Total Heart Replacement with Dual Centrifugal Ventricular Assist Devices

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In an ovine feasibility study, we implanted two HeartMate-III centrifugal ventricular assist devices (VADs) for total heart replacement. With cardiopulmonary bypass support, both ventricles were transected at the atrioventricular groove, preserving a rim of ventricular tissue. The atrioventricular valves were excised, and the aorta and pulmonary artery were transected above the ventriculoarterial valves. An interatrial septal window was created by excising the foramen ovale. The VADs' sewing rings were attached to the left and right ventricular remnants, respectively. Outflow grafts were anastomosed to the aorta and pulmonary artery. The left VAD operated continuously at 4,500 rpm. Right VAD speed increased from 2,000 to 4,500 rpm in 500 rpm increments. Outflow graft flow, pressure, oxygen saturation, and shunt direction were recorded. The pulmonary artery to aortic ratio of flow and pressure increased from 0.26 and 0.15 (at 2,000 rpm) to 1.21 and 0.53, respectively (at 4,500 rpm). The interatrial shunt, which was right to left at lower right VAD speeds, progressed to bidirectional, then to left dominant as right VAD speed increased. Outflow-graft oxygen saturation was reflective of the shunt direction. In this acute experiment, total heart replacement with continuous flow VADs satisfactorily balanced left and right ventricular flows and preserved the physiologic circulatory response. *ASAIO Journal* 2005; 51:224–229.

Congestive heart failure (CHF) remains an important and increasing cause of cardiovascular disability and premature death in the United States.[1] Despite advances in medical therapy, heart transplantation is still the primary therapeutic option for patients with end-stage CHF.[2] However, the limited availability of donor hearts has led to the use of ventricular assist devices (VADs) to save patients who would otherwise not survive until transplantation.[3] Initially, these devices were pulsatile and required prosthetic valves, flexing membranes, and external vent tubes.[4] During the past decade, however, the usefulness of continuous flow devices increasingly has been explored for mechanical circulatory assistance. The design of these devices can be based upon axial[5,6] or centrifugal[7] flow principles. Because they are smaller than conventional pumps, have no valves or diaphragms, and need no compliance chamber, continuous flow pumps have the potential for improved safety, better durability, and lower cost. They have proved highly reliable in clinical use. For more than 5 years, the Jarvik 2000 FlowMaker axial flow pump (Jarvik Heart, Inc., New York, NY) has been implanted without a single instance of pump failure; one patient has now had the device for more than 4.5 years and continues to do well.

Current total artificial hearts (TAHs) are pulsatile. To produce a physiologic cardiac output, they are suitable for implantation only in adults of greater than average size.[8] Therefore, complete cardiac (biventricular) replacement with continuous flow pumps is an interesting alternative, as these devices open up the potential benefits of this technology to patients of smaller size while remaining suitable for larger patients as well. Much like the Starling response achieved with pulsatile pumps, centrifugal pump output can increase with a growing preload; however, unlike pulsatile pumps, centrifugal devices are also sensitive to the afterload. This characteristic may allow pumps placed in series, as in the classic Saxton and Andrews experiment,[9] to autoregulate their output in response to instantaneous variations in systemic and pulmonary pressures and return flows.

In the present study, we used two centrifugal pumps (the HeartMate III, Thoratec Corporation, Pleasanton, CA) for biventricular replacement in a sheep model. We addressed the challenge of preload imbalance between the pulmonary and systemic pumps by surgically creating a large atrial septal defect (ASD). We hoped that the resulting blood flow between the atria would adjust the left- and right-sided flow imbalance with minimal effects upon oxygenation.

Materials and Methods

HeartMate III

The HeartMate III is a compact, implantable, centrifugal VAD with a magnetically levitated rotor and no mechanical bearings. The steady state pump pressure head *versus* volume flow rate (H-Q) characteristically shows that the pump can generate 7 L of flow against 135 mm Hg between 4,500–5,000 rpm at its design point (**Figure 1**). The pump's design has been described in detail elsewhere.[10]

Animal Model

A sheep weighing 59 kg was used in the study. The animal received humane care in compliance with the *Principles of Laboratory Animal Care* (National Society of Medical Research) and the *Guide for the Care and Use of Laboratory Animals* (National Institutes of Health publication No. 85–23, revised 1996). Our Institutional Animal Care and Use Committee approved all of the protocols.

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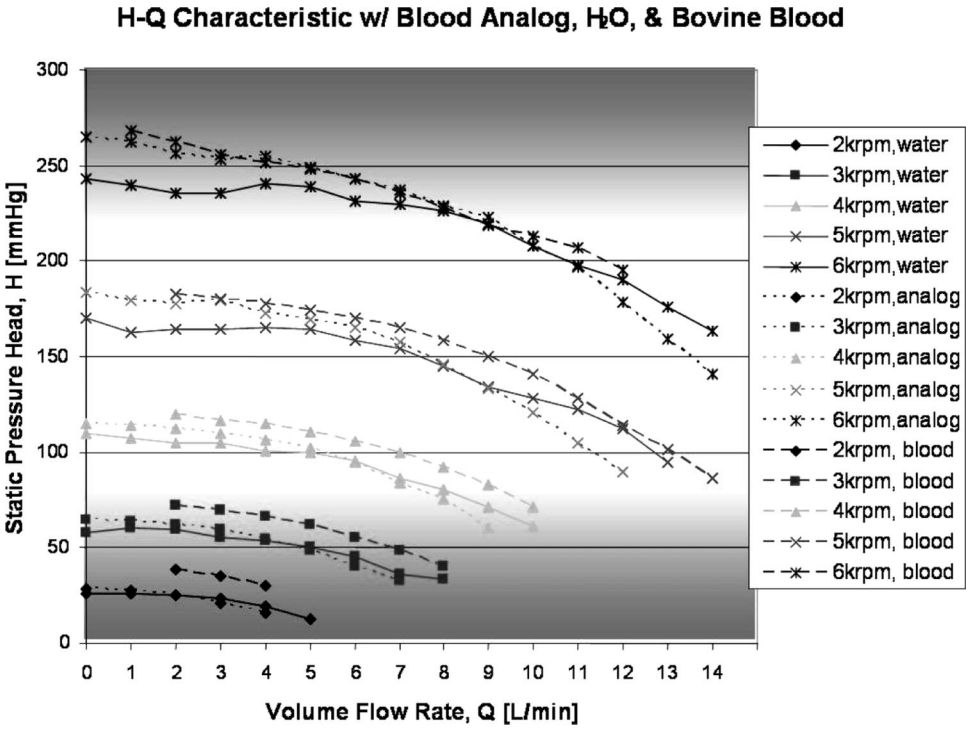

Figure 1. H-Q characteristic with blood analog, water, and bovine blood. The pump can generate 7 L of flow against 135 mm Hg between 4,500–5,000 rpm at its design point. H-Q, steady-state pump pressure head *versus* volume flow rate.

Anesthesia and Surgical Preparation

A standard anesthesia protocol was followed. Food was withheld for 12 hours before induction of anesthesia. The sheep was premedicated with glycopyrrolate (0.02 mg/kg) and xylazine (0.2–0.7 mg/kg) intramuscularly. A 12 F triple lumen venous catheter was inserted percutaneously into the right external jugular vein. Anesthesia was induced with intravenous ketamine (10–20 mg/kg). A cuffed endotracheal tube and an orogastric decompression tube were inserted. General anesthesia was maintained with isoflurane (1–3%) in oxygen (40–100%). The sheep was placed upon the operating table in the right lateral decubitus position. Electrocardiographic leads were connected, and a rectal temperature probe was inserted.

Device Implantation

The left carotid artery and jugular vein were exposed for cardiopulmonary bypass (CPB) cannulation. A left thoracotomy was then performed in the fifth intercostal space, and the fifth rib was removed. Once the heart was exposed, heparin (3 mg/kg) was administered. A 17F cannula was placed in the left common carotid artery and connected to the arterial line of the heart-lung machine (Terumo SX-10 membrane oxygenator and Terumo roller pump; Terumo, Inc., Tokyo, Japan). After the superior and inferior vena cavas were selectively cannulated and were attached to the venous line with a Y connector, CPB was initiated. The aorta was cross-clamped, and the body temperature was cooled to 30°C.

The left and right ventricles were transected 1 cm below the atrioventricular (AV) groove, leaving a rim of ventricular tissue suitable for device attachment. The AV valves were excised, and the aorta and pulmonary artery (PA) were transected at the AV groove, leaving a rim of ventricular tissue suitable for device attachment. A septal defect (1 cm^2) was created between the atria by excising the foramen ovale. The sewing rings of both pumps were sutured to the retained ventricular rims with 2–0 polypropylene sutures reinforced with Teflon felt pledgets. The right and left inflow cannulas were inserted into the sewing rings of their respective cuffs. The 16 mm Dacron outflow grafts were anastomosed in end to end fashion to the aorta and PA, respectively, and were connected to the corresponding pumps. After the pumps and grafts were deaired, both pumps were started. Once the body temperature was normalized (37.7–38.8 °C), the sheep was slowly weaned from CPB. **Figure 2** shows the implanted dual pumps functioning as a total heart replacement system.

Intraoperative Hemodynamic Assessment

A pressure catheter was inserted *via* the left internal thoracic artery and was advanced proximally into the immediate vicinity of the aortic valve to measure the aortic pressure (AoP). Once surgery was completed, a pressure catheter was also placed in the common PA to measure the pulmonary artery pressure (PAP). Two 16 mm ultrasonic flow probes (Transonics, Inc., Ithaca, NY) were then placed on the right and left outflow grafts to measure the right ventricular assist device (RVAD) and left ventricular assist device (LVAD) outputs (Q_R and Q_L, respectively). The data were continuously recorded by a 16 channel computer data acquisition system (Ponemah System, version 3.3; Gould Instrument Systems Inc., Valley View, OH).

The LVAD was operated at a constant speed of 4,500 rpm. The RVAD speed was gradually increased from 2,000 to 4,500 rpm at 500 rpm intervals. The hemodynamic values were assessed for 10 minutes at each pump setting.

In the absence of directly measured right and left atrial pressures (RAPs and LAPs, respectively), these parameters

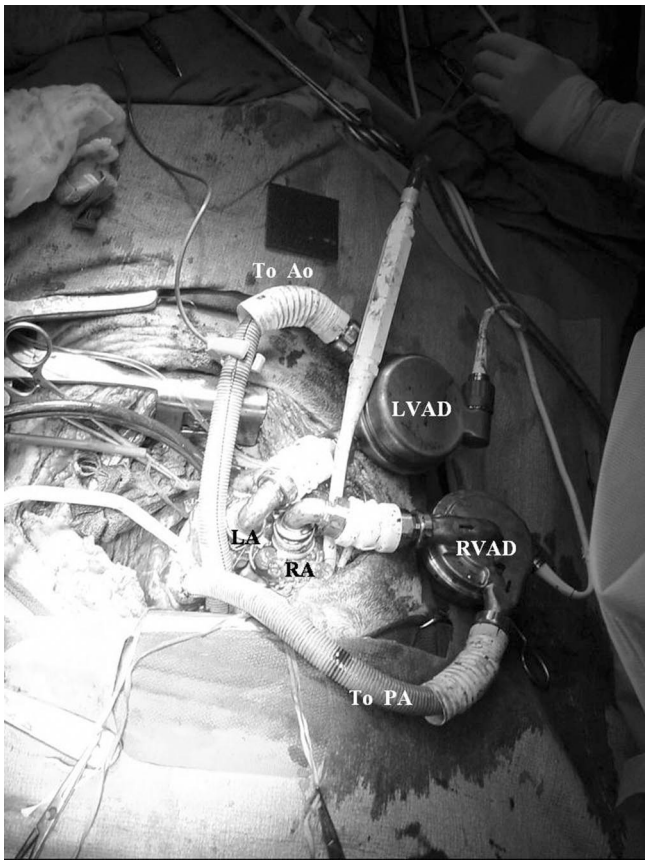

Figure 2. The implanted dual pumps functioning as a total heart replacement system. Ao, aorta; LVAD, left ventricular assist device; PA, pulmonary artery; RVAD, right ventricular assist device.

were calculated from H-Q curves for known rpm, pump flow, and back pressure (PAP and AoP).

Echocardiographic Assessment

Serial two-dimensional, transepicardial studies were conducted at each pump speed. Echocardiographic assessment was performed according to the guidelines of the American Society of Echocardiography[11] with a Sonos 2000 ultrasound system (Hewlett-Packard, Palo Alto, CA), equipped with a 2.5 MHz phased array transducer. Color Doppler echocardiography and injection of agitated saline contrast material into the right atrium were used to assess interatrial shunts at different pump settings.

Blood Gas Analysis

An 18 gauge angiocatheter was inserted into the right (PA) and left (aortic) outflow grafts to draw blood samples. One sample was taken from each side, at each pump speed, to assess the oxygen saturation in the outflow grafts. A Novastat Profile M blood gas analyzer (Nova Biomedical Company, Waltham, MA) was used for blood gas analysis.

Results

Table 1 shows the effects of increased RVAD speed upon the left and right pumps' outflow, mean PAP, AoP, RAP, LAP, interatrial shunt, oxygen saturation, and atrial collapse.

As the RVAD speed was increased, the PA/aortic flow (Qp/Qs) ratio increased from 0.26 and 0.15 at 2,000 rpm to 1.21 and 0.53 at 4,500 rpm. Higher RVAD speeds also resulted in an increased PA/AoP ratio and a decreased right to left atrial shunt, which gradually became a left dominant bidirectional shunt, as shown by color Doppler echocardiography (**Figure 3, A and B**).

The calculated right and left atrial pressures reflected the echocardiographic shunt directions, the shunt becoming bidirectional when the interatrial pressures equalized between the left and right sides.

The results of blood gas analysis in the outflow grafts were also consistent with the echocardiographic findings, showing a gradual increase in right-sided oxygen saturation at increased RVAD speeds.

At no pump speed did the atria collapse.

Discussion

In 1955, experiments by Wesolowski[12] suggested that an arterial pressure pulse might not be necessary to maintain peripheral vascular tone. However, no chronic experiments were performed that would give researchers the confidence to develop nonpulsatile devices for long-term support. Therefore, investigators focused upon developing pulsatile blood pumps to support patients with end-stage heart failure. In 1980, the National Heart, Lung, and Blood Institute (NHLBI) issued a request for proposal (RFP) for the development of a totally implantable, transcutaneously powered, pulsatile LVAD that could support patients for at least 2 years. However, develop-

Table 1. Effects of Increased Right Ventricular Assist Device Speed Upon Left and Right Outflow Graft Flow, Systemic and Pulmonary Pressures, Interatrial Shunting, Oxygen Saturation, and Atrial Collapse

	RVAD/LVAD Speed (rpm)					
Variable	2,000/4,500	2,500/4,500	3,000/4,500	3,500/4,500	4,000/4,500	4,500/4,500
PA/Ao flows (L/min)	2.8/10.6	3.8/8.9	5.0/8.4	8.3/9.8	9.6/10.0	10.9/9.0
PA/Ao pressures (mm Hg)	12/78	26/69	29/75	40/92	40/90	45/84
Interatrial shunt (ECHO)	R to L	R to L	R to L	BD	BD	BD
PA/Ao O_2 saturation (%)	83.4/87.1	89.8/94.8	94.9/96.5	97.0/99.6	96.7/99.6	97.7/99.6
R/L atrial collapse	No	No	No	No	No	No

Ao, aortic; BD, bidirectional; ECHO, echocardiographic; L, left; LA, left atrium; LVAD, left ventricular assist device; PA, pulmonary artery; R, right; RA, right atrium; RVAD, right ventricular assist device.

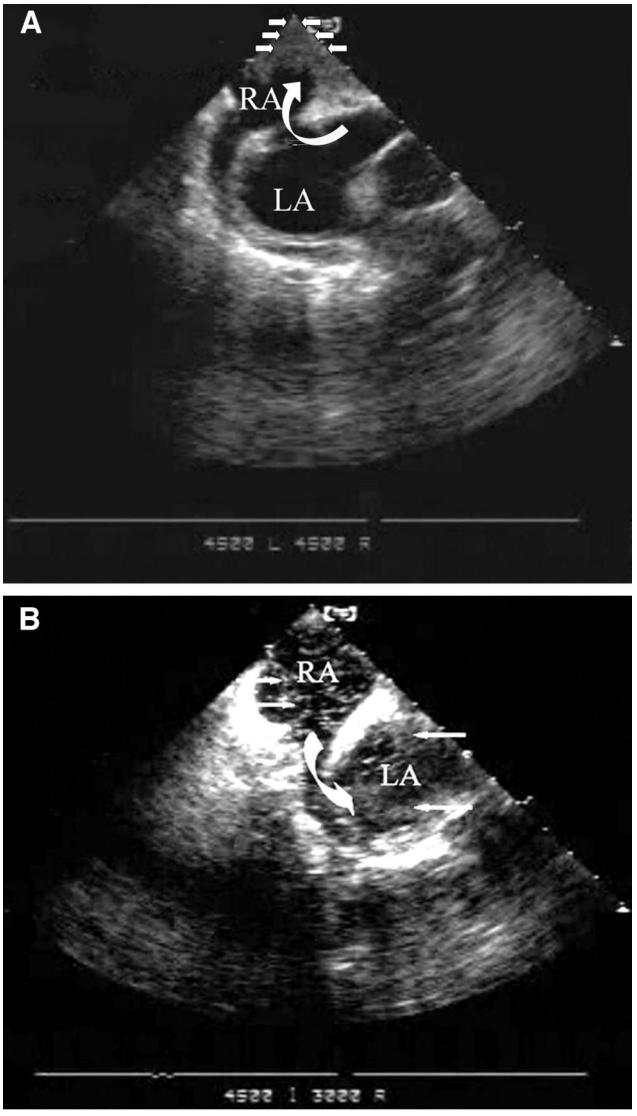

Figure 3. Echocardiograms showing (A) a right to left shunt when the right ventricular assist device was set at 3,000 rpm, while the left ventricular assist device was operating at 4,500 rpm (large arrow). The bubbles injected into the right atrium were disseminated in the right and left atria (small arrows). (B) Left to right shunt when both pumps were set at 4,500 rpm (large arrow). The bubbles injected into the right atrium were sucked into the appendix (small arrows). LA, left atrium; RA, right atrium

ment of such a pump was hindered by the inability to design a compliance chamber that could be implanted for 2 years without venting (venting was prohibited in the initial RFP). This difficulty led the senior author (O.H.F.) to attempt to use implantable continuous flow pumps as an alternative to the pulsatile technology.

An early procedure using continuous flow pumps was reported in 1979,[13,14] when two extracorporeal Blackshear-Medtronic centrifugal pumps were used extracorporeally for a calf with a fibrillated heart; the calf was kept asystolic for 34 days. In 1985, our laboratories undertook biventricular replacement in a porcine model, using a pair of totally implantable continuous flow Alpha Pumps (Biomedicus Inc., Eden Prairie, MN) (**Figure 4**). These centrifugal pumps represented a special modification of the Rafferty-Kletschka stacked cone impeller design; they were a precursor of the current AB 180 (Medtronic) and had been miniaturized to accommodate full intrathoracic placement. The Alpha Pumps were implanted as biventricular assist devices in two pigs. The chest was closed, and the animals survived for 5 days. On the last day, the ventricles were fibrillated to achieve totally nonpulsatile circulation. Atrial filling pressures were monitored continuously and corrected as necessary. The animals tolerated mechanical circulatory support well with minimal hemolysis but had skin necrosis at the site of transcutaneous transmission of the magnetic coupling, which we were also testing.

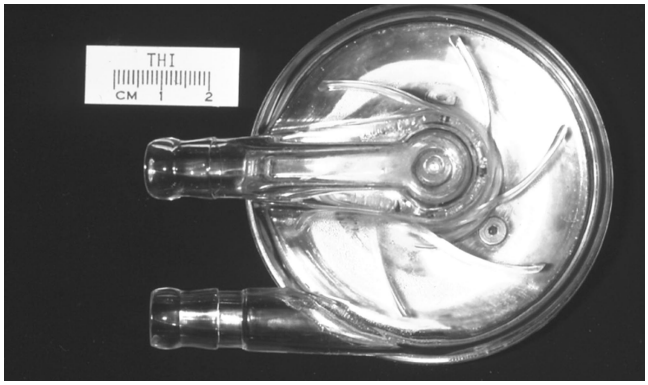

Figure 4. The Alpha Pump, which represented a special modification of the Rafferty-Kletschka stacked cone impeller design. Alpha Pumps were a precursor of the current AB 180 (Medtronic) and were miniaturized to accommodate full intrathoracic placement.

In 1989, we successfully used biventricular Biomedicus pumps (Biomedicus-Medtronic) as bridges to transplantation in a 9 year old boy with total asystole.[15] Experience with this device and the Hemopump (first used clinically in 1988),[16] showed that short-term nonpulsatile support could be achieved without hemolysis and with normalization of end organ function. Indeed, clinical success with the Hemopump led to further development of the long-term, implantable, continuous flow LVADs in wide use today.[17]

Total heart replacement with dual pulsatile Thoratec VADs (Thoratec Corporation, Pleasanton, CA) in two patients has been previously reported. The first patient, who had chronic cardiac allograft rejection, was successfully supported for 9 months.[18] The second patient, who had an ischemic cardiomyopathy and thrombus formation involving all four cardiac chambers, was supported for 26 days.[19] In both cases, the devices were positioned extracorporeally because of their large size. Indeed, device size is a fundamental problem of biventricular implantable cardiac replacement. This problem is compounded by the accoutrements necessary for implanting a portable, untethered, long-term support device. The chief advantage of nonpulsatile pumps over their pulsatile counterparts is a reduced size, which facilitates the intracorporeal placement of two pumps as well as their necessary components.

In the present case, after biventricular excision, dual centrifugal pumps were attached to the preserved atria. This allowed the totally nonpulsatile systemic and pulmonary circulations to be studied in the acute setting.

The left thoracotomy is an ideal approach for total heart

replacement with dual centrifugal VADs in the ovine model. The atria, PA, and aorta are easily accessible with this approach, which allows rapid anastomosis of the right and left outflow grafts and sewing rings, followed by dual VAD implantation. The ventricular remnants provide enough tissue support for anastomosis of the sewing rings. The native atria are preserved, both to serve as a reservoir and to allow proper balance of the left and right ventricular flow by means of a surgically created atrial communication. The left-right balancing capacity of the interatrial shunt in a total artificial heart system was previously reported by the University of Utah group, which subsequently validated this concept *in vitro* and *in vivo*.[20–24] To our knowledge, we are the first to have applied this concept to cardiac replacement with dual centrifugal pumps.

After completing the present study, we implanted dual centrifugal pumps in four animals with chronic heart failure. This time, we implanted Jarvik 2000 pumps in one calf and two sheep, which survived for 20 days, 5 days, and 1 day, respectively; we also implanted dual MicroMed pumps in one calf for 1 day. This experience will be described separately in a report that is now in preparation. We plan to further test both the short-and long-term effects of completely nonpulsatile circulation after ventricular excision and replacement with total implantable pumps in animal models. In the present experiment, increasing the RVAD speed at a given LVAD setting resulted in higher PA flows and pressures, with little or no change in aortic flows and pressures. The interatrial window maintained a hemodynamic balance and kept the oxygen saturation in equilibrium between the left- and right-sided circulations without atrial collapse, even in the presence of mismatched LVAD and RVAD flows. At equal pump speeds, however, because of a slight left to right shunt, PA flow exceeded aortic flow. A desirable balance was achieved by keeping the RVAD speed slightly lower than the LVAD speed. With the RVAD operating at 4,000 rpm, pulmonary and systemic flows were almost equal (9.6 and 10.0 L/min, respectively), and the PAP and AoP were acceptable even under such exaggerated high flow conditions. The best hemodynamic results were observed, however, with the RVAD operating at 3,000–3,500 rpm and the LVAD at 4,500 rpm.

Conclusion

When implanted for total heart replacement, the dual continuous flow centrifugal pumps successfully maintained the pulmonary and systemic circulation in our acute ovine model. Compared with the larger TAH, dual continuous flow pumps would offer support to smaller patients with end-stage heart failure. Moreover, to date, experience with implantable axial flow pumps has shown their surprising durability and reliability; the inevitable wear anticipated with all mechanical devices should occur gradually and be detectable in time to allow suitable device replacement. The ability of continuous flow pumps to adjust their output in response to varying inflow pressures may permit autoregulation of left and right sided flows; nevertheless, creation of an ASD safely protects against the potential buildup of high left sided pressures and low right atrial pressures, which could lead to a disastrous clinical outcome. Experiments are continuing to further validate these concepts in the *in vivo* model. A concern about any surgically created ASD may be its untimely closure. However, in the physiologic model described in the present report, the continuous flow should protect against such an eventuality. Our experiment showed the feasibility of performing biventricular replacement with dual continuous flow pumps and using an atrial communication to correct the physiologic left and right atrial output imbalance while preserving satisfactory systemic oxygenation. This approach to long-term support has important clinical implications and should be vigorously pursued.

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