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Optimization of axial-pump pressure sensitivity for a continuous-flow total artificial heart

O. H. Frazier, MD,[a] Hassan A. Khalil, BS,[a] Robert J. Benkowski, BS,[b] and William E. Cohn, MD[a]

From the [a]Department of Cardiovascular Surgery, Texas Heart Institute at St. Luke's Episcopal Hospital, Houston; and [b]MicroMed Technology, Inc., Houston, Texas.

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total artificial heart;
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mechanical modeling;
mechanical circulatory support;
perfusion-nonpulsatile

BACKGROUND: In this study, we describe the potential advantages of a continuous-flow total artificial heart (CFTAH) comprising two small, non-pulsatile pumps with optimized responsiveness to the pressure gradient.

METHODS: We modified a MicroMed DeBakey axial-flow pump by increasing its inducer–impeller inlet angle, thereby increasing its pressure responsivity. We obtained the in vitro pressure gradient response and compared it with those of the clinically used, unmodified MicroMed DeBakey pump, Jarvik 2000 FlowMaker and HeartMate II.

RESULTS: The modified pump showed an increased response to changes in the pressure gradient at pump flow rates of between 2 and 4 liters/min. The maximum pressure responsivity of the modified pump was 2.5 liters/min/mm Hg; the corresponding maximum responsivities of the Jarvik 2000, HeartMate II and MicroMed DeBakey ventricular assist devices (VADs) were 0.12, 0.09 and 0.38 liters/min/mm Hg, respectively.

CONCLUSIONS: Because of the inherent properties of non-pulsatile pumps, the CFTAH may potentially respond to changes in inflow and outflow pressures while maintaining physiologic flow rates sufficient for normal daily activity. In addition, the hemodynamic interplay between the two optimized pumps should allow a physiologic response to normal flow imbalances between the pulmonary and systemic circulations. Improved responsiveness to inflow pressure may further simplify and improve the CFTAH and affect its potential clinical use as a meaningful therapy for terminal heart failure.

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Although heart transplantation remains the surgical treatment of choice for terminal congestive heart failure, the limitations of donor heart availability, the inherent time-related transplant mortality, the necessity for life-long immunosuppressive therapy, and the convoluted logistics related to immunologic testing, patient selection and organ procurement all underscore the need for the alternative treatments, including mechanical circulatory support. The use of ventricular assist devices (VADs), either as bridges to transplantation or for long-term ventricular support, has increased markedly over the last decade. Several types of VADs have already been approved by the U.S. Food and Drug Administration, whereas others are undergoing clinical trials in North America and Europe. The current generation of VADs includes pulseless axial-flow or centrifugal pumps, which are more durable than their pulsatile counterparts. Clinical success with these pumps[1] has led us to investigate the potential benefit of a novel, continuous-flow total artificial heart (CFTAH) comprising two continuous-flow pumps (CFPs). The device would possess all the benefits of CFPs, including their smaller size, simpler mecha-

Reprint requests: O.H. Frazier, MD, Department of Cardiovascular Surgery, Texas Heart Institute, P.O. Box 20345, MC 3-147, Houston, TX 77225-0345. Telephone: 832-355-3000. Fax: 832-355-6798.

E-mail address: lschwenke@heart.thi.tmc.edu

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nism of operation, fewer moving parts and greater durability. The CFTAH also would be implantable in smaller patients, particularly women and children, who would otherwise be ineligible for larger, pulsatile total heart replacement. Moreover, we believe that the autoregulatory potential of CFPs can be exploited in the CFTAH, allowing automated pump regulation on the basis of venous return (i.e., physiologic requirements), therefore minimizing and perhaps altogether eliminating the need for the external adjustment of pump speed.

Because of the CFTAH's relatively small size and operational simplicity, surgical placement of this system is less complex than implantation of a pulsatile artificial heart. In our laboratories, we have implanted in sheep and calves a variety of CFTAH systems, including those comprising the HeartMate II and HeartMate III (Thoratec Corp., Pleasanton, CA), the MicroMed DeBakey (MicroMed Technology, Inc., Houston, TX), the Jarvik 2000 FlowMaker (Jarvik Heart, New York, NY) and the HeartWare CFP (HeartWare, Ltd., Sydney, Australia).[2,3] For these studies, both ventricles were excised and the inflow cuffs of each pump were sewn to the atrial remnants. (Complete excision of the native heart ensures the non-pulsatile nature of the CFTAH.) More recently, we have enlarged the atrial reservoir with rigid Dacron chambers, thereby protecting against atrial collapse. Even with the larger chambers, the CFTAH is still smaller than a pulsatile artificial heart. Prolonged survival and normal physiologic responses have been demonstrated in experimental animals.[3]

Methods

For the MicroMed DeBakey VAD, the inducer–impeller inlet angle was increased to enhance the pressure responsiveness, similar to that of an airplane's wing at take-off (Figure 1). The pressure–flow relationships of a Jarvik 2000, HeartMate II, MicroMed DeBakey and modified MicroMed pump were measured in a mock circuit, as described elsewhere.[4] The inflow pressure, or pump pre-load, was maintained at 10 mm Hg. The after-load was adjusted by using a screw clamp on the outflow tubing. The outlet pressure was measured with a fluid-filled transducer (Edwards LifeSciences, Irvine, CA) low-pass filtered at 1 Hz (Model 3364; Krohn-Hite, Brockton, MA) and recorded on a computer equipped with a data acquisition board (dSPACE, Inc., Novi, MI) and a ControlDesk graphical user interface (version 2.6.5; dSPACE, Inc.).

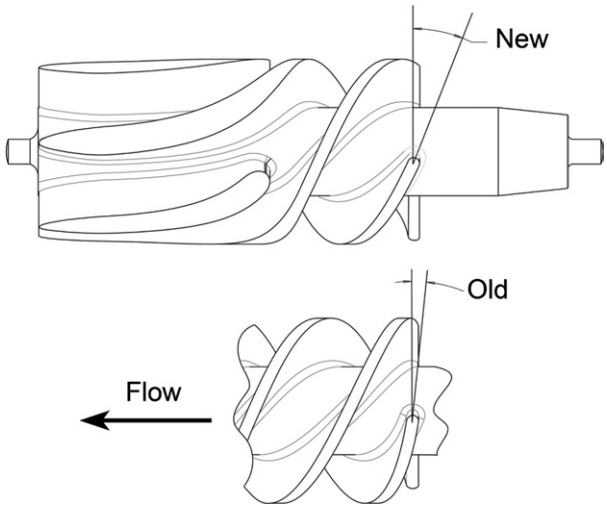

Figure 1 MicroMed pump rotor, illustrating the change in inducer–impeller inlet angle.

Table 1 Range of Pump Speeds Tested

Pump	Speed range (rpm)
Jarvik 2000	8,000–12,000
HeartMate II	7,000–10,600
MicroMed DeBakey	7,500–12,000
Modified MicroMed	6,500–12,000

Flow in both the native heart and the CFPs is determined by the difference (ΔP) between the inflow pressure (pre-load) and the outflow resistance (after-load). Varying either parameter results in a change in the ΔP across the pump and, thereby, a change in pump output. In this approach, we maintained a constant pre-load of 10 mm Hg and changed the ΔP by varying the outflow resistance. The responses of the 4 axial-flow pumps to the varying ΔP were then recorded at flow-rate increments of 0.25 liter/min. Table 1 shows the range of pump speeds tested. For each pump, we plotted the resulting pressure–flow curves for different pump speeds and calculated the pressure sensitivity (change in flow rate ÷ change in ΔP) by using centered, finite-divided differences in Excel (Microsoft, Inc., Redmond, WA).

Results

Figure 2 shows the pump characteristic curves of the Jarvik 2000, the HeartMate II and the clinical and modified MicroMed DeBakey pumps. Tables 2 through 5 show the corresponding calculated pressure responsiveness of these devices. Figure 3 compares the maximum pressure sensitivities of the pumps.

Discussion

Whether the pressure responsiveness of a continuous-flow VAD can be increased to a level compatible with long-term total circulatory support without having to manually alter the pump speed is a topic of intense interest in our laboratory. It has been a long-held hypothesis of the senior investigator (O.H.F.) that design modifications to CFPs could enhance their autoregulatory potential and allow total heart replacement without internal automated speed control in response to patient activity. Current pulsatile TAH re-

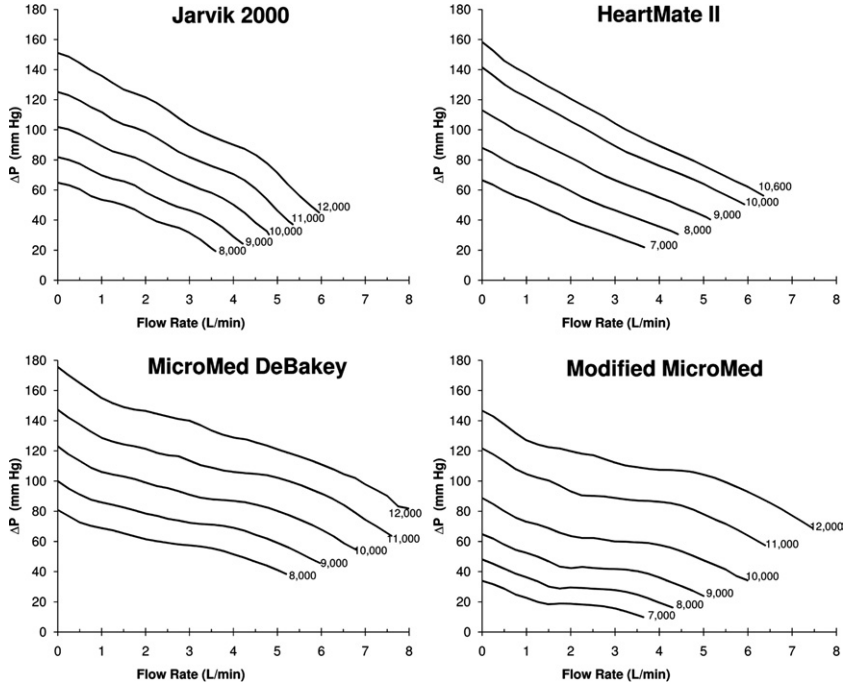

Figure 2 Pressure–flow curves of the Jarvik 2000, HeartMate II, clinical MicroMed DeBakey and modified MicroMed pumps.

placements allow pump flows of between 4 and 10 liters/min. Although this level of output can also be achieved with CFP technology, we hypothesize that enhancing the autoregulatory potential of CFPs used in a TAH configuration will more closely emulate the body's natural response to increased venous return.

Currently, only one clinically used VAD (the Jarvik 2000 Heart) will allow patients to manually adjust the pump speed. After patients are discharged from the hospital, they wear a controller and adjust the pump speed according to their activity level. With other types of VADs, adjusting the pump speed requires a larger controller, used only in the hospital setting. However, even without speed changes, CFPs inherently increase their output in response to increased inflow pressure (pre-load) or, more generally, in response to reduced pump ΔP. The potential of CFPs to autoregulate themselves, similar to the native heart, was first described in 1960 by Saxton and Andrews.[5] They suggested that this autoregulatory mechanism could allow for the development of a more ideally physiologic artificial heart. Although Akimoto and colleagues[6] showed inflow pressure responsivity of a CFP in series with the native heart, such responsivity when the heart is totally excised was only recently demonstrated in our laboratories.[2,3]

It seems clear that changes in the inlet angle and vane geometry in an axial-flow pump affect the sensitivity of pump output to changes in the pressure gradient against which the pump is flowing. This gradient is determined by calculating the difference between inflow pressure and outflow pressure. If two pumps are connected in series, as is necessary in a heart replacement, this has some notable consequences. The pulmonary, or right-sided, pump delivers blood through the pulmonary vasculature to the left atrium. If the right pump delivers blood too rapidly, the left atrial pressure gradually rises. If it delivers blood too slowly, the left atrial pressure gradually decreases. Similarly, excessive function of the systemic or left-sided pump causes an increase in right atrial pressure, whereas inadequate function causes a decrease. Because left and right atrial pressures are major determinants in calculating the

Table 2 Pressure Responsivity of the Jarvik 2000 Ventricular Assist Device[a]

Pump speed (rpm)	Flow rate (liters/min) 1	2	3	4	5
12,000	0.060	0.079	0.057	0.093	0.034
11,000	0.060	0.072	0.077	0.074	0.034
10,000	0.066	0.067	0.081	0.052	
9,000	0.083	0.061	0.104	0.043	
8,000	0.125	0.063	0.064		

[a]Data expressed as liters/min/mm Hg.

Table 3 Pressure Responsivity of the HeartMate II Ventricular Assist Device[a]

Pump speed (rpm)	Flow rate (liters/min) 1	2	3	4	5	6
10,600	0.060	0.061	0.057	0.078	0.069	0.066
10,000	0.065	0.062	0.063	0.085	0.070	
9,000	0.068	0.068	0.082	0.087	0.072	
8,000	0.079	0.065	0.094	0.093		
7,000	0.086	0.075	0.091			

[a]Data expressed as liters/min/mm Hg.

Table 4 Pressure Responsivity of the Clinical MicroMed DeBakey Ventricular Assist Device[a]

Pump speed (rpm)	Flow rate (liters/min)							
	1	2	3	4	5	6	7	8
12,000	0.058	0.183	0.124	0.167	0.102	0.085	0.061	0.086
11,000	0.074	0.118	0.086	0.300	0.127	0.078	0.054	
10,000	0.111	0.109	0.117	0.336[b]	0.096	0.066		
9,000	0.147	0.141	0.222	0.147	0.082			
8,000	0.165	0.159	0.364[b]	0.107				

[a]Data expressed as liters/min/mm Hg.
[b]Values >0.3 liters/min/mm Hg.

pressure gradients across the left and right pumps and, therefore, how much flow each pump is producing, each pump plays an important role in determining the flow of the other. The degree to which this happens can be adjusted by modifying the inflow vanes and, in so doing, changing the amount of pump sensitivity to the pump pressure gradient. Maintaining a balance between the systemic and pulmonary circulations is something that the natural heart does well but pulsatile artificial hearts do poorly. This ability to autonomously equilibrate flow between two axial-flow pumps may mitigate this challenge. We have now demonstrated this clearly in 15 calves at >1 week after replacement of the native heart with a CFTAH, as we have described here.

It is also known that, during exercise, venous compliance decreases, resulting in increased venous return to the heart. This, in conjunction with the chronotropic response to exercise, causes the cardiac output to increase with exercise in the intact circulation. We have demonstrated the same effect in 2 calves exercising on a motorized treadmill at 3 weeks and 6 weeks, respectively, after total heart replacement with CFPs. By adjusting the inlet angle, as we have described, this effect could be one of the mechanisms that would allow a CFTAH to be exercise-responsive.

Figure 4, which represents the measured pressure–flow relationship of the modified MicroMed pump operating at 11,500 rpm, can be used to illustrate the notion of optimized axial-pump responsivity to pressure. Figure 4 shows that if this speed is chosen for the left pump of the CFTAH, the pump flow rate in the physiologic range can be obtained given normal peripheral vascular resistance and adequate venous return (approximately 5 liters/min at rest). In addition, Figure 4 shows two other interesting points. First, systemic flow can be significantly reduced with an increase in peripheral vascular resistance (labeled "A"). Note that, at the low and high limits of the flow rates, the pressure sensitivity of the pump is comparable to that of other axial-flow VADs (approximately 0.07 liter/min/mm Hg). Second, in the vicinity of 4 liters/min at 11,500 rpm (labeled "B"), the optimized pressure sensitivity of the modified MicroMed pump would automatically adjust the pump flow rate based on small changes in pump pre-load.

Enhanced pressure sensitivity may also reduce the possibility of atrial collapse under conditions of reduced venous return to either pump of the CFTAH. For example, a small reduction in the venous return, or pre-load, to the left pump of the CFTAH results in a small increase in left pump ΔP. If the pump is operating at a region of enhanced pressure sensitivity, this ΔP rise would cause a significant reduction in the left pump flow rate. As the left pump flow rate gradually decreases, less volume is removed from the left atrium, and the left pump pre-load progressively increases to maintain an intermediate, physiologically acceptable steady-state flow rate. In addition, operating the left and right pumps at the pressure-sensitive regions of their respective pressure–flow curves enhances autoregulation and achieves a natural flow balance, making a complex control

Table 5 Pressure Responsivity of the Modified MicroMed Pump[a]

Pump speed (rpm)	Flow rate (liters/min)						
	1	2	3	4	5	6	7
12,000	0.067	0.146	0.112	0.625[b]	0.128	0.074	0.057
11,000	0.088	0.078	0.243	0.364[b]	0.076	0.062	
10,000	0.109	0.147	0.385[b]	0.161	0.082		
9,000	0.111	2.550[b]	0.850[b]	0.093			
8,000	0.098	—[c]	0.278	0.090			
7,000	0.102	0.817[b]	0.150				

[a]Data expressed as liters/min/mm Hg.
[b]Values >0.3 liters/min/mm Hg.
[c]Negative value.

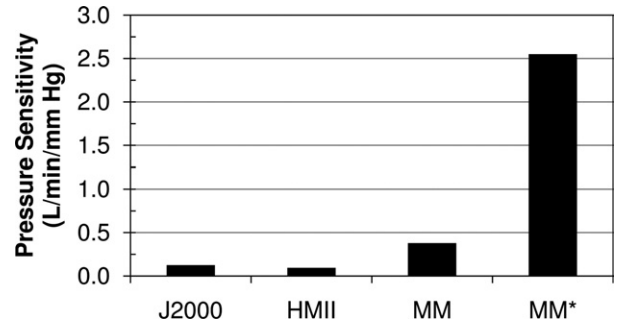

Figure 3 Maximum pressure sensitivity of four axial-flow pumps. HMII, HeartMate II; J2000, Jarvik 2000; MM, MicroMed DeBakey; MM*, modified MicroMed.

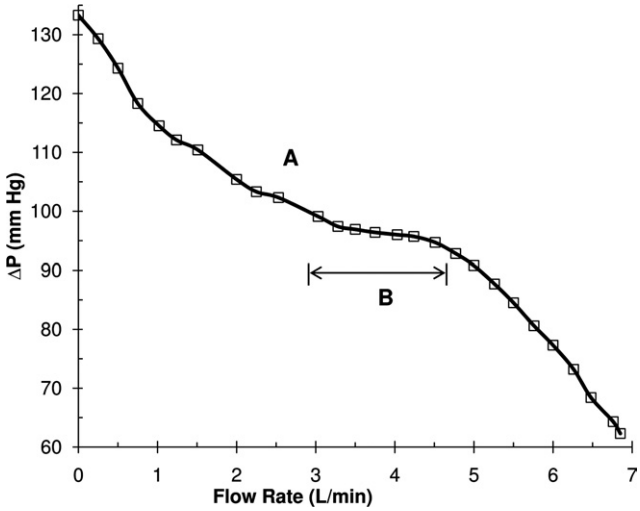

Figure 4 Pressure–flow curve of the modified MicroMed pump at 11,500 rpm, showing a region of improved pressure sensitivity.

system for the CFTAH unnecessary, except in extreme conditions of hypertension and hypovolemia.[7]

In our previous in vivo studies, we demonstrated that internal autoregulation at constant pump speeds can be achieved by varying the inflow pressures.[3] In the present study, we achieved a similar experimental demonstration of this responsivity by varying the outflow pressure and leaving the inflow pressure constant, thereby changing the pressure differential of the pump—the real key to autoregulatory performance. By using this methodology, we have demonstrated that the modified MicroMed axial-flow pump has an in vitro responsivity approaching that of the natural heart.[8] At the low and high extremes of flow, the pressure responsivity of the modified pump was similar to that of other clinically used axial-flow pumps; maximal pressure responsivity was obtained at intermediate, near-physiologic flow rates (approximately 2 to 4 liters/min). To show the differences in pressure responsivity of our modified pump compared with that of the Jarvik 2000, HeartMate II and clinical MicroMed DeBakey devices, we compared the responsivity at pump speed increments of 1,000 rpm and flow-rate increments of 1 liter/min, although we collected data at many intermediate pump speeds by using a smaller flow rate increment (see Methods). We realize that precise comparison of the pressure sensitivities of these pumps must be done at the same ΔP and flow rate, not at equivalent pump speeds.[4] In this study, we simplified the analysis by using the pump speed as a surrogate indicator of ΔP because we intended to detect broad differences between our modified pump and other clinically used pumps.

Although existing pulsatile devices have reduced morbidity and mortality rates among patients with terminal heart failure, the durability of these pumps is limited to <2 years. As for totally implantable artificial hearts, the pulsatile AbioCor Implantable Replacement Heart (AbioCor, Inc., Danvers, MA) is the only clinically available TAH designed for permanent use, but the longest any patient has been supported is about 1.5 years.[9] Implantable CFPs, however, have not been pumped to failure, and patients have been supported for up to 7.5 years without evidence of pump wear. Such long-term performance could be of enormous importance in the application of CFPs for total heart replacement.

In conclusion, we have demonstrated, in vitro, a near-physiologic pressure response of a modified CFP. Such technology offers the potential for development of a small, durable, long-term total heart replacement.

Disclosure Statement

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The authors have no conflicts of interest to disclose. The content is solely the responsibility of the authors and does not necessarily represent the official views of THI, NHLBI or the National Institutes of Health.

References

1. Garcia S, Kandar F, Boyle A, et al. Effects of pulsatile- and continuous-flow left ventricular assist devices on left ventricular unloading. J Heart Lung Transplant 2008;27:261-7.
2. Frazier OH, Tuzun E, Cohn W, et al. Total heart replacement with dual centrifugal ventricular assist devices. ASAIO J 2005;51:224-9.
3. Frazier OH, Tuzun E, Cohn WE, et al. Total heart replacement using dual intracorporeal continuous-flow pumps in a chronic bovine model: a feasibility study. ASAIO J 2006;52:145-9.
4. Khalil HA, Cohn WE, Metcalfe RW, et al. Preload sensitivity of the Jarvik 2000 and HeartMate II left ventricular assist devices. ASAIO J 2008;54:245-8.
5. Saxton GA Jr, Andrews CB. An ideal heart pump with hydrodynamic characteristics analogous to the mammalian heart. Trans Am Soc Artif Intern Organs 1960;6:288-91.
6. Akimoto T, Yamazaki K, Litwak P, et al. Rotary blood pump flow spontaneously increases during exercise under constant pump speed: results of a chronic study. Artif Organs 1999;23:797-801.
7. Khalil HA, Kerr DT, Franchek MA, et al. Continuous flow total artificial heart: modeling and feedback control in a mock circulatory system. ASAIO J 2008;54:249-55.
8. Guyton AC, Hall JE. Textbook of medical physiology, 10th ed. Philadelphia: Saunders; 2000.
9. Gemmato CJ, Forrester MD, Myers TJ, et al. Thirty-five years of mechanical circulatory support at the Texas Heart Institute: an updated overview. Tex Heart Inst J 2005;32:168-77.