

Design Rationale and Preclinical Evaluation of the HeartMate 3 Left Ventricular Assist System for Hemocompatibility

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The HeartMate 3 (HM3) left ventricular assist device (LVAD) is designed to support advanced heart failure patients. This centrifugal flow pump has a magnetically levitated rotor, artificial pulse, textured blood-contacting surfaces, optimized fluid dynamics, large blood-flow gaps, and low shear stress. Preclinical tests were conducted to assess hemocompatibility. A computational fluid dynamics (CFD) model guided design for low shear stress and sufficient washing. Hemolysis testing was conducted on six pumps. Plasma-free hemoglobin (PfHb) and modified index of hemolysis (MIH) were compared with HeartMate II (HMII). CFD showed secondary flow path residence times between 27 and 798 min, comparable with main flow residence times between 118 and 587 min; HM3 vs. HMII shear stress exposure above 150 Pa was 3.3 vs. 11 mm³ within the pump volume and 134 vs. 604 mm² on surfaces. In *in vitro* hemolysis tests at 2, 5, and 10 L/min, average pfHb 6 hours after test initiation was 58, 74, and 157 mg/dl, compared with 112, 123, and 353 mg/dl for HMII. The HM3/HMII ratio of average MIH at 2, 5, and 10 L/min was 0.29, 0.36, and 0.22. Eight 60 day bovine implants were tested with average flow rates from 5.6 to 6.4 L/min with no device failures, thrombosis, or hemolysis. Results support advancing HM3 to clinical trials. *ASAIO Journal* 2016; 62:375–383.

Key Words: HeartMate 3, Preclinical testing, hemocompatibility, magnetic levitation

Circulatory support with an implantable left ventricular assist device (LVAD) is an important treatment option for advanced heart failure. Following the transition from pulsatile to continuous-flow devices, lower adverse event rates and better survival have improved acceptance and usage of the technology. Since clinical studies were initiated approximately 15 years ago, the HeartMate II LVAD (HMII, St. Jude Medical, Inc., Pleasanton, CA) has been implanted in more than 23,000 patients worldwide. Studies have shown a consistent decline in major adverse events, while physical status and quality of life have been improved in the majority of patients.^{1–4} Nevertheless, complications related to the technology remain, and attention

has turned from the wear-out mechanisms associated with early pulsatile devices toward the reduction of clinical adverse events that persist with all rotary blood pumps. The primary focus of current research is on pump thrombosis, thromboembolism, bleeding, stroke, infection, and aortic insufficiency.^{5–8} Improved hemocompatibility of blood pumps is essential for continued improvement in survival and quality of life.

A fundamental strategy for the design of the HeartMate 3 LVAD (HM3, St. Jude Medical, Inc., Pleasanton, CA) was to adopt the aspects of mechanical circulatory support technology that have worked well (e.g., the reliability and small size of a rotary pump), but also to pursue a different technological path that addresses the factors implicated in the most significant adverse events. This path involves a magnetically levitated rotor (Full MagLev, St. Jude Medical, Inc., Pleasanton, CA) and its consequent wide blood-flow gaps, low shear stresses, and artificial pulse capability. A common way to avoid rotor contact is a hydrodynamic bearing, for which a thin layer of blood is entrained between the rotor and pump housing to an extent that the fluid force balances the axial attraction of the rotor to the motor iron.^{9,10} The HM3 with Full MagLev flow technology utilizes a magnetic bearing, an alternative approach to achieve rotor levitation without imposing high shear and compressive forces on blood.^{11,12} This feature, along with textured blood-contacting surfaces, wide flow gaps, and an artificial pulse are the principle characteristics of the HM3. Ultimately, the goal of the HM3 design is to improve hemocompatibility with a reduction in thrombotic and hemorrhagic adverse events.

To assess hemocompatibility and performance of the HM3, computational fluid dynamics (CFD), *in vitro* hemolysis, and *in vivo* implant studies were performed. Several CFD-based hemocompatibility metrics and *in vitro* hemolysis measurements were compared with the corresponding values of HMII, used as an experimental control. Here, we describe the system design characteristics of HM3 and present the results of the preclinical studies.

Materials and Methods

Device Description

The HM3 system is intended for long-term continuous-flow support of patients with advanced heart failure. The LVAD is surgically positioned in the pericardial space, with an inflow cannula inserted into the left ventricular apex and an outflow graft anastomosed to the ascending aorta (Figure 1). The implanted components include the inflow cannula, pump housing, motor, control electronics, outflow graft and bend relief, and percutaneous driveline (Figure 2).

The HM3 utilizes a centrifugal flow pump that has a capacity to pump blood up to 10 L/min. Left ventricular blood is drawn

From the St. Jude Medical, Inc., Pleasanton, California.

Submitted for consideration February 2016; accepted for publication in revised form May 2016.

The HeartMate 3 LVAD is an investigational device in the United States.

Disclosure: All of the authors are employees of St. Jude Medical, Inc.

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DOI: 10.1097/MAT.0000000000000388

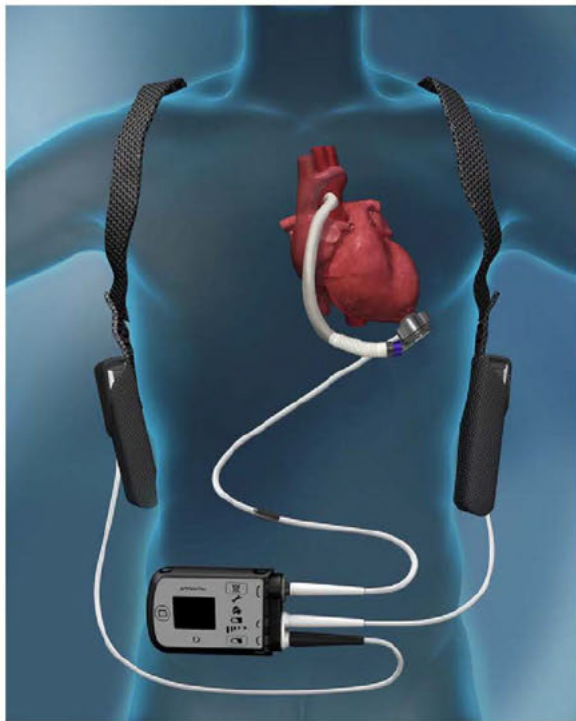


Figure 1. Main components of the HM3 system. HM3, HeartMate 3.

into the inflow cannula along a central axis and is expelled at right angles by and between the impeller blades of a rotor rotating about the central axis. Blood is angularly accelerated

and travels around a volute before it is diffused to a desired pressure and flow rate by being directed tangentially into the outflow graft. The pump rotor is fully supported by magnetic levitation, obviating mechanical or fluid bearings and essentially eliminating mechanical wear as a reliability factor. Both drive (i.e., rotation) and levitation of the rotor is accomplished using a single stator comprising iron pole pieces, a back-iron, copper coils, and position sensors. Measuring the position of a permanent magnet in the rotor and controlling the current in the drive and levitation coils enables active control of the radial position and rotational speed of the rotor. Because the permanent magnet is attracted to the iron pole pieces, the rotor passively resists excursion in the axial direction, whether translating or tilting. The electronics and software necessary to control motor drive and levitation are integrated into the lower housing with the stator; these components plus the rotor comprise the motor.

The 20 mm diameter inflow cannula is rigidly affixed to the pump cover. A felt cuff is sewn to the left ventricle at or near the apex. A coring knife is used through the center of this cuff to resect a plug of myocardium. The inflow cannula is then introduced through this cored hole and the pump is readily secured to a titanium ring rigidly affixed to the cuff. The outflow cannula assembly includes a 14 mm sealed woven polyester graft, the distal end of which is cut to desired length and sutured to the ascending aorta. A reinforced tube around the graft serves as a bend relief to prevent kinking and abrasion. The bend relief can be attached or removed and reattached during the implantation procedure, or during pump replacement if necessary.

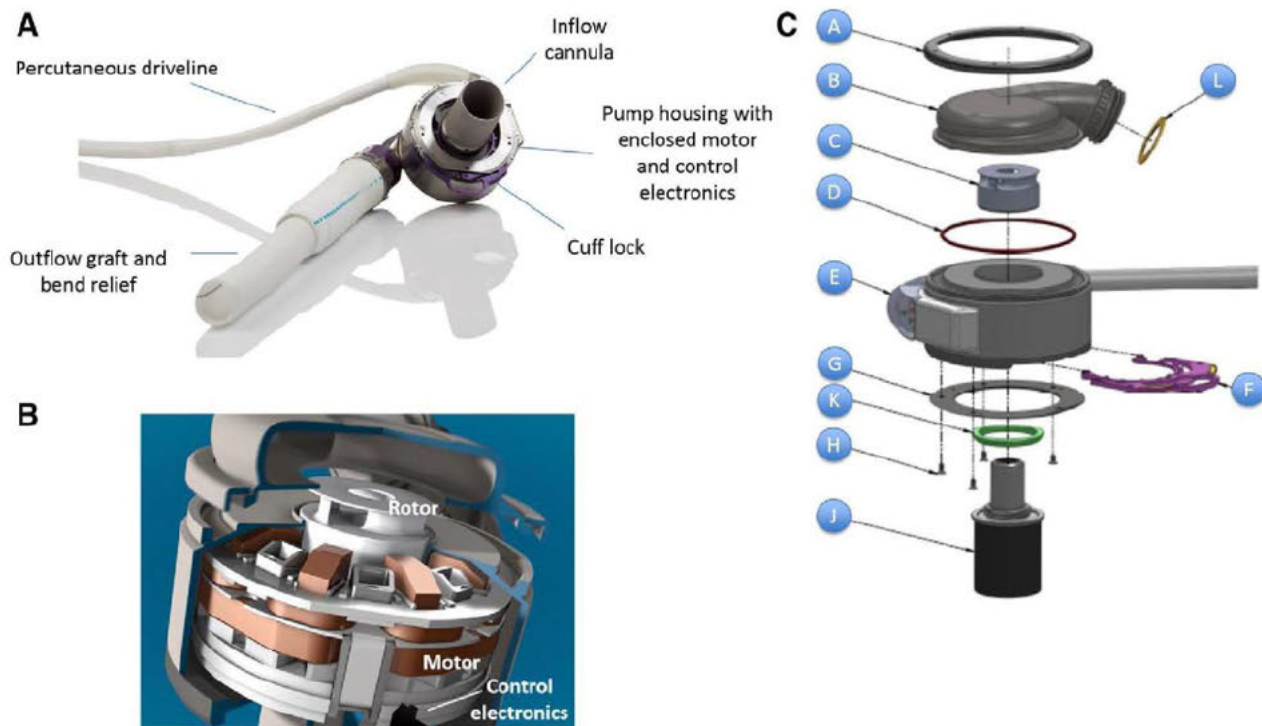
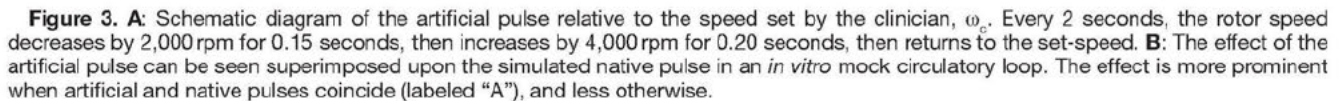


Figure 2. **A:** Implanted components of the HM3 include the pump with an integral inflow cannula, cuff lock for quickly securing the pump, outflow graft and bend relief, and percutaneous driveline. **B:** Enclosed in the pump housing is a rotor and, hermetically sealed from the blood flow, a motor and control electronics. **C:** An exploded view of the HM3 expose: the pump cover screw ring (A), pump cover (B), rotor (C), o-ring (D), motor assembly (E), cuff lock (F), cuff lock cover (G), cuff lock cover screws (H), inflow cannula (J), and sealing washers (K and L). HM3, HeartMate 3.



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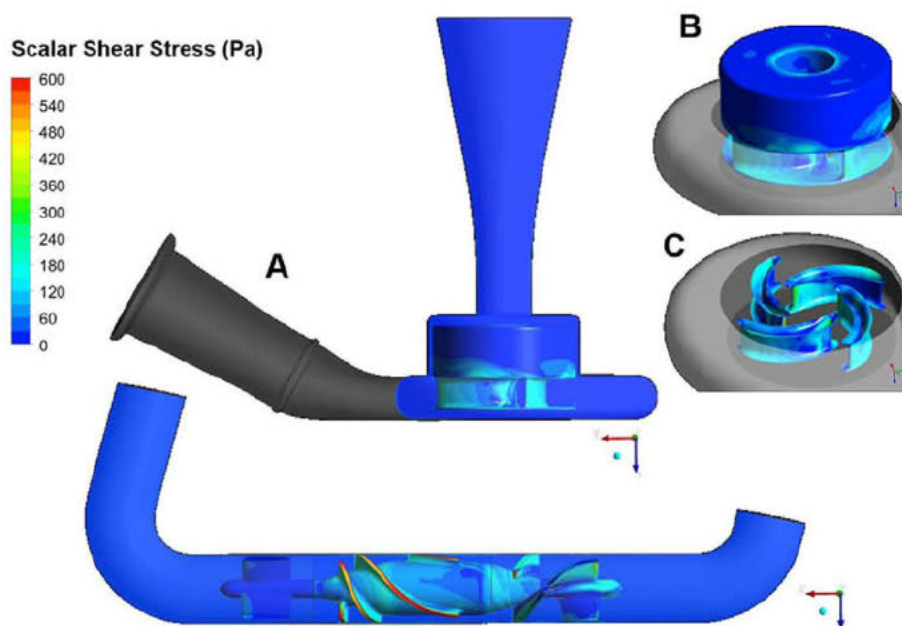


Figure 4. Scalar shear stress surface contour plots at 5.4 L/min and 65 mm Hg of HM3 and HMII (A), HM3 rotor well (B), and HM3 rotor blades (C). HMII, HeartMate II; HM3, HeartMate 3.

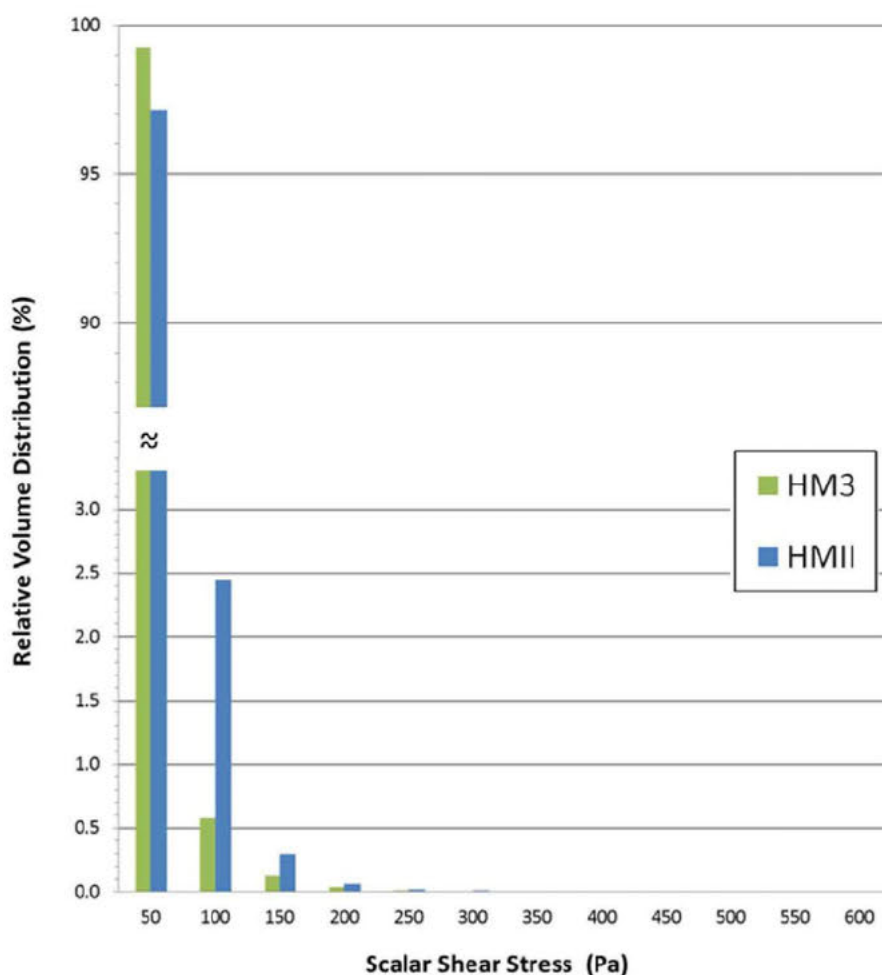


Figure 5. Scalar shear stress histogram at 5.4 L/min and 65 mm Hg of the HM3 and HMII. HMII, HeartMate II; HM3, HeartMate 3.

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Table 1. CFD-Derived Numerical Hemocompatibility Comparison Between HM3 and HMII at the Nominal Operating Condition of 5.4 L/min and 65 mm Hg

Parameter	HMII	HM3	HM3/HMII (%)
Hemolysis index (%)	0.0654	0.0089	14
Area exposed to wall shear stress >150 Pa (mm ²) (%)	604 (26)	134 (7.7)	22
Maximum rotor wall shear stress (Pa)	1,800	600	33
Volume exposed to scalar shear stress >150 Pa (mm ³) (%)	11 (0.09)	3.3 (0.03)	29
Volume exposed to scalar shear stress >50 Pa (mm ³) (%)	334 (2.7)	52.7 (0.48)	16

CFD, computational fluid dynamics; HMII, HeartMate II; HM3, HeartMate 3.

Hemolysis index (HI) was calculated for each operating point using the Eulerian numerical model for hemolysis derived by Goubergrits and Affeld,¹³ which is based on the Giersiepen equation:

$$\frac{\Delta \text{pfHb}}{\text{Hb}} = 3.62 \times 10^{-5} \times \tau^{2.416} \times t^{0.785}, \quad (1)$$

where ΔpfHb is the change in concentration of plasma-free hemoglobin, Hb is hemoglobin, τ is shear stress, and t is time.

Hemolysis Testing

Hemolysis assessment was performed per ASTM F1841^{14,15} using bovine blood, and the results from the HM3 were compared with the clinically approved HMII. Six test devices (HM3) and six predicate devices (HMII) were tested using flow and pressure parameters representing the anticipated clinical flow operating range: 2 L/min (low flow), 5 L/min (nominal flow), and 10 L/min (high flow). For all cases, the pressure across the pump was fixed at 100 mm Hg. Fixing pressure is a slightly different approach than used for the CFD study, but it was done to ensure that the hemolysis study captured the worst-case, *i.e.*, highest speed, conditions, and that the CFD study would capture the fullest range of flow dynamics, including the lowest blade velocities at low flows. The test devices ran in artificial pulse mode while the predicate devices ran at constant speed, representing clinical use in both cases.

Circulatory loops were constructed using a 1 L blood reservoir and Tygon tubing immersed in a water bath kept at 37°C. A total of six loops (three candidates and three predicate devices) as well as a static control loop were tested during the same day for 6 hours using the same blood pool. Before beginning each test, a blood sample was taken to establish the pfHb baseline. Blood samples were taken hourly for 6 hours and the pfHb was measured. Testing was repeated five times for each of three test devices, three predicate devices, and one control device at each operating condition (low, nominal, and high). This led to 105 pfHb vs. time curves.

Also calculated was the modified index of hemolysis (MIH), which is normalized by hematocrit and hemoglobin:

$$\text{MIH} = \Delta \text{pfHb} \times V \times \frac{100 - \text{Ht}}{100} \times \frac{10^6}{Q \times T \times \text{Hb}}, \quad (2)$$

where Hb is the total blood hemoglobin concentration at time zero (mg/L), Ht is hematocrit (%), Q is flow rate (L/min), T is the sampling time interval (min), V is the circuit volume (L), ΔpfHb is the increase of pfHb concentration (mg/L) over sampling time interval.

In Vivo Tests

The HM3 was implanted in ten Corriente Crossbreed bovine calves weighing 80–100 kg to assess pump performance and safety. Pump operating parameters, hemodynamics, and laboratory values for assessing organ function were collected during the planned 60 day evaluation period. All adverse events were recorded. After termination of each study, a complete necropsy was performed to determine the presence of end-organ pathology related to the device.

Implantation was accomplished through a left thoracotomy with cardiopulmonary bypass support, achieved by cannulation of the left carotid artery (arterial return) and left jugular vein (venous inflow). An apical cuff was sewn to the apex of the heart, the apex was cored, and the pump inflow was inserted into the left ventricle and secured. The outflow graft was anastomosed to the descending aorta. Ultrasonic flow probes were placed on the outflow graft of the LVAD and the main pulmonary artery. The LVAD was operated in the pulse mode with the speed setting adjusted to achieve a target flow rate of 5.4 ± 1.0 liters per minute (LPM). Anticoagulation with heparin (25,000 units per 250 ml D5W from postoperative day (POD) 0 to POD 3 to 5, titrated between 1 and 12 ml/hour to maintain ACT between 200 and 250 seconds), and then Coumadin (initiated POD 2 or 3 and continued SID 0.0 to 10.0 mg IV/PO throughout), was achieved with a target INR in the range of 1.5 to 3.0.

Table 2. HM3 CFD-Derived Numerical Hemocompatibility Comparison Among Flow Conditions Across the Operating Range

Parameter	Low Flow (2.0 L/min)	Nominal Flow (5.4 L/min)	High Flow (10 L/min)
Hemolysis index (%)	0.0023	0.0089	0.0297
Area exposed to wall shear stress >150 Pa (mm ²)	4	134	604
Maximum rotor wall shear stress (Pa)	250	600	1,000
Volume exposed to scalar shear stress >150 Pa (mm ³)	0.03	3.3	20
Volume exposed to scalar shear stress >50 Pa (mm ³)	10.5	52.7	225

CFD, computational fluid dynamics; HM3, HeartMate 3.

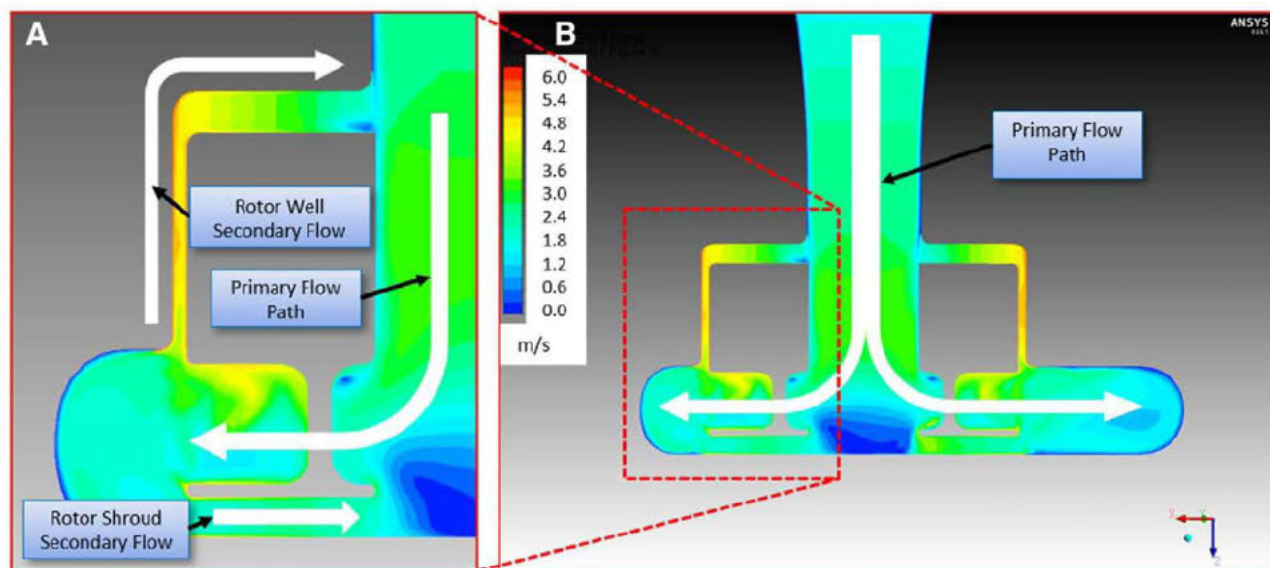


Figure 6. Velocity contour plot (cross section) of the HM3 illustrating primary and secondary flow paths. HM3, HeartMate 3.

The animal studies were conducted according to Good Laboratory Practices and an independent quality assurance unit monitored the study.

Results

Computational fluid dynamics-based hemocompatibility of HM3 was analyzed by reporting volumetric shear stress distribution, shear-exposed areas, and the HI, and compared with the corresponding values for HMII, when it is applicable. **Figure 4** illustrates the shear stress distribution across the longitudinal axis of HM3 and also HMII both operating at

the nominal condition; 5.4 L/min at 65 mm Hg pump head. Overall, shear stress distribution is relatively homogenous and smooth across the flow passages for both pump types. Typical high shear areas for the axial impeller were confined at the blade tip, whereas HM3 impeller blades exhibit shear stress at the concave side of the blade leading edge and the convex side of the blade trailing edge (**Figure 4B**). The shear stress histogram for the nominal operating condition (**Figure 5**) indicates that more than 99% of the blood volume inside HM3 is exposed to low shear stresses (<50 Pa), compared with 97% of pump volume in HMII. Importantly, less than 0.03% (3.3 mm³) of HM3 is exposed to high shear values

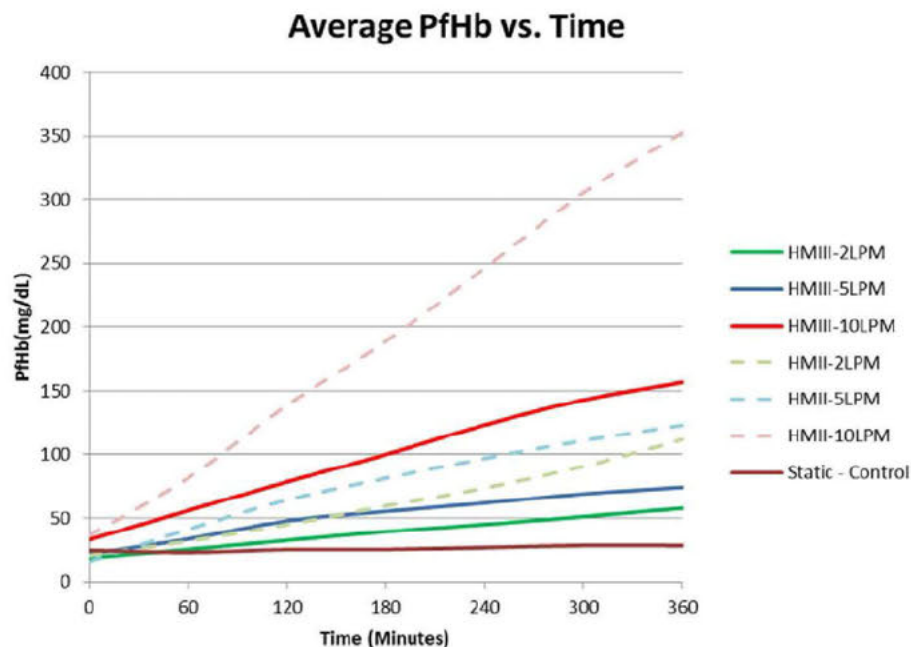


Figure 7. Average plasma-free hemoglobin over the course of the 6 hour tests for the HM3 and the HMII. HMII, HeartMate II; HM3, HeartMate 3.

Table 3. The Average ($\pm$ Standard Deviation) Pump Speed, Pump Flow, and Pulmonary Artery Flow for Each *In Vivo* Study

Study #	Pump Speed (rpm)	Pump Flow–Outflow Graft (L/min)	Pulmonary Artery Flow (L/min)
1	6,237 $\pm$ 83	6.1 $\pm$ 0.5	10.7 $\pm$ 3.0
2	6,531 $\pm$ 203	6.2 $\pm$ 0.5	14.7 $\pm$ 4.3
3	6,299 $\pm$ 14	6.0 $\pm$ 0.5	16.5 $\pm$ 3.8
4	5,781 $\pm$ 100	5.9 $\pm$ 0.4	11.1 $\pm$ 1.7
5	6,065 $\pm$ 102	5.6 $\pm$ 0.4	12.4 $\pm$ 2.1
6	6,199 $\pm$ 13	5.6 $\pm$ 0.3	15.9 $\pm$ 3.4
7	6,197 $\pm$ 41	5.6 $\pm$ 0.4	15.5 $\pm$ 3.7
8	6,250 $\pm$ 88	5.9 $\pm$ 0.7	9.2 $\pm$ 1.7

>150 Pa, compared with 0.09% (11 mm³) of HMII. Similarly, the surface area with wall shear stress exceeding 150 Pa was 7.7% (134 mm²) of the impeller in HM3, compared with 26% (604 mm²) in HMII. In agreement with shear stress loading comparisons, CFD estimation of the HI for HM3 was 14% that of HMII. Comparison of shear stress-based hemocompatibility

indices across two pumps is summarized in Table 1. Table 2 provides insight as to how blood damage indices vary across the operating range.

Surface washing through the secondary flow paths of HM3 was evaluated by estimating the local residence time inside gaps and comparing to the mean residence time of blood traveling through the pump primary flow path (Figure 6), *i.e.*, mean transit time. Computational fluid dynamics simulations showed that mean transit time of blood through HM3 is 587, 219, and 118 min for the 2.0, 5.4, and 10.0 L/min cases, respectively. These values were used as the target residence times inside the secondary flow path to avoid stasis and promote washing. Flow rates in the secondary flow path above the rotor shroud were between 232 and 720 ml/min across the full operating range of the pump, which corresponds to average residence times between 27 and 85 milliseconds. Flow rates through the rotor well secondary flow path (Figure 4) range between 40 and 100 ml/min, resulting in average residence times between 319 and 798 milliseconds.

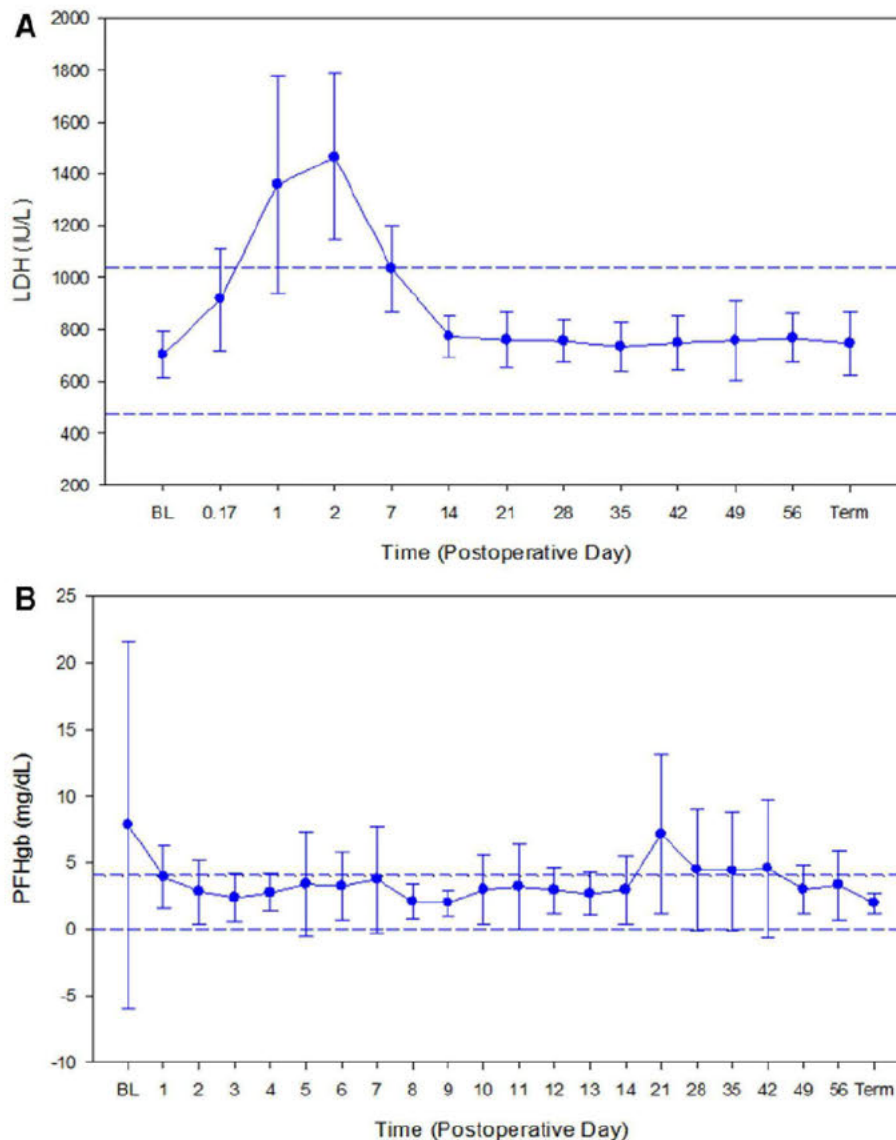


Figure 8. The average ($\pm$ standard deviation) for lactic dehydrogenase (A) and the plasma-free hemoglobin (B) for the eight animals.

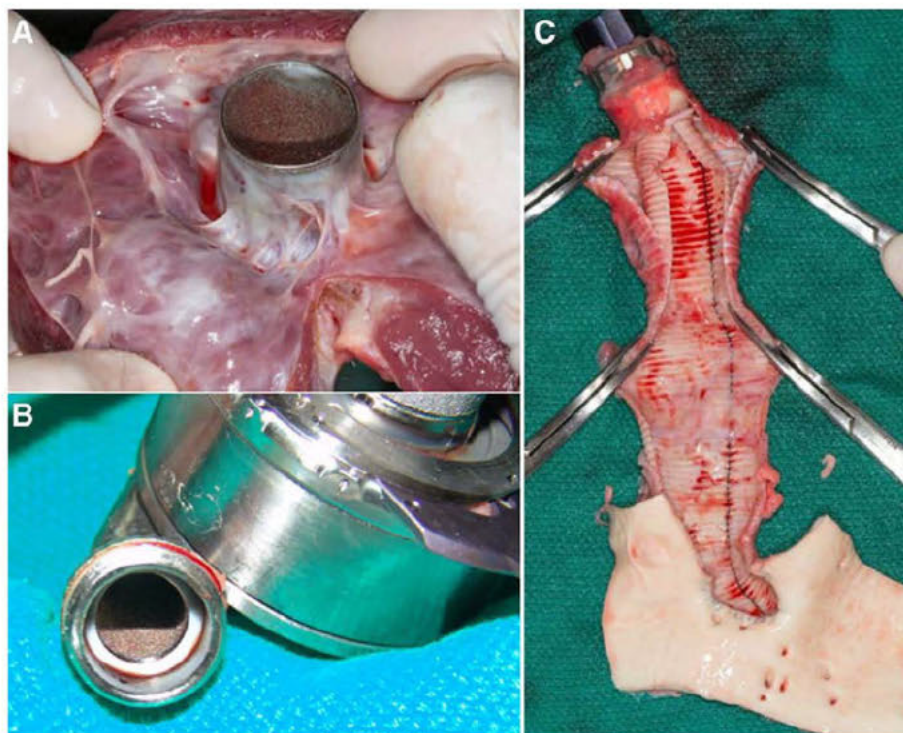


Figure 9. Representative photos of pump components after 60 days of support: inflow conduit within the left ventricle (A), the outflow connector (B), and the outflow graft, sectioned longitudinally and reflected to expose the aortic anastomosis (C).

The average pfHb at the end of the 6 hour *in vitro* tests consistently showed less hemolysis for the HM3 compared with HMII (Figure 7). The mean pfHb at each of the three test conditions (2, 5, and 10 L/min) for the HM3 was, respectively, 57.8 ± 35.8 , 74.1 ± 34.4 , and 156.6 ± 42.6 mg/dl compared with 111.7 ± 35.9 , 122.9 ± 34.1 , and 352.6 ± 83.0 mg/dl for the HMII at the same conditions. Paired *t* tests show these differences are significant at all three test conditions, with *p* values of 0.00016, 0.000007, and 0.000016, respectively. The ratio of HM3 to HMII pfHb was 0.52, 0.60, and 0.44 for the 2.0, 5.0, and 10.0 L/min cases, respectively.

In addition, the calculated MIH for the HM3 was 2.1, 3.5, and 2.3 for the 2.0, 5.0, and 10.0 L/min conditions compared with 7.3, 9.8, and 10.6 for the HMII. The ratios of HM3 to HMII MIH were 0.29, 0.36, and 0.22 for the 2.0, 5.0, and 10.0 L/min cases, respectively, thus demonstrating between 22% and 36% of HMII MIH.

In the *in vivo* experiments, eight of the 10 animals survived beyond the 60 day target time and were electively euthanized on days 61 to 64. Two studies were terminated on the first postoperative day for reasons unrelated to the device: one due to intractable fibrillation and the other due to iatrogenic blood loss. The pump flow was consistently maintained within the targeted average pump flow range of 4.4–6.4 L/min for each animal (Table 3). The pulmonary artery flow increased over the duration of the study in each animal, as was expected due to animal growth. There were no reported device malfunctions throughout the study. The average pfHb and the lactic dehydrogenase values for the entire group of animals indicated that hemolysis did not occur (Figure 8). Gross necropsy did not reveal any systemic effects. Device observations of the blood contacting surfaces included unremarkable pannus formation

and collagen islands typical of historical textured surface experience (Figure 9).

Discussion

The design of the HM3 LVAS includes features that are well established through extensive clinical research on previous HeartMate models with good biocompatibility and low thromboembolism. The small size and durability of the HMII, when compared with HeartMate XVE, has provided a better quality of life and longer expected survival for more than 23,000 patients. The fundamental strategy with the development of the HM3 is to retain certain HeartMate features that have these demonstrated advantages, but to deliberately depart from the disadvantages of mechanical and hydrodynamic bearing approaches.¹⁶ The design goals of the HM3 are to minimize the degree of shear force on blood components, lessen surgery during implantation, reduce the surface area of the biomaterial–blood interface, and enhance continuous blood flow with an artificial pulse. It is anticipated that these features will reduce bleeding complications, thrombogenesis, stroke, and end-organ dysfunction.

This HM3 LVAD is placed within the pericardial space without the need for an abdominal pocket, thereby reducing the amount of surgery for implantation. Full MagLev and the wide blood-flow gaps minimize shear-induced blood component damage. The lack of mechanical bearings eliminates friction, heat generation, and the possibility of component wear. The relatively large gaps surrounding the magnetically levitated rotor are 10 to 20 times greater than typical hydrodynamic bearings. The large gaps enable the sharp speed changes employed by the HM3 artificial pulse.^{17,18} By alternating the

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speed every 2 seconds, changing blood flow within the LVAD precludes the organization of recirculation and stasis zones. The role pulsatility plays in von Willebrand factor degradation leads to a hypothesis that gastrointestinal bleeding, hemorrhagic stroke, and epistaxis may be reduced by reducing effects on blood proteins and reducing platelet activation, although clinical experience will be required to substantiate that.^{19,20} Furthermore, as with prior generations of HeartMate devices, the adherence and stability for cellular attachment offered by the textured blood-contacting surfaces may also ease the need for anticoagulation therapy and minimize the risk of thromboembolism.

Hemolysis testing and CFD analysis collectively suggest that the HM3 LVAD maintains low blood cell shear exposure and low hemolysis levels relative to a predicate device, HMII, which has demonstrated considerable clinical success. Comparative analysis indicate that blood volumes exposed to high shear loading and associated estimated hemolysis is equal or lower than HMII values using identical numerical methods. *In vitro* tests demonstrated that HM3 had consistently lower hemolysis than HMII across the entire operating range. The CFD model was limited to the constant rotor speed case for which features such as artificial pulse were not included, a limitation of the model. Similarly, the bench testing of hemolysis per ASTM F1841 protocol is a comparative test to assess the hemolytic risk of an LVAD, e.g., HM3, relative to HMII used as a control, primarily due to the normal variations in animal blood fragility.^{15,16} Therefore, absolute pFHb values reported herein do not represent values expected in clinic.

Preclinical testing has shown the HM3 to be safe with low levels of hemolysis and promising hemocompatibility. Differences between the bovine and clinical models, such as the bovine model's smaller ratio of mechanical support to cardiac output and more distal outflow graft anastomosis on the aorta are limitations of the study. A clinical trial evaluating safety and efficacy has been completed in Europe, with subsequent CE Mark approval, and a larger trial is ongoing in the United States.²¹

Acknowledgment

The authors thank Tim Myers for manuscript preparation.

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