filament 140 may then be used to guide a conduit or other cannula to the septum, the conduit or cannula having an anastomosis device to be installed in the septum.

It is further noted that various acts or portions of the described embodiment may be used independent of others. Thus, the present invention contemplates transeptal access to the left side of the heart for use in other procedures, or in procedures where the oxygenated blood is routed differently than described in the example embodiments set forth above.

While the invention may be susceptible to various modifications and alternative forms, specific embodiments have been shown by way of example in the drawings and have been described in detail herein. However, it should be understood that the invention is not intended to be limited to the particular forms disclosed. Rather, the invention includes all modifications, equivalents, and alternatives falling within the spirit and scope of the invention as defined by the following appended claims.

What is claimed is:

1. A method for percutaneously connecting a ventricular assist device to a heart, the method comprising:
   - accessing one of a right atrium and a right ventricle of the heart with a catheter through an inferior vena cava;
   - puncturing a septum of the heart to access oxygenated blood in one of a left atrium and a left ventricle of the heart;
   - implanting an anastomosis device having a tubular structure in the septum;
   - withdrawing the catheter from the heart and leaving a filament fixedly attached to the implanted anastomosis device;
   - guiding a snare device through the superior vena cava;
   - snaring the fixed filament with the snare device and pulling the filament back through superior vena cava;
   - guiding a conduit to the implanted anastomosis device through use of the fixed filament;
   - coupling the conduit to the implanted tubular structure of the anastomosis device;
   - flowing oxygenated blood from one of the left atrium and the left ventricle through the conduit; and
   - returning the oxygenated blood from the conduit to an artery.

2. The method according to claim 1, wherein accessing one of a right atrium and a right ventricle of the heart with a catheter through an inferior vena cava further comprises accessing the inferior vena cava through a femoral vein.

3. The method according to claim 2, wherein guiding a snare device into the right atrium through the superior vena cava further comprises guiding the snare device through one of a jugular vein and a subclavian vein.

4. The method according to claim 3, wherein snaring the filament with the snare device and pulling the filament back through superior vena cava further comprises pulling the filament back through the jugular vein or the subclavian vein.

5. The method according to claim 4, wherein returning the oxygenated blood from the conduit to an artery further comprises percutaneously accessing the aorta through one of a brachial artery, a subclavian artery and a carotid artery.

6. The method according to claim 1, wherein flowing oxygenated blood from one of a left atrium and the left ventricle through the conduit and returning the oxygenated blood from the conduit to an artery further includes positioning a pumping device at a location in a flow path of the oxygenated blood between the superior vena cava and the aorta.

7. The method according to claim 1, wherein flowing oxygenated blood from one of the left atrium and the left ventricle through the conduit and returning the oxygenated blood from the conduit to an artery further includes positioning a pumping device within at least one of the right atrium, the left atrium, the right ventricle and the left ventricle.

* * * * *