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IN VIVO ACUTE PERFORMANCE OF THE CLEVELAND CLINIC SELF-REGULATING CONTINUOUS-FLOW TOTAL ARTIFICIAL HEART

Hideyuki Fumoto, MD, David J. Horvath, MSME, Santosh Rao, MD, Alex L. Massiello, MEBME, Tetsuya Horai, MD, Tohru Takaseya, MD, PhD, Yoko Arakawa, MD, Nicole Mielke, BS, Ji-Feng Chen, BS, Raymond Dessoify, AA, Kiyotaka Fukamachi, MD, PhD, and Leonard A. R. Golding, MB, BS, FRACS

Department of Biomedical Engineering, Lerner Research Institute, Cleveland Clinic, Cleveland, OH 44195

Abstract

Background—The purpose of this study was to evaluate the acute *in vivo* pump performance of a unique valveless, sensorless, pulsatile, continuous flow total artificial heart (CFTAH) that passively self-balances left and right circulations without electronic intervention.

Methods—The CFTAH was implanted in two calves with pump and hemodynamic data recorded at baseline over the full range of pump operational speeds (2,000-3,000 rpm) in 200-rpm increments, pulsatility variance, and under a series of induced hemodynamic states created by varying circulating blood volume and systemic and pulmonary vascular resistance (SVR and PVR).

Results—Sixty of the 63 induced hemodynamic states in Case #1 and 73 of 78 states in Case #2 met our design goal of a balanced flow and maximum atrial pressure difference of 10 mm Hg. The correlation of calculated vs. measured flow and SVR was high ($R^2 = 0.857$ and 0.832 , respectively), allowing validation of an additional level of automatic active control. By varying the amplitude of sinusoidal modulation of the speed waveform, 9 mm Hg of induced pulmonary and 18 mm Hg of systemic arterial pressure pulsation were achieved.

Conclusions—These results validated CFTAH self-balancing of left and right circulation, induced arterial flow and pressure pulsatility, accurate calculated flow and SVR parameters and the performance of an automatic active control mode in an acute *in vivo* setting in response to a wide range of imposed physiologic perturbations.

In 1964, the National Institutes of Health established the artificial heart program to promote the development of the total artificial heart (TAH) and other cardiac assist devices, due largely to the efforts of pioneering Dr. Michael DeBakey. In 1969, the first implantation of a temporary TAH into a human was done by Dr. Denton Cooley.¹ In 1982, Dr. William DeVries became the first to implant a permanent TAH (Jarvik-7) into a dying patient.² Today, the existing clinical TAH devices - the AbioCor™ (Abiomed®, Danvers, MA) and the CardioWest™ (SynCardia, Tucson, AZ)³⁻⁷ - are still large, pulsatile devices, preventing their use in many

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Corresponding Author: Leonard A. R. Golding, MB, BS, FRACS Department of Biomedical Engineering / ND20 Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195 Phone: (216) 444-1205; Fax: (216) 444-9198; E-mail: goldinl@ccf.org.

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male patients and most female patients. Furthermore they contain 4 valves with a polymer diaphragm that limit durability and increase the potential for thromboembolic events.

The Cleveland Clinic has developed a unique valveless, sensorless, pulsatile, continuous-flow total artificial heart (CFTAH) that self-balances left and right circulation without electronic intervention. Preliminary results from *in vitro* mock circulatory loop testing have demonstrated passive self-regulation of CFTAH flows and atrial pressures while preserving flow and pressure pulsatility by sinusoidal modulation of the speed waveform.⁸ The purpose of this corresponding *in vivo* study was to evaluate the pump performance in an acute setting in response to a wide range of imposed physiologic perturbations to validate its *in vitro* performance characteristics.

Materials and Methods

Configuration and Characteristics of the CFTAH

The CFTAH is small at 6 cm in diameter and 10 cm in body length, with a priming volume of 37 ml (Figure 1). As previously described in detail,⁸ this design allows for a degree of free axial movement of one moving part (rotating assembly) in the direction of differential forces across the rotating assembly caused by atrial pressure differences. This axial movement changes the opening of an aperture at the outlet diameter (OD) of the right impeller, affecting relative left/right performance in a direction to correct the atrial pressure imbalance.

Additionally, the CFTAH uses speed modulation to create a simulated cardiac cycle of induced arterial pulsatile flows and pressures that can be used as a potential additional means of physiologic control for the CFTAH. The addition of an automatic speed control mode that responds to sensorless derived physiologic inputs calculates a target pump flow based on sensed systemic vascular resistance (SVR) and implements automatic speed changes to adjust the sensed pump output to match the targeted flow. Also implemented in this control algorithm is an inverse relationship between SVR and the amplitude of speed modulation ($\pm 25\%$ of the mean pump speed to a nonpulsatile condition).

The pump is powered through a 3-conductor percutaneous cable to the speed control module which is powered using a 20 VDC supply. The clinical version will use batteries and/or a power supply. The power consumption is approximately 13 Watts at 8 L/min with 20 mm Hg and 80 mm Hg of right and left afterloads, respectively, which generates 11.6 Watts of heat. About 40% is generated primarily in the stator windings and dissipated by heat transfer from the surface of the stator assembly, which has a very large surface area of 97 square cm. The remaining energy is dissipated directly to the blood via impeller inefficiency and hydrodynamic bearing drag.

Study Design and Animal Model

Two male Holstein calves (91.0 and 100.2 kg) were used for acute studies. The present study was approved by the Cleveland Clinic's Institutional Animal Care and Use Committee, and all animals received humane care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources and published by the National Institutes of Health (NIH Publication No. 86-23, revised 1996).

Surgical Procedures

Through a median sternotomy under general anesthesia, cardiopulmonary bypass (CPB) was established after full heparinization (300 IU/kg). Both ventricles were resected at the atrioventricular groove, and inflow cuffs were sutured to the atria. The aorta and the pulmonary artery were anastomosed to outflow grafts. Both chambers of the CFTAH pump were primed with 25% albumin solution with 20 U heparin per cubic centimeter of albumin added, then

they were connected to the inflow and outflow conduits. After both atria and pump housings were de-aired, the CFTAH was started with rapid weaning from CPB. Pump performance was evaluated at baseline after hemodynamic stability was established, followed by the induced hemodynamic states described below.

Hemodynamic Analysis of Pump Performance

The following data were continuously monitored with the chest remained open: 1) right and left atrial pressure (RAP and LAP) via a fluid-filled catheter on the atrial cuffs, 2) systemic arterial pressure (AoP) via a fluid-filled catheter in the carotid artery or on the left pump outlet graft, 3) pulmonary arterial pressure (PAP) via a fluid-filled catheter on the right pump outflow graft, 4) right and left pump flows via Transonic ultrasonic flow probes, and 5) pump speed motor current from the CFTAH controller. In Case #1, pump flows were measured with 28-mm-diameter ultrasonic perivascular flow probes (Transonic Systems Inc., Ithaca, NY) placed on the right and left outflow grafts. In Case #2, a Transonic inline flow probe was placed in the left pump inlet pathway and a 28-mm Transonic perivascular flow probe was used on the right pump outlet. Hemodynamic and pump performance parameters were digitized in real time at a sampling rate of 200 Hz with a PowerLab data acquisition system (ADInstruments, Inc., Mountain View, CA) and stored on a hard disk. The data were analyzed using Excel® software (Excel 2000, Microsoft® Corporation, Redmond, WA).

Evaluation of Pump Performance under various hemodynamic states

Because it is a great challenge for any TAH to balance the flow and atrial pressures at mismatches of SVR and pulmonary vascular resistance (PVR), the study was designed to expose the CFTAH to as many conditions of varying vascular resistance as possible. Physiologic and pump performance data were recorded at the following series of induced hemodynamic steady states: 1) baseline, 2) high SVR, 3) high PVR, 4) high SVR + high PVR, 5) low circulating blood volume (CBV) (RAP = 0-2 mm Hg), 6) high CBV (RAP > 10 mm Hg), 7) low SVR + low PVR, and 8) low SVR + high PVR. A state of high SVR (1,600-2,400 dyne·sec·cm⁻⁵) or high PVR (400-600 dyne·sec·cm⁻⁵) was induced by partially clamping the left or right outflow graft, respectively. A low CBV was induced by venous drainage of blood into the CPB reservoir and high CBV by saline infusion. A state of low SVR + low PVR was induced with nitroprusside administration, and a state of low SVR + high PVR by partially clamping the right outflow graft during nitroprusside administration.

Under all conditions, pump performance was evaluated by three methods. First, the pump was placed in automatic control mode and allowed to operate until a hemodynamic steady state was reached. Next, the pump was operated in fixed-speed mode, and pump speed was manually adjusted to optimize hemodynamics. Finally, a full dataset was taken at 200-rpm increments of pump speed from the minimum to maximum pump speed capability.

Cyclic Speed Modulation Frequency and Amplitude Effect on Hemodynamics

Sinusoidal speed modulation frequency (60, 80, 100 and 120 bpm) and amplitude (max/min speed ± 15 and 25% of the mean speed) were investigated for their effects on the induced systemic and pulmonary arterial pulse pressures and total pump flow. A second level of control was implemented based on an inverse relationship between the amplitude of the sinusoidal speed signal (max/min speed ± 0 -25% of the mean speed) and calculated SVR to improve atrial balance during high SVR conditions.

Results

Anatomical fitting

The CFTAH fit well anatomically in these 91- and 100-kg calves with uncomplicated surgical procedures in both cases using a median sternotomy approach (Figure 2).

Validation of Passive Self-Regulation of Pump Flows and Atrial Pressures

Figures 3 and 4 show that over a very wide range of vascular resistances tested, 60 of the 63 induced hemodynamic states in Case #1 and 73 of 78 states in Case #2 met our design goal of a maximum atrial pressure difference of 10 mm Hg [(LAP - RAP) between +10 and -10 mm Hg]. The extended range of SVR and PVR relationships tested is demonstrated in both figures, with the enclosed box showing the normal range of values for SVR and PVR. In Case #1 (Figure 3), the only conditions in which the atrial balance criteria were not met occurred (a) at one condition of very high PVR (804 dyne·sec·cm⁻⁵) where LAP - RAP was -11 mm Hg and (b) at two data points at high pump speeds (2,800 and 3,000 rpm) and high CBV (3 L of saline infused) where LAP - RAP was +11 and +13 mm Hg, respectively. The LAP vs. RAP relationships for Case #2 are shown in Figure 5. For all conditions tested, LAP remained below 14 mm Hg, except for one condition of high CBV (LAP = 18.2). RAP remained above 0 mm Hg, except for three conditions of intermittent partial right atrial suction (described below).

Evaluation of Pump Performance over the Full Range of Operational Speeds

Figure 6 shows pump performance and hemodynamic parameters at baseline conditions over the full range of pump operational speeds in Case #2. Pump flow increased (6.0-10.7 L/min) while atrial pressures remained within physiologic ranges (1-9 mm Hg) with a maximum atrial pressure difference of 6.3 mm Hg. Figure 7 shows the CFTAH response to high SVR + high PVR conditions (1,198-1,579 and 392-432 dyne·sec·cm⁻⁵, respectively) over the speed range of 2,000-3,000 rpm in Case #2. Pump flow increase was limited (4.0-6.7 L/min) while atrial pressures remained within physiologic ranges (5-9 mm Hg) with a maximum atrial pressure difference of 2.0 mm Hg. The limited flow response under these high-afterload conditions [AoP (138 mm Hg) and PAP (41 mm Hg)] prevents hypertension and possible end-organ systemic damage.

Validation of CFTAH Algorithm Flow and SVR Calculations

Figures 8 and 9 show measured pump flow and SVR vs. calculated pump flow and SVR for Case #2. Linear regression performed on the flow and SVR data showed R² values of 0.86 and 0.83, respectively, validating the accuracy of the pump flow and SVR calculations demonstrated in our *in vitro* data.⁸

Automatic Control Mode Response to Induced Hemodynamic Conditions

Figure 10 from Case #2 shows the pump and hemodynamic changes under automatic control while increasing SVR from 637 to 1,333 dyne·sec·cm⁻⁵. The automatic control mode data plotted represents the final steady-state condition achieved by automatic control in response to the rapid increase in SVR. Under this high SVR condition, average pump speed was actively increased (from 2,500 to 3,000 rpm) to match the derived target flow, which limited the AoP increase from 73 to 131 mm Hg via a decrease in pump flow by 1.3 L/min. If the controller did not increase speed, the pump output would decrease significantly in response to this high SVR state; however, if it kept its target flow at or higher than the baseline of 8.9 L/min, the AoP would have been driven much higher than 131 mm Hg. The atrial pressures and atrial balance remained within normal limits and a decrease in pump speed modulation amplitude from ±25% of average speed to approximately ±10% was implemented to improve the atrial balance.

Effects of Cyclic Speed Modulation Frequency and Amplitude on Hemodynamics

The hemodynamic response (Figure 11) from Case #2 to changing the speed modulation frequency from 60 to 120 bpm in 20 bpm increments validated *in vitro* findings that pump flow is not significantly affected by modulation frequency. Similarly, mean pump flow also remained unchanged at 6.1-6.2 L/min when the amplitude of the sinusoidal speed modulation was varied from $\pm 25\%$ to 15% to 0% of the mean speed, validating *in vitro* findings that pump flow is not significantly affected by the amplitude of the cyclic speed modulation. The degree of induced arterial pulsation demonstrated was 18 mm Hg for the AoP pulse pressure at $\pm 25\%$ speed amplitude modulation and 11 mm Hg at $\pm 15\%$. The pulmonary circulation similarly showed a 15 and 9 mm Hg pulse pressure induced on the PAP waveform at $\pm 25\%$ and $\pm 15\%$, respectively. Figure 12 from Case # 1 demonstrates a similar relationship between the amplitude of speed modulation and induced arterial pressure pulsation.

Atrial Suction

For all conditions tested in the expected speed range for the CFTAH (2,000-2,800 rpm), the incidence of an atrial pre-suction or suction condition, defined by our laboratories as RAP or LAP of less than -3.0 mm Hg, was limited to only 15 out of 141 recorded steady-state conditions at altered physiologic states of varying CBV, SVR, and PV. The only conditions under which the atrial balance criteria were not met occurred during the combination of operation at maximum pump speed (3,000 rpm) and at high PVR and low CBV. Under these conditions, low RAP and very high pump speeds resulted in intermittent partial right atrial suction. A suction condition results in only partial occlusion, because the sudden drop in left or right pump inlet pressure causes an immediate and automatic response in the pump. If the right inlet pressure drops, the rotating assembly moves to the right, and the right pump aperture closes to relieve the suction condition. If the left inlet pressure drops, the rotating assembly moves to the left, and the right aperture opens, increasing the right aperture, boosting the right output and filling the left atrium. This cycle of partial occlusion repeats until the speed is reduced to eliminate the condition. Of the 15 cases studied, only two cases showed either RAP or LAP below -8 mm Hg. Intermittent suction was reversed by decreasing mean pump speed, decreasing speed modulation amplitude or correcting the pathologic physiologic state.

Discussion

These acute studies successfully demonstrated the following surgical and performance characteristics: (1) good anatomical fit with uncomplicated surgical implantation procedures, (2) good overall pump performance over the full range of operational speeds with pump flows in excess of 10 L/min, (3) good correlation of measured pump flow and SVR values with calculated pump flow and SVR values, (4) passive autoregulation of flows and pressures demonstrated by excellent atrial pressure balance in response to 141 recorded steady states at various altered physiologic states, (5) significantly induced arterial pressure pulse and flow pulsation using cyclic speed modulation, (6) successful implementation of the sensorless CFTAH Automatic Speed Control, and (7) over the range of 2000 to 2800 rpm, the incidence of atrial suction, defined by RAP or LAP of less than -8 mm Hg, was limited to only two out of 141 recorded steady-state conditions at various altered physiologic states.

The CFTAH device is an ultra-simple, implantable TAH, which has only one moving part and only one electromechanical component. There is no need for problematic components found in other pulsatile TAH devices such as valves, sensors, actuation mechanisms, or flexible blood pumping elements. This novel design reduces the overall size (6 cm diameter and 10 cm in body length with a priming volume of 37 ml), eliminating size limitation to male and female end-stage heart failure patients in need of a TAH. Its simplicity greatly increases the reliability and biocompatibility of TAH devices and significantly reduces the cost. Its small percutaneous

drive cable requires only the three motor phases and no other leads for sensors or active bearing controls and should produce a very low incidence of drive line and pump pocket infections currently seen with continuous-flow percutaneous ventricular assist devices.

Although these acute experiments were performed using relatively big calves (91 and 100 kg), the pericardial space was sufficient for this small CFTAH, as shown in Figure 2. We are confident that we will be able to use much smaller calves (body weights as low as 60 kg) without any fitting issues in future experiments.

There were several limitations in this study. The number of animals was very small, and the experiment duration was limited to 4-6 hours. We did not evaluate biocompatibility, because these were acute experiments and the materials used for this prototype device were not ideal for biocompatibility testing; however, our initial bench hemolysis studies with calf blood showed surprisingly low values (normalized index of hemolysis of 0.008 mg/dL) considering the nonoptimal materials used.

Conclusion

This *in vivo* study validated the passive self-regulation of left and right circulation of this innovative CFTAH seen in earlier *in vitro* testing in response to a wide range of imposed physiologic perturbations of RVR, SVR, and CBV along with induced arterial pressure and flow pulsatility and implementation of an automatic control algorithm based on sensorless physiologic feedback.

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Figure 1.
(A) Assembled continuous-flow total artificial heart (CFTAH) and (B) Partial disassembly of CFTAH pump.

Figure 2.
A picture of the CFTAH implantation in a calf's pericardial space (Case #1).

Figure 3.

Case #1; PVR vs. SVR for all conditions tested at pump speeds 2,200-3,000 rpm.

Figure 4.
Case #2, PVR vs. SVR for all conditions tested at pump speeds 2,200-3,000 rpm.

Figure 5.
Case #2, RAP vs. LAP relationship for all conditions tested at pump speeds at 2,200-3,000 rpm.

Figure 6.

Case #2, Hemodynamic response to speed increase at baseline. All data at a sinusoidal speed modulation rate of 80 bpm and $\pm 25\%$ mean speed amplitude.

Figure 7.

Case #2, Hemodynamic response to speed increase at high SVR + high PVR. All data at a sinusoidal speed modulation rate of 80 bpm and $\pm 25\%$ mean speed amplitude.

Figure 8.
Case #2, Measured pump flow vs. calculated pump flow.

Figure 9.
Case #2, Measured SVR vs. calculated SVR.

Figure 10.
Case #2, Automatic control mode response to increasing SVR.

Figure 11.

Case #2, Speed modulation rate vs. pump flow at 2,600 rpm and $\pm 25\%$ sinusoidal speed modulation amplitude.

Figure 12.
Case #1, Sinusoidal speed modulation amplitude effects.