

Design Features, Developmental Status, and Experimental Results With the Heartmate III Centrifugal Left Ventricular Assist System With a Magnetically Levitated Rotor

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A long-term left ventricular assist system for permanent use in advanced heart failure is being developed on the basis of a compact centrifugal pump with a magnetically levitated rotor and single-fault-tolerant electronics. Key features include its "bearingless" (magnetic levitation) design, textured surfaces similar to the HeartMate XVE left ventricular assist device (LVAD) to reduce anticoagulation requirements and thromboembolism, a sensorless flow estimator, and an induced pulse mode for achieving an increased level of pulsatility with continuous flow assistance. *In vitro* design verification testing is underway. Preclinical testing has been performed in calves demonstrating good *in vivo* performance at an average flow rate of 6 L/min (maximum: >11 L/min) and normal end-organ function and host response. Induced pulse mode demonstrated the ability to produce a physiological pulse pressure *in vivo*. Thirteen LVADs have achieved between 16 to 40 months of long-term *in vitro* reliability testing and will be continued until failure. Both percutaneous and fully implanted systems are in development, with a modular connection for upgrading without replacing the LVAD. *ASAIO Journal* 2007; 53:310–315.

As patients are supported for longer and longer durations on current-generation left ventricular assist devices (LVADs), it is clear that for ultimate acceptance and significant clinical impact in the treatment of heart failure, there is a need for next-generation devices to have improved long-term durability, reduced complications, and improved quality of life with low anticoagulation requirements. With the increasing maturity and acceptance of circulatory support devices, reliability goals for devices under development are now measured in years or even decades. Long-term support and myocardial recovery are now main avenues of research,^{1,2} as bridging to transplant has become relatively routine.

The one device presently approved for permanent support (or destination therapy) is the HeartMate XVE LVAD, which has been used in more than 5000 patients for bridge to transplantation and destination therapy.³ Key features include low anticoagulation requirements and freedom from thromboem-

bolic complications. Encouraging improvements in outcomes for destination therapy with this device have been published,⁴ but the life of that device is intrinsically limited by parts that wear: mechanical bearings, polymeric diaphragms, and bio-prosthetic valves.

Unlike pulsatile volume displacement pumps such as the HeartMate XVE, the new devices being developed by us are continuous flow left ventricular assist systems (LVAS), the HeartMate II and HeartMate III. The HeartMate II is a small, quiet, axial-flow LVAS, which is now in clinical trials with encouraging early results.^{5–8} This device, with its one moving part and mechanical, blood-immersed bearings, was designed for a 5+ year life, and the *in vitro* test results and analysis of clinical explants demonstrate the potential to achieve or exceed this goal.⁹

The third LVAS being developed in this family of devices for treatment of advanced heart failure, which is the focus of this paper, is the HeartMate III LVAS, featuring a centrifugal pump with magnetic bearings intended for circulatory support for 10 years or longer. The design of this system and the progress of its development have been presented in previous reports.^{10–14} The purpose of this review is to describe the design features of this device, along with a status report of its preclinical testing. Unique features of this system include its "bearingless" (magnetic levitation) design, textured surfaces similar to the HeartMate XVE to reduce anticoagulation requirements to only daily aspirin compared with requirements of warfarin and antiplatelet therapy for most other devices, an artificial pulse mode for achieving a level of pulsatility with continuous flow assistance, a sensorless flow estimator, and a modular connection for percutaneous to transcutaneous system upgrades.

Materials and Methods

Device Description

The HeartMate III LVAS is intended for long-term use in patients with advanced heart failure. The LVAS is based on a compact centrifugal pump (6.9 cm diameter × 3.0 cm; weight, 500 g) with a magnetically levitated rotor (**Figure 1**) and is being developed in a collaboration between Thoratec Corporation and Levitronix GmbH (Zurich, Switzerland). The use of a magnetic bearing eliminates all friction wear. Single-fault-tolerant redundancy of all implanted electronic components ensures uninterrupted performance in the event of any single failure that may occur, affording an opportunity for remedy. All control circuitry has been incorporated in the pump to significantly reduce wire count, thereby increasing system reliability. Further, the cable has been attached to the pump

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Submitted for consideration September 2006; accepted for publication in revised form January 2007.

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DOI: 10.1097/MAT.0b013e3180536694

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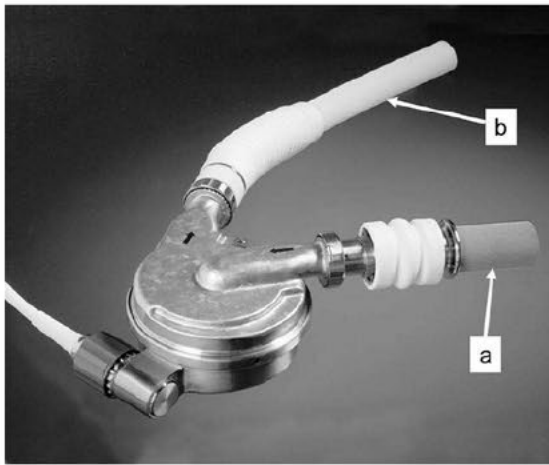


Figure 1. HeartMate III LVAD showing left ventricular apical inflow conduit (a) and LVAD outflow graft for attachment to aorta (b).

with a hermetic connector, facilitating modular replacement and separating pump reliability from cable reliability. The detachable cable also permits eventual modular upgrade from a percutaneous system to a fully sealed, transcutaneously powered system.

The pump is attached to the heart and circulatory system by a flexible inflow cannula inserted into the left ventricular apex and anastomosis of the outflow graft to the ascending aorta. The pump's impeller draws blood from the ventricle and imparts angular acceleration to the flow, the energy of which is then converted to pressure as it is diffused and delivered to the aorta. To minimize the risk of thrombogenesis and hemolysis, relatively large gaps are provided above and below the rotor to wash surfaces outside of the main flow path (**Figure 2**).

Motor function and magnetic levitation are achieved in a single, integrated unit incorporated with all control electronics in the pump's lower housing (**Figure 3**), resulting in efficient and compact performance.¹³ Rotation and radial levitation are

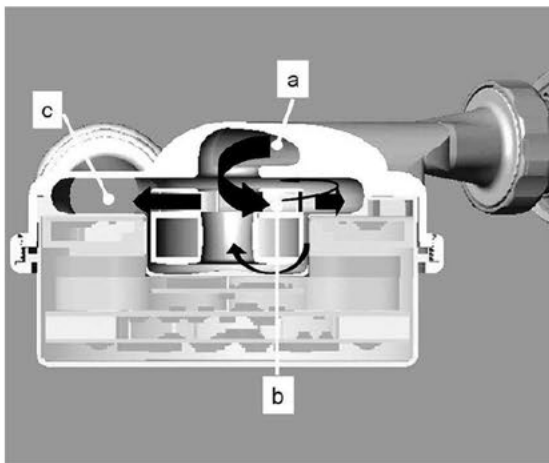


Figure 2. Cross section through the HeartMate III LVAD showing (a) the main flow path from the inflow section, (b) through the impeller and the backflow paths above the shroud and between the rotor and motor, and (c) into the outflow section. The motor and its electronics, isolated from the blood flow, are visible in the lower half of the illustration.

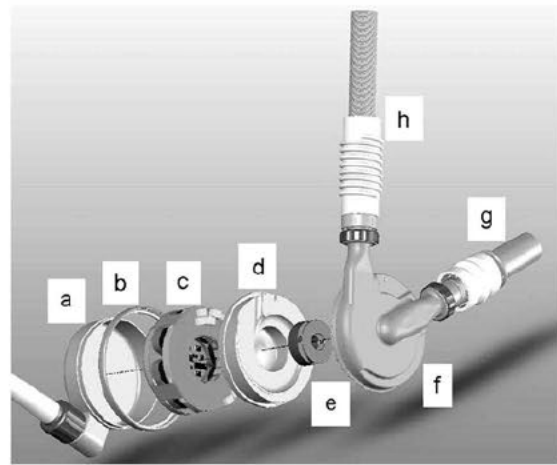


Figure 3. Exploded view of the HeartMate III LVAD showing, from left to right, (a) the lower housing (with cable attached), (b) screw ring, (c) motor, (d) upper housing, (e) rotor, and (f) pump cover, with (g) inflow and (h) outflow cannulas attached.

achieved through active control; the remaining degrees of freedom—axial motion and tilting—are achieved by passive magnetic support, without consumption of power. Testing has shown that the levitation system can withstand accelerations more than seven times that due to gravity. The stiff suspension makes this levitation system distinct from other possible configurations, such as the use of the blood as an active element as with a hydrodynamic bearing, or permitting occasional contact between the rotor and housing.

A key feature of the HeartMate III LVAD is the use of sintered titanium to create texture on all blood contacting surfaces of the pump except the smooth titanium impeller, following the approach of the HeartMate XVE. Historically, such surfaces have promoted the growth of a stable, adherent biological lining that lowers thromboembolic risk with only platelet modifiers such as aspirin.

Given the difficulty in producing a reliable, stable, implantable flow transducer for ultra-long-term use, the HeartMate III LVAD uses a sensorless flow estimator. An algorithm calculates mean flow and phasic flow waveforms, without the use of a flow meter, from the known relation between instantaneous power, rotational speed, and flow.

Both percutaneous and completely implanted versions of the LVAS are in development. For the percutaneous version, a belt-mounted system driver provides user control, power transmission, and alarms. With its portable configuration, a patient can freely ambulate for about 6 hours on a pair of rechargeable batteries worn in holsters under the arms. In the tethered configuration, uninterrupted power to the device is provided from an ordinary wall outlet. A complete array of system parameters may be interrogated and, if required, changed by the physician using the system monitor (**Figure 4**). All of the peripheral equipment—batteries, battery charger, power module, and system monitor—provide a common platform for use with all of the HeartMate LVADs.

Development and Test Plan

An exhaustive battery of preclinical tests—more than 100 protocols—have been developed to verify each design input

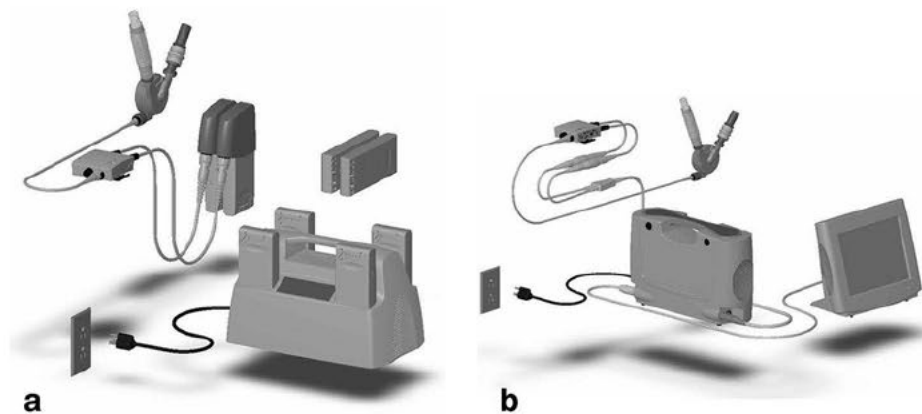


Figure 4. HeartMate III LVAS. (a) Ambulatory configuration with its wearable system driver and batteries, along with the battery charger, (b) tethered configuration with system driver and system monitor connected to the power module. The batteries, charger, system driver, and system monitor shown are from the proposed new equipment platform to be launched that will serve the entire HeartMate line.

requirement and validate user requirements. Testing includes full evaluation of the operational performance envelope, electrical safety including emissions and immunity, biologic compatibility, computational fluid dynamics (CFD) and flow visualization, *in vivo* performance in animals, long-term reliability, and human factors. The basis of testing was built on the international standards EN 45502-1:1997, AAMI/EN/ISO 10993-1:1994, and EN 60601-1 and dozens of derivative or related standards.

In Vitro Reliability Testing. HeartMate III LVADs were placed in mock circulatory test loops similar to the human cardiovascular system, including a pulsatile left ventricle simulated with a HeartMate IP blood pump. The LVAD was immersed in 37°C saline, which also serves as the circulating fluid. The flow conditions are changed according to a regular, periodic schedule among three conditions: high flow (10 L/min, 110 mm Hg), medium flow (7 L/min, 140 mm Hg), and low flow (2 L/min, 70 mm Hg), the latter deliberately specified below the minimum operation condition of 3 L/min to produce maximal internal heating. These conditions were designed to target the fluctuating loads imposed on the LVAD by the native circulation, physiologic humidity and temperature, corrosion, and the varying circulatory support demand by patients of varying health and activity level. Tests were performed in two stages: five initial prototype LVADs using a preliminary cable design permanently attached to the LVAD, and 10 LVADs started 2 years later representing the anticipated clinical version with a removable cable. This time-terminated study will be evaluated on 10 devices at 5 years, seeking to establish 80% reliability with a 60% confidence level,¹⁵ with the provision that units will be subsequently run to failure.

Computational Fluid Dynamics and Flow Visualization. CFD analyses were performed at low (3 L/min), normal (7 L/min), and high (10 L/min) steady-flow conditions.¹⁴ Experimental particle imaging flow visualization (PIFV) was performed on the pump, using 13 different viewing planes under each condition. The development of static pressure predicted by the CFD model was confirmed by *in vitro* testing, and PIFV in specially equipped transparent pumps was used to qualitatively confirm that flow patterns and velocities were accurately predicted by CFD.

In Vivo Testing. Nineteen long-term *in vivo* studies have been performed in calves, excluding cases terminated early due to surgical complications.¹¹ The HM III was implanted through a left thoracotomy. The outflow graft was anasto-

mosed to the thoracic aorta and the inflow conduit was secured to the left ventricle. Flow probes were placed on the outflow graft and the pulmonary artery. The pump speed was adjusted to maintain a flow of ≈ 6.0 L/min. Animals were typically supported for 30 to 90 days and then electively killed for evaluation of major organs and histology. Five studies were run under Good Laboratory Practices (GLP) with the LVAD design that represents the intended clinical device.

Artificial Pulse Mode. LVAD-induced pulsatile flow was created by rapidly changing the pump operation from low to high speeds. Feasibility tests were done in sheep and then studied in more depth *in vitro*. In an ovine ventricular replacement model to remove effects of native contractility,^{16,17} a HeartMate III supporting the systemic circulation was run in pulse mode with the speed modulated between 1500 and 5500 rpm at 60 bpm, 30% duty cycle, and 24 krpm/s rate of speed increase and decrease. The pulmonary circulation was supported by a second HeartMate III at constant speed. Aortic pressure was monitored in the ascending and descending aorta as distally as the iliac bifurcation. The amount of pulsatility was quantified by using energy-equivalent pressure (EEP).¹⁸ Subsequently, an *in vitro* mock loop was tuned to closely simulate those conditions and the effect of increasing the rate of speed change to 86, 228, and 381 krpm/s was investigated.

Sensorless Flow Estimator. A software algorithm has been developed to exploit the consistent relation between the HeartMate III pump's power consumption and its volume flow rate, enabling a prediction of flow given the known variables rotor speed and electrical current. Testing has occurred over a full range of flow conditions in a laboratory mock loop (2 to 10 L/min against pressures between 80 mm Hg and 135 mm Hg) and in bovine calf studies with the animal both at rest and challenged with exercise. A Transonic ultrasonic flowmeter, manually calibrated by volume measurement, was used on the outflow graft for comparison.

Results

Pressure-Flow Relation

The characteristic relation between differential pressure across the pump and flow through the pump (the H-Q curve) for the HeartMate III centrifugal pump is compared with that from the HeartMate II axial flow pump for two different speed

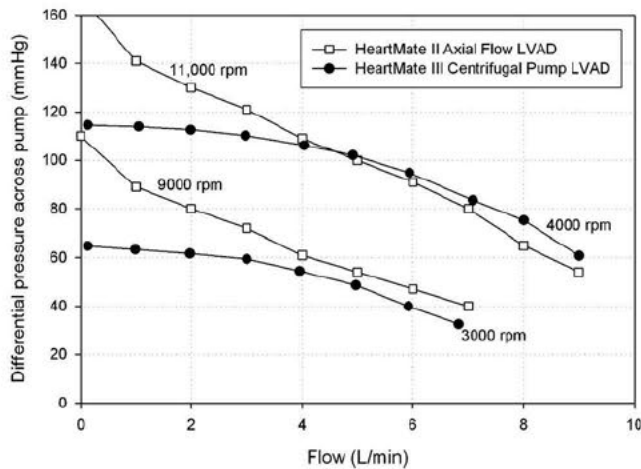


Figure 5. Typical pressure-flow relations for the HeartMate III centrifugal pump are compared with the HeartMate II axial flow pump at two different speed ranges. The pressure-flow curves are similar at high flows, but the HeartMate III has a “flatter” relation at lower flows.

ranges (Figure 5). The relations for these two pump designs are similar at higher flow rates, but the HeartMate III has a flatter H-Q curve in the lower flow ranges. To achieve flows in the physiologic range of 5 to 7 L/min at left ventricular-to-aortic differential pressures of 50 to 90 mm Hg, the HeartMate III will be run between 3000 and 4000 rpm.

Computational Fluid Dynamics and Flow Visualization

Both CFD and PIFV confirmed well-behaved flow fields in the main components of the pump: inlet, volute, and outlet, with more details provided in a previous report.¹⁴ CFD predicted excellent washing of the rotor inlet and rotor cavity by virtue of pressure-driven backflows in the rotor-housing gaps and an unsteady vortex within the centrally open rotor.¹⁴ Overall, the design was characterized by highly washed surfaces, relatively low shear stresses, and unsteadiness in localized areas of low velocity, protective against blood stasis.

In Vivo Testing

For the GLP series of 5 animals, the average duration of support was 85 days (range, 62 to 91). Flow averaged 6.0 ± 1.2 L/min at a power consumption of 8.5 ± 1.0 W. During changes in speed in one animal from 3250 to 4500 rpm, average pump flow increased from 4 L/min to over 11 L/min (Figure 6). In addition, the flow waveform showed diminishing pulsatility as the pump unloaded the left ventricle and took over more of the cardiac output, which in this calf averaged 14 to 16 L/min. A key finding consistent across the *in vivo* experience has been the similarity between the HeartMate III and historical HeartMate XVE gross and histologic textured surface examinations. All measures of end-organ function returned to normal soon after implantation (Figure 7). Neither hemolysis (PHgb <10 mg/dL) nor tissue heating (<2°C) were clinically relevant. At explant, the kidneys, liver, and pancreas were free of infarct.

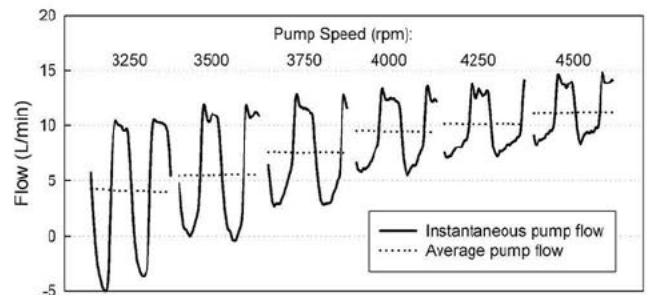


Figure 6. Mean flow and pulsatile flow produced naturally by variations in left ventricular pressure in a calf over a range of pump speeds, showing the ability of the HeartMate III to achieve a volume flow rate of more than 11 L/min and showing diminished pulsatility with more left ventricular unloading produced at higher speeds.

Artificial Pulse Mode

Examples of *in vivo* and *in vitro* pressure and flow waveforms produced with pulse mode are shown in Figure 8. Pulse pressure in the ovine aorta (thoracic to iliac) ranged from 19 to 33 mm Hg, with dp/dt between 147 and 233 mm Hg/s. *In vitro* testing of incremental changes of rates of speed change in a loop simulating those conditions showed that tripling the baseline rate from 24 to 86 krpm/s has a dramatic effect on the pulse at start of systole: dp/dt was quadrupled from 218 to

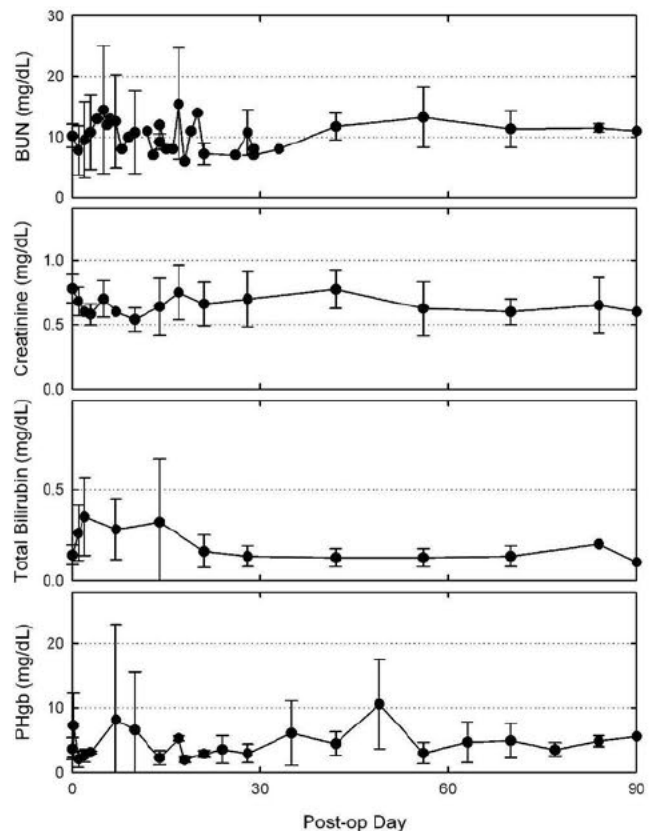


Figure 7. Results from the 5 GLP studies in calves demonstrate normal renal and hepatic function and low hemolysis as evidenced by blood urea nitrogen (BUN), creatinine, total bilirubin, and plasma-free hemoglobin (PHgb).

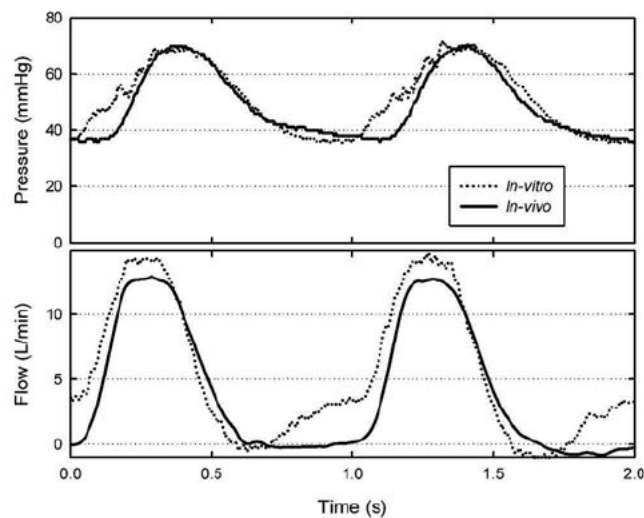


Figure 8. Artificial pulse mode produced physiologic pulse pressure and flow waveforms both *in vivo* and *in vitro*, shown here at 5500 rpm/1500 rpm, 60 bpm, 30% duty cycle, 24 krpm/s. The *in vitro* mock circulatory loop was tuned such that pulse pressure, dp/dt , and flow (dashed lines) closely matched the measured waveform from the *in vivo* study (solid lines).

1014 mm Hg/s, with a significant jump in EEP from 12.7% to 15.1% above mean arterial pressure, with little additional effect at higher rates.

Long-term Reliability Testing

Thirty months after launch of the first test of five pumps, there were two malfunctions in the original percutaneous cable design from galvanic corrosion due to short circuits in the wire bundles permanently wired to the pump. The remaining three units continue to operate today, more than four years after the test started. With the new connector design replacing the permanent connection, there have been no failures in the 10-pump test after 24 months of testing. Power consumption and the pressure-flow characteristics have been stable throughout the test.

Discussion

The design philosophy of the HeartMate III is to provide a long-term LVAS that will meet the needs of a large population of patients with advanced heart failure, with maximal reliability, durability, and acceptable freedom from major complications. We have attempted to address the principal deficiencies of the first-generation devices with a small, quiet, continuous flow centrifugal pump incorporating a magnetically suspended rotor for maximal long term durability, with the goal of a 10-year life. With the encouraging clinical results in the first 500 patients with the HeartMate II axial flow LVAD, explant results from clinical pumps and *in vitro* durability testing have shown evidence suggesting that it also may be possible to achieve these durability goals by using blood-immersed bearings,⁹ and thus a magnetic levitation centrifugal pump may not be the only solution. At the same time, we sought to retain features that have worked well in first-generation devices, such as the textured surfaces in the HeartMate XVE LVAS, which has

set the clinical standard for low thromboembolic complications with minimal anticoagulation.

First-generation devices have successfully demonstrated the hemodynamic restorative ability of pulsatile flow. However, it also appears that reduced pulse perfusion provided by continuous flow devices, as modulated by changes in left ventricular pressure from residual LV contractility, is also providing excellent hemodynamic support. Although it is relatively early in our clinical experience with continuous flow devices, successful reduced pulse perfusion is being achieved without apparent negative effects on peripheral end-organ physiology.⁸ Much more clinical data are needed to determine the long-term effects of various levels of no pulsatility or reduced pulsatility, but we have incorporated an artificial pulse mode that will provide enhanced pulsatility over that normally available from continuous flow pumps, which with sufficient energy and dp/dt may prove valuable for accelerating major organ recovery, promoting myocardial regeneration, or improving washing of prosthetic or biologic surfaces such as the aortic valve that may be prone to thrombosis.¹⁷ An artificial pulse feature involves the electrical inefficiency of switching speeds and the incremental heat generation and power consumption associated with this mode. It may also have an effect on other factors such as hemolysis and pump motion although currently not discernible. These issues will be fully evaluated in long-term animal studies with chronic use of the artificial pulse.

Modern computational capability has permitted increasingly sophisticated analysis of pump hydrodynamics that has become an integral part of the design process. Although the most important uses of CFD software remain comparative evaluations of prospective designs and troubleshooting problems encountered during prototype testing, regulatory agencies such as the FDA now expect to see CFD analyses in premarket submissions. Extensive evaluation of HeartMate III hydrodynamics has shown well-behaved flow fields, theoretically predicted and confirmed experimentally.¹⁴

The use of a sensorless flow estimator is an important feature for ultra-long-term support. An intrinsic advantage of operation of the HeartMate III without mechanical bearings is that power consumption to achieve any particular flow condition does not tend to drift over time, as it might with blood-immersed mechanical bearings susceptible to blood component adhesion. The HeartMate III flow estimator exploits the consistent relation between power consumption and volume flow rate (when rotor speed is known), and our goal is to predict flow within the accuracy attainable with Swan-Ganz catheters or ultrasonic flow probes: generally within 15% to 20%.¹⁹

The clinical need for a system that requires minimal anticoagulation with low thromboembolic complications, especially for older patient populations, is so compelling that we have incorporated sintered titanium textured surfaces similar to that in the Heartmate XVE. Human explants of this morphology show a well-adherent fibrocellular lining, providing a stable pseudoneointima that has provided an enhanced freedom from thromboembolism. However, the use of textured surfaces in continuous flow pumps is controversial, and it will not work in areas of pumps with very small clearances. After finding severe thrombus in a previous design of the HeartMate II axial flow pump that originated in the small clearance areas on the textured sintered titanium inlet and outlet stators, we redesigned the pump with smooth titanium stators while retaining

textured titanium in the conduits, which has solved the problem.^{5–8} The larger clearances in the design of the HeartMate III are more like the HeartMate XVE, and thus we are confident of achieving the benefits of textured surfaces without problems seen in very small clearance pump designs.

Traditional “real-time” (i.e., not accelerated) endurance testing of pulsatile LVADs (e.g., HeartMate XVE) has primarily targeted the reliability of parts that wear out, such as bearings and diaphragms. Because the expected life-limiting factor for HeartMate III, with its magnetically suspended rotor (and no mechanical wear), is electrical component failure, our long-term reliability test was designed to impose fluctuating loads of an artificial ventricle. Thus, power and control electronics are continually exercised throughout. Extreme stability of power consumption and the pressure-flow characteristic, which are sensitive indicators of electrical performance over long-term evaluations, are encouraging.

Clinical experience with continuous flow pumps have shown the potential for reduced complications from infection^{6,7} compared with the larger pulsatile pumps, at least over the observations periods that are generally in the 6- to 24-month period. The smaller pump and small, more flexible percutaneous lead in our HeartMate II experience, which is similar to that designed for the HeartMate III, is designed to be far less prone to infection than our pulsatile pumps. Therefore, we believe that percutaneous leads can be made a viable clinical solution for support periods of well over 1 year, probably reaching several years. However, for maximum freedom from infection, and for improved physical and psychological quality of life, especially for significantly longer durations, it is ultimately desired to have a completely implanted, sealed system with transcutaneous energy transmission (TET). Completely implanted systems omit the risks associated with the percutaneous lead, but there is a price of more implanted hardware, included implanted batteries, TET coils, electronics, and cables, increasing complexity and reducing overall system reliability. On the other hand, a percutaneous system is simpler and can be used clinically sooner. We believe that both percutaneous and transcutaneous systems will be required and thus have designed the device for modularity, allowing for upgrade from a percutaneous system or a replacement of the percutaneous lead without replacing the LVAD.

In summary, a long-term LVAS for permanent use in advanced heart failure is being developed based on a compact centrifugal pump with a magnetically levitated rotor. *In vitro* design verification testing is underway, preclinical *in vivo* testing has been performed in calves, long-term *in vitro* reliability testing is ongoing, and an induced pulse mode has been developed and has demonstrated the ability to produce a physiological pulse pressure *in vivo*.

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