An advanced universal circulatory assist device for left and right ventricular support: First report of an acute in vivo implant

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ABSTRACT

Background: The Advanced ventricular assist device (Advanced VAD) is designed as a universal pump intended to prevent backflow in the event of pump stoppage, to maintain physiological pulse pressure, and to be used as both a left and right VAD. The purpose of this study was to evaluate the performance of the Advanced VAD as both a left and right VAD in an acute in vivo study in calves.

Methods: The Advanced VAD was implanted through a median sternotomy in 5 healthy calves (weight, 71.4-91.2 kg) as a left VAD (n = 3) or a right VAD (n = 2). After implantation, hemodynamic parameters, including general performance and pump stoppage, were evaluated.

Results: The Advanced VAD was successfully implanted as a left and right VAD without cardiopulmonary bypass. The speed range of the Advanced VAD was 2500 to 3500 rpm as a left VAD and 2000 to 2500 rpm as a right VAD. Up to 4.3 L/min was achieved for both left and right VAD configurations. To demonstrate the automatic shut-off feature, the pump was stopped without clamping the outflow graft. The outflow graft was then clamped, which produced no significant changes in the arterial pressure waveform. The pulse pressures under the left VAD configuration were 38 mm Hg, 17 mm Hg, 14 mm Hg, and 16 mm Hg at baseline, 2500 rpm, 3000 rpm, and 3500 rpm, respectively.

Conclusions: This acute in vivo study demonstrated the pump performance, anatomical fitting as both left VAD and right VAD, and regurgitant flow shut-off feature of the Advanced VAD. (JTCVS Open 2020;3:140-8)
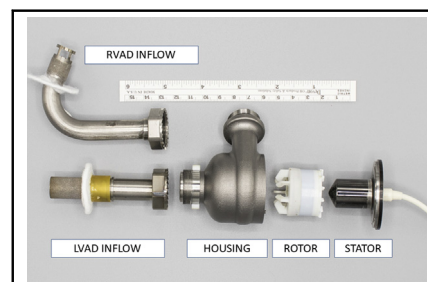
Advanced ventricular assist device components.

CENTRAL MESSAGE

An acute in vivo study was conducted to evaluate the performance of the new ventricular assist device with wide operational range, pulsatility augmentation, and regurgitant flow shut-off features.

PERSPECTIVE

To address the limitations of current ventricular assist therapy, such as loss of pulsatility, severe backflow during pump stoppage, and right ventricular failure, we developed the Advanced ventricular assist device. This in vivo acute study demonstrated the pump performance, anatomical fitting as both left and right heart support, and pulsatile flow and regurgitant flow shut-off feature of the pump.

Abbreviations and Acronyms
AoP = aortic pressure
CF = continuous flow
dP = pump differential pressure
LVAD = left ventricular assist device
PVR = pulmonary vascular resistance
RVAD = right ventricular assist device
SVR = systemic vascular resistance
VAD = ventricular assist device

▶ Video clip is available online.

Ventricular assist devices (VADs) have been widely used to treat end-stage heart failure. According to the eighth annual report from the Interagency Registry for Mechanically Assisted Circulatory Support, 18,591 Food and Drug Administration–approved VADs were implanted between June 2006 and December 2016 at 185 participating hospitals, and more than 90% were continuous-flow (CF) left ventricular assist devices (LVADs).[1] The rate of patient enrollment has grown to exceed 2500 implants per year for durable mechanical circulatory assist devices such as LVADs and total artificial hearts. Device strategy is changing such that the number of LVADs implanted as destination therapy has continued to grow. However, as support duration increases, clinical limitations and specific complications of CF-LVADs have become apparent. These include a loss of arterial pulsatility,[2-4] development of aortic regurgitation,[5] pump thrombosis or hemolysis,[6,7] severe backflow during pump stoppage, difficulty evaluating native heart function and weanability,[8,9] and acute or late right heart failure.[10,11]

In addition, despite major breakthroughs with CF mechanical circulatory system technology in recent years, major efforts were made to deliver LVADs to clinical practice. However, there are still no durable right ventricular assist devices (RVADs) available to address right heart failure. Existing VADs are not specifically designed for right ventricular support, which is limited by LVAD operational range.[12]

The Advanced VAD, which is under development at our institution and is intended to be used as a universal device (suitable for left and right heart assist or biventricular support), is designed to address those limitations by introducing an automatic and dynamic pump performance regulation property also found in our CF total artificial heart.[13] This pump's novel feature is that the rotor can move axially to regulate the impeller discharge aperture size, depending on the pressure difference between the inlet

and outlet and pump speed. This feature makes the pump more sensitive to pressure differences in the pump, allowing the performance to dynamically change during the cardiac cycle. We have shown previously in vitro that: (1) this pump can increase pulse pressure compared with existing CF-LVADs; (2) the regurgitant flow shut-off feature prevents backflow during pump stoppage, enabling a more accurate evaluation of native heart function; and (3) the wide performance range allows the device to be used as an LVAD, an RVAD, and a biventricular assist device with 2 pumps.[14] The purpose of the present study was to evaluate the performance and the specific properties of the Advanced VAD in an acute animal model under both LVAD and RVAD configurations.

METHODS

Device Description

The cross-section of the pump is shown in Figure 1, A. This is a magnetically and hydrodynamically levitated centrifugal pump, and the performance range is 2000 to 3500 rpm and up to 10 L/min. The pump is controlled with a custom-built control unit consisting of a microcontroller-based motor drive circuit with a built-in power supply and rotary dial speed selector. The pump components, including titanium inflow cannulae are shown in Figure 1, B. The pump length is 57 mm and pump diameter is 44 mm, with a total pump displacement volume of 70 mL and a priming volume of 15 mL. The housing components of the current prototype are made of titanium, and the rotor is made of plastic with reduced clearance modification from previous study results.[15] The LVAD inflow cannula is open ended and straight and the length is 69 mm and 14 mm in diameter. The RVAD inflow cannula is open-ended with 2 side holes and angled, and the length is 125 mm and 14 mm in diameter.

The novel design aspect of the pump is that the motor magnet in the rotor is shorter than the motor stator winding (Figure 1, A), so that the rotor can move axially to some extent[13] (US Patent: US 2018/0311426 A1). The axial spacing between the impeller and housing (aperture) varies because of this axial movement at startup and during operation (Figure 1, A), depending on the pressure difference in the pump (pump differential pressure [dP]) and rotational speed and range of the aperture opening (Video 1). A magnetic force acts to close the aperture, and the hydraulic forces during rotor rotation act to open it. This small but dynamic axial movement of the rotor changes the performance in response to the cardiac cycle. During diastole (pump dP is high), the rotor moves toward the aperture and decreases the flow. During systole (pump dP is low), the rotor moves against the aperture and increases the flow. In this way, the Advanced VAD is expected to provide increased pulsatility of the pump flow and pressure (pulse augmentation). When the rotor stops (power off), the hydraulic forces diminish, and the magnetic force immediately moves the rotor to close the aperture and shut down the flow (regurgitant flow shut-off). If the pump runs in a lower-pressure environment such as the pulmonary circulation, the aperture opening is automatically reduced, and the entire pump performance is decreased to provide adequate flow to the pulmonary circulation (RVAD use).

In Vitro Study

Bench testing with the Advanced VAD was performed on the static mock loop to obtain pressure-flow curves at various pump speeds before each in vivo experiment. A glycerin/water mixture (specific gravity, 1.060) was used as the working fluid. Vascular resistances were modeled with manual valves, arterial compliances were modeled with closed pneumatic reservoirs, and the pump inlets were fed from open reservoirs. In each test, data were recorded across the full range of operation (rotational
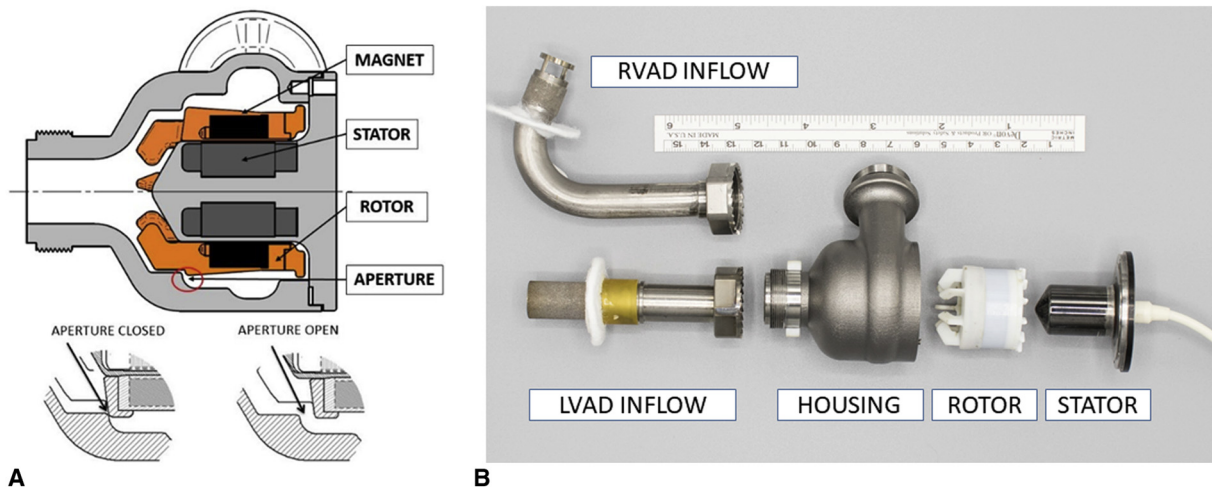
FIGURE 1. A, Cross-section illustration of the Advanced ventricular assist device: the pump is made of a housing, a stator, and a rotor. The rotor can move axially depending on pressure difference in the pump, and can change the space at the aperture. B, The photo of the Advanced ventricular assist device components: the straight inflow cannula was used for left ventricular support, and the angled inflow cannula was used for right ventricular support. *RVAD*, Right ventricular assist device; *LVAD*, left ventricular assist device.

speed of 2000-3500 rpm, aortic pressure of 20-120 mm Hg). The pressure rise was calculated as the outlet minus inlet pressures.

Surgical Approach

The study was approved by the Cleveland Clinic's Institutional Animal Care and Use Committee (#2016-1596). A total of 5 acute in vivo studies were performed using male Jersey calves (mean body weight = 83.2 kg, range = 72.4-91.2 kg).

Under general anesthesia, arterial pressure (AoP) and central venous pressure monitoring were placed in the carotid and jugular veins, respectively. A median sternotomy was performed, and heparin (300 U/kg) was administered for systemic heparinization. No cardiopulmonary support was used. The outflow graft was end-to-side anastomosed to the ascending

VIDEO 1. The video shows the pump components and novel features. The pump consists of the housing, the rotor, and the stator. The axial spacing between the impeller and housing (aperture) varies because the rotor moves axially at startup and during operation, depending on the pressure difference in the pump and rotational speed. In this way, the pump is expected to provide increased pulsatility of the pump flow and pressure (pulse augmentation). When the rotor stops (power off), the hydraulic forces diminish, and the magnetic force immediately moves the rotor to close the aperture and shut down the flow (regurgitant flow shut-off). Video available at: https://www.jtcvs.org/article/S2666-2736(20)30055-3/fulltext.
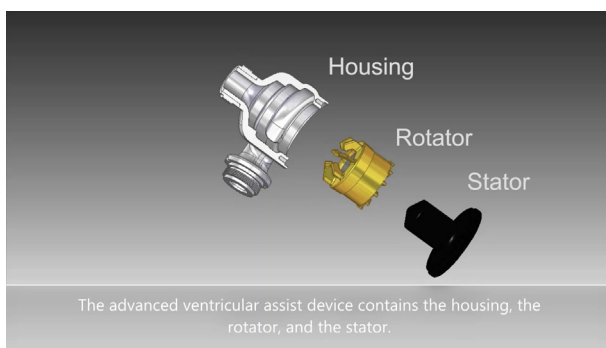
aorta (RVAD: pulmonary trunk). The pressure line was placed in the left ventricle through the left atrial appendage. Purse string sutures were placed on the apex (RVAD: right ventricular free wall) and cored with a coring tool, then an inlet cannula was inserted and secured. The outflow conduit was connected to the pump and de-aired, and the pump was started. Upon testing completion, the animal was fully heparinized (500 U/kg), the pump was stopped, and the study was terminated.

Hemodynamic Conditions

The measured hemodynamic and pump performance data included the following: (1) heart rate; (2) central venous pressure (fluid-filled catheter at the jugular vein); (3) AoP (fluid-filled catheter in the peripheral artery and on the outlet graft); (4) pulmonary artery pressure (fluid-filled catheter to the outflow graft, only for the RVAD study); (5) left ventricular pressure or pump inlet pressure (fluid-filled catheter); (6) pump flow (inline flow probe [ME-13 PXN Inline Flow Sensor; Transonic, Ithaca, NY], in the outlet conduit); (7) motor current (analog output from the control module); and (8) motor speed (analog output from the control module). In each condition, these hemodynamics were recorded about 5 seconds after the steady state was reached.

Hemodynamic and pump performance data were collected in the following manner:

(1) Speed range test. Data were obtained at baseline (without pump support) and at 2000 rpm, 2500 rpm, 3000 rpm, and 3500 rpm.
(2) Pump stoppage test. The pump was stopped to evaluate the shut-off feature. The pump was run at 3000 rpm for the LVAD configuration and at 2000 or 2500 rpm for the RVAD configuration. The pump was stopped for ≥5 seconds using the controller, and then the outflow conduit was clamped to verify the effectiveness of the automatic shut-off feature. The hemodynamic parameters and regurgitation flow were recorded a total of 10 times.
(3) Inlet cannula malposition suction control test. While in fixed-speed mode, the inlet cannula was rotated toward the interventricular septum, lateral wall, or aortic valve until flow obstruction occurred.
(4) High systemic vascular resistance (SVR) or pulmonary vascular resistance (PVR) test. High SVR or PVR was induced by clamping the outflow graft or aorta (RVAD: the pulmonary artery) partially, approximating 50%, 75%, and 90% obstruction.

(5) Low SVR or PVR test. A state of low SVR or PVR (LVAD: < 800 ± 50 dyne•sec•cm^{-5}, AoP: 50-70 mm Hg, RVAD: < 100 ± 50 dyne•sec•cm^{-5}, mean pulmonary artery pressure: 5-10 mm Hg) was induced by isoflurane (up to 5%).

Acute hemodynamic and pump performance parameters were digitized in real time at a sampling rate of 200 Hz with a PowerLab (ADInstruments Inc, Colorado Springs, Colo) data acquisition system. The data were analyzed using a custom-made visual basic program in Excel software (Microsoft Corporation, Redmond, Wash). The pulse pressure was calculated as (maximum AoP – minimum AoP).

RESULTS

Overall Outcome

The Advanced VAD was successfully implanted as an LVAD (n = 3) and as an RVAD (n = 2) without cardiopulmonary bypass support (Figure 2, A: LVAD; Figure 2, B: RVAD). There were no complications during the procedure, and anatomical fitting was acceptable. The speed range of the Advanced VAD was 2000 to 3500 rpm as an LVAD and 2000 to 3000 rpm as an RVAD, and up to 4.3 L/min (1.1-4.3 L/min) was achieved for both configurations. The pump performance was compared with a bench test (Figure 3, A). The pump performance was observed to be lower in vivo at high speed (3000 or 3500 rpm) due to some degree of inlet suction; the overall pump performance was shown to be consistent throughout the experiments with the values observed during preoperative in vitro device testing. Figure 3, B, shows representative dynamic pressure flow loops of the Advanced VAD during cardiac cycles implanted as an LVAD. The widest pressure flow loop was observed at 2500 rpm, indicating the greatest pulsatility. The smallest loops were observed at 3000 rpm and 3500 rpm.

The charts from both the LVAD and RVAD studies from selected experiments are shown in Figure 4. In Figure 4, A (LVAD configuration), as pump speed increased from 2000 to 2500 rpm, the pump flow increased from 1.5 L/min to 2.9 L/min, and the average inlet pressure decreased from 30 mm Hg to 23 mm Hg. However, at 3000 rpm and 3500 rpm, the average inlet pressure went down to 3 mm Hg and –28 mm Hg, respectively, and the pump flow did not increase (3.0 L/min, 3.0 L/min respectively) due to inlet suction. During the inlet cannula malposition test, we successfully produced the suction condition; pump flow decreased when the inlet attached to the ventricular wall (1.3-3.0 L/min). The pump was sensitive to high and low SVR, as the pump flow significantly decreased as SVR increased and caused the suction with low SVR. In the RVAD configuration (Figure 4, B), as pump speed increased from 2000 to 2500, the pump flow increased from 3.2 to 4.3 L/min, but the inlet pressure dropped to negative, meaning inlet suction, so we decided to use the data with 2000 rpm. RVAD was more stable in the cannula malposition than LVAD. RVAD is also sensitive to high PVR, as the pump flow significantly decreased as PVR increased.

Regurgitant Flow Prevention Testing

The regurgitant flow (backflow) feature of the Advanced VAD was successfully evaluated in this series of studies for both the LVAD and RVAD configurations. The representative waveforms observed for the following modes were recorded: on-pump; off-pump without clamping; and off-pump with clamping (Figure 5, A). When the pump was stopped, there was trivial regurgitant flow through the pump. Therefore, there were no changes in the arterial pressure waveform observed when the outflow graft was clamped, suggesting that the pump-off test could be fully achievable without clamping the outflow conduit. Regurgitant flow after stopping the pump for each pump configuration is shown in Figure 5, B. When the pump was stopped, the mean regurgitant flow was –0.3 ± 0.0 L/min for the LVAD configuration and –0.7 ± 0.3 L/min for the RVAD configuration. The regurgitant flow tended to be lower for the LVAD configuration than for the RVAD configuration, but was less than 1.0 L/min in all experiments.

Pulse Augmentation Testing

Figure 6, A, shows the representative waveforms for AoP, pump outlet pressure at the outflow conduit, and pump flow at 2500 rpm with the Advanced VAD support as an LVAD. The pump support demonstrated an effective operational pressure pulsatility at the pump outlet and flow pulsatility. As shown in Figure 6, A, the aperture of the pump closes at the bottom of the flow curve and opens at the peak of the flow curve. Despite the pressure, pulsatility appeared somewhat absorbed at the outflow conduit. This was one of the several most effectively achieved pulse augmentations during the in vivo study, and at this point, the pulse pressure of AoP was 15 mm Hg, the pulse pressure of pump outlet was 63 mm Hg, and the flow range was from 0.2 L/min to 6.0 L/min Figure 6, B, shows the mean pressure and flow pulsatility for the LVAD experiments. The mean pulse pressures for the LVAD configuration (n = 3) were 38 mm Hg (range: 32-45 mm Hg), 17 mm Hg (range: 15-19 mm Hg), 14 mm Hg (range: 6-19 mm Hg), and 16 mm Hg (range: 8-18 mm Hg) at baseline, 2500 rpm, 3000 rpm, and 3500 rpm, respectively. The mean flow pulsatilities (peak flow – minimum flow) were 5.0 L/min, 3.9 L/min, and 4.2 L/min at 2500 rpm, 3000 rpm, and 3500 rpm, respectively.

DISCUSSION

The device performance was successfully tested in this series of in vivo studies. To our knowledge, this is the first report of the in vivo use of a VAD that is designed to be used as LVAD and RVAD support. The Advanced VAD is also the first device designed to address the complications related to the presence of regurgitant flow by enabling a shut-off feature. The device
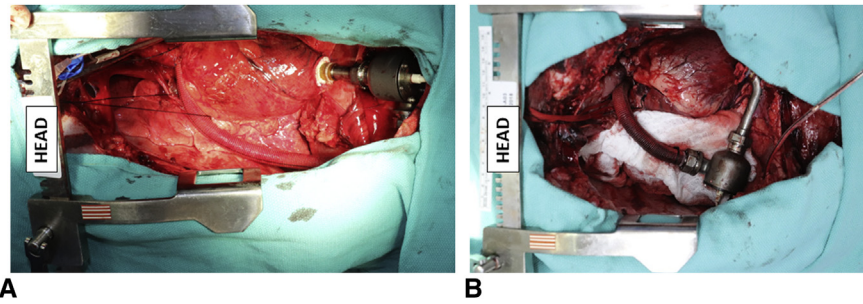
FIGURE 2. Intraoperative images of pump implantation. A, Left ventricular assist device: the inflow cannula was inserted into the left ventricular apex and the outflow graft was anastomosed to the ascending aorta. The pump sat on the diaphragm. B, Right ventricular assist device: the inflow cannula was inserted into the right ventricular diaphragmatic surface and the outflow graft was anastomosed to the pulmonary trunk. The pump sat in the right pleural cavity.

is also designed to provide pulse augmentation during circulatory support. In this acute in vivo study, we demonstrated that the Advanced VAD implantation was technically feasible, did not require cardiopulmonary

bypass support, and showed intended hemodynamic performance at an acceptable range as a universal pump. The device is intended to be used as a single LVAD and/or RVAD and can provide adequate blood flow for
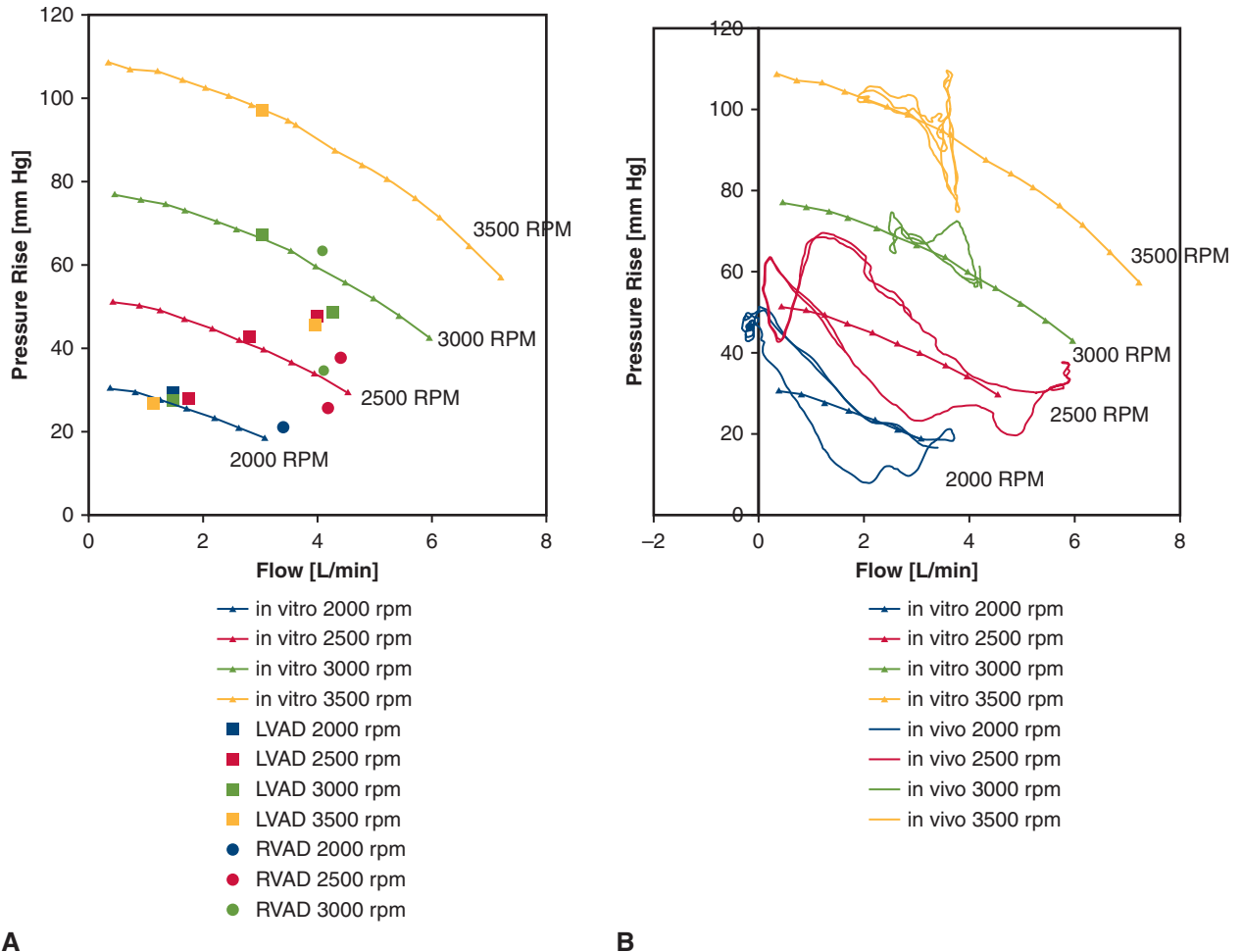

FIGURE 3. A, The pressure flow curves of the Advanced ventricular assist device from an in vitro study and the pump performance during an in vivo study: pressure rise was calculated as the outlet pressure minus inlet pressure (left ventricular pressure); the flow was measured at the outflow conduit. B, The representative pressure-flow loop during in vivo study: in vitro results are also shown as pressure flow curves. *LVAD*, Left ventricular assist device; *RVAD*, right ventricular assist device.
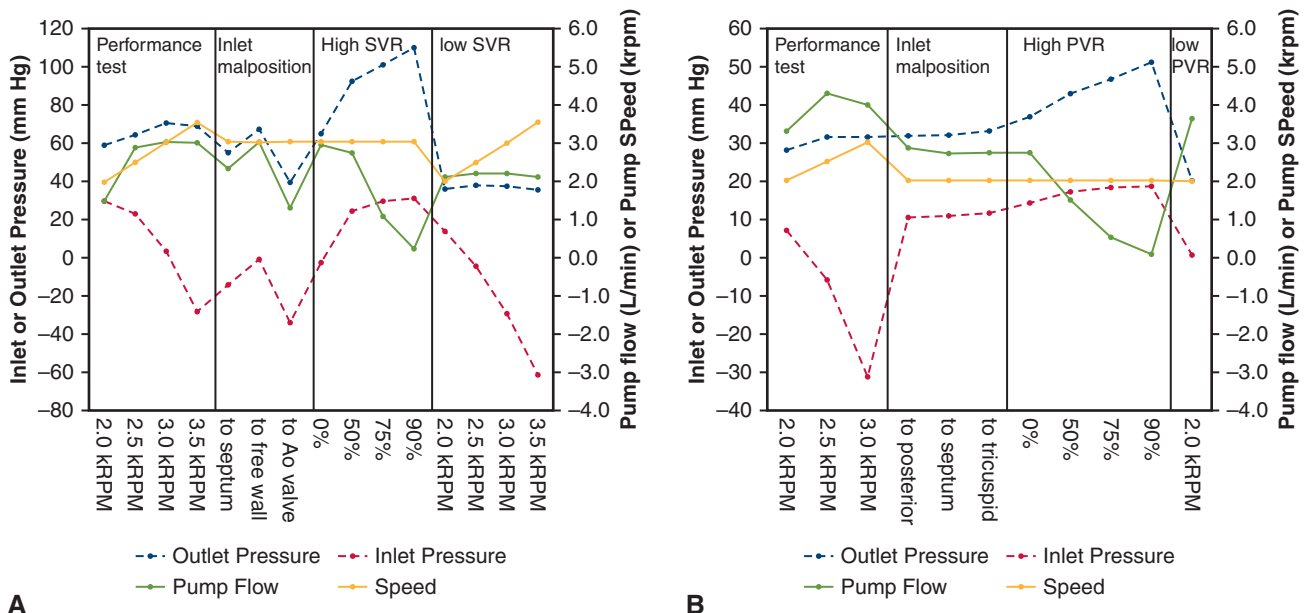
FIGURE 4. Representative chart of inlet pressure, outlet pressure, pump flow, and pump speed from left ventricular assist device configuration (A), and right ventricular assist device configuration (B) during in vivo experiments. *SVR*, Systemic vascular resistance; *PVR*, pulmonary vascular resistance.

either condition. In addition, the effectiveness of the regurgitant flow shut-off feature and the potential pulse augmentation feature of the pump has been successfully tested in this series.

We observed that the regurgitant flow shut-off feature of this pump was reproducible in vivo. This specific feature enables evaluation of the native ventricular function without clamping or occluding the outflow graft and makes explantation of the pump much easier.

Several groups reported their outcomes based on various clinical protocols and approaches for weaning the pump. Knierim and colleagues[16] reported their weaning protocol and success rate among 424 patients implanted with LVADs, and reported 14 patients who underwent LVAD explantation. These authors demonstrated three steps of their weaning evaluation protocol, which included screening, echocardiography at "baseline," "zero net flow," and "pump stop conditions," as
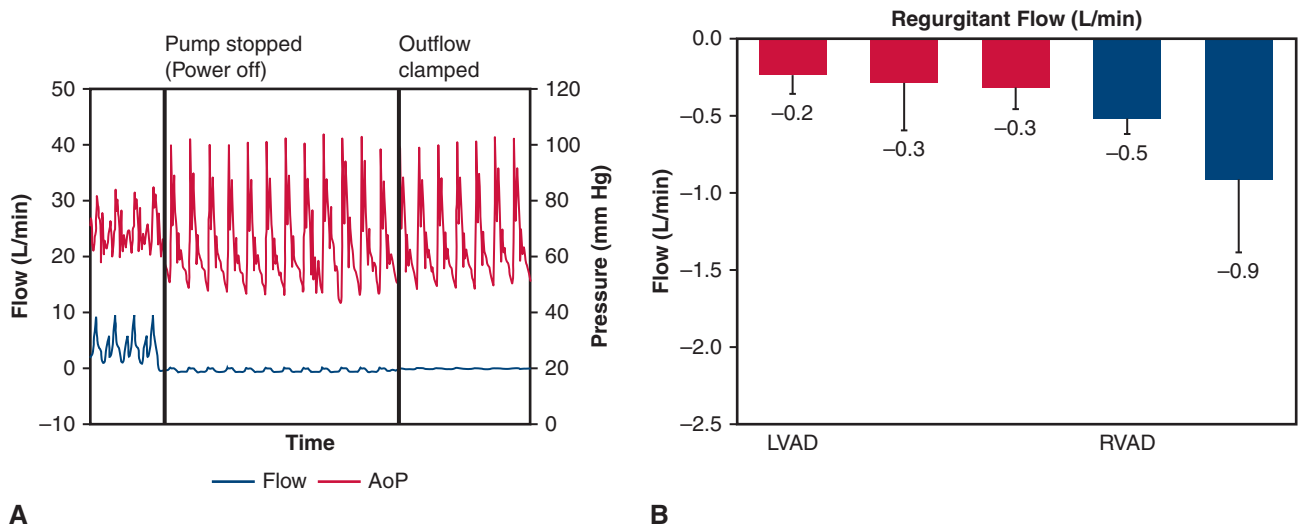

FIGURE 5. A, The representative waveforms for aortic pressure and pump flow when the pump was stopped (power off) without outflow graft clamping, and when the outflow graft was clamped. When the pump was stopped, the pump flow immediately fell to almost zero without regurgitant flow, and the flow waveform showed almost no change after the outflow graft was clamped, demonstrating the regurgitant shut-off feature of the pump. B, Mean regurgitant flow for the LVAD (*red*) and RVAD (*blue*): Mean regurgitant flow was −0.3 ± 0.0 L/min for the LVAD configuration and −0.7 ± 0.3 L/min for the RVAD configuration. *AoP*, Aortic pressure; *LVAD*, left ventricular assist device; *RVAD*, right ventricular assist device.
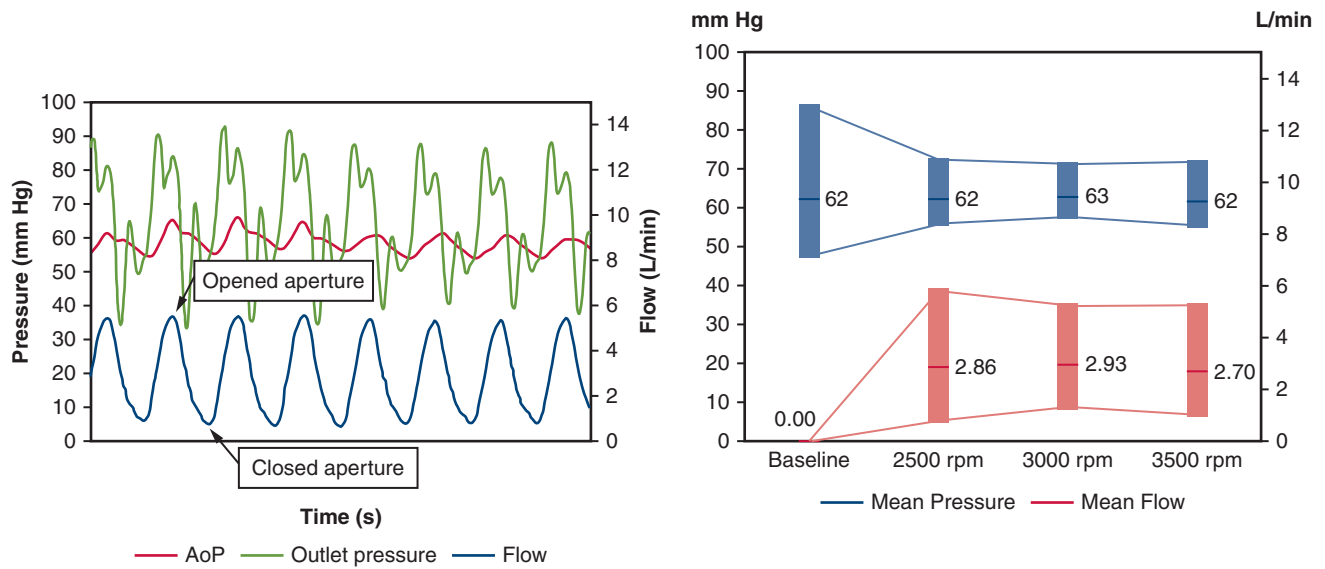
FIGURE 6. A, Representative waveform of AoP, pump outlet pressure, and pump flow at 2500 rpm as an LVAD: the aperture of the pump opened during systole and closed during diastole as indicated in figure. B, Pressure and flow pulsatility in the LVAD configuration. The range of the bar shows the pressure and flow pulsatility; the *middle line* inside the bar show the mean AoP or pump flow. *AoP*, Aortic pressure.

well as right heart catheterization with graft occlusion and pump stoppage. No complications during the evaluation were reported, but as discussed, the "zero net flow" condition could not be considered accurate, as the "pump stop condition" causes massive regurgitant flow and acute myocardial stress,[17] and the balloon occlusion of the outflow graft creates the potential for complications, such as bleeding and thromboembolism.[18] Our previous in vitro studies to evaluate the HeartMate II (Abbott Inc, Chicago, Ill) and HVAD (HeartWare Inc, Framingham, Mass) performance at very low pump speeds showed that even at low speed, those pumps have a significant contribution to mean AoP and total flow, especially under heart failure conditions.[8,9] The Advanced VAD would allow pump evaluation without regurgitation during echocardiographic assessment and thus would assist with the evaluation and assessment of weaning strategies in heart failure patients implanted with this VAD.

The Advanced VAD is designed to perform universally as both an LVAD and an RVAD. In the RVAD configuration with low rotational speed, the rotor moves to close the aperture and reduce pump performance, so this pump has a wider performance range than other existing devices. The typical operational range required for the CF-RVAD is to generate pump flows of 2 to 6 L/min while raising the pump outlet pressure by 20 to 50 mm Hg from that at the pump inlet port.[19] As reported in the in vitro study, the Advanced VAD can generate up to 6 L/min while raising the pump outlet pressure 20 to 50 mm Hg at 2500 rpm. In the in vivo study, the mean pump flow was

3.8 L/min and 4.3 L/min at 2000 rpm and 2500 rpm, respectively, suggesting that a rotational speed between 2000 and 2500 rpm should be appropriate for right ventricular support, and 3000 and 3500 rpm for left ventricular support. From the HVAD pressure flow curve, which was recorded in our institution, the pump speed was 1800 rpm to get similar flow at RVAD pressure rise, which is less than the recommended clinical speed range (2400-3200 rpm).

HVAD is currently the most frequently used as an RVAD (off-label use). To fit LVAD performance to right heart support, many physicians use a relatively long outflow graft or narrow the outflow graft to increase the afterload,[20,21] and the pump inflow is inserted into the right atrium to prevent suction.[21] Restricting the outflow graft changes the flow distribution in the graft and has a potential risk of thrombus formation. The restriction cannot be adjusted after implantation, while the Advanced VAD adjusts its performance automatically.[22] Shah and colleagues[23] reported a multicenter study of 46 patients who received a durable biventricular VAD (HVAD); suspected RVAD thrombosis developed in 17 patients (37%). There was a trend toward lower rates of suspected RVAD thrombosis with a right ventricle cannulation (26%) compared with a right atrial cannulation (48%, P = .13) implant. Patients with an RVAD thrombosis had a lower pump operational speed (2300 rpm) than patients without RVAD thrombosis (2450 rpm, P = .22). Although studies have shown acceptable results, using the HVAD as an RVAD may not be optimal, and a pump suitable for the hemodynamics of the pulmonary circulation still needs to be developed.[24]
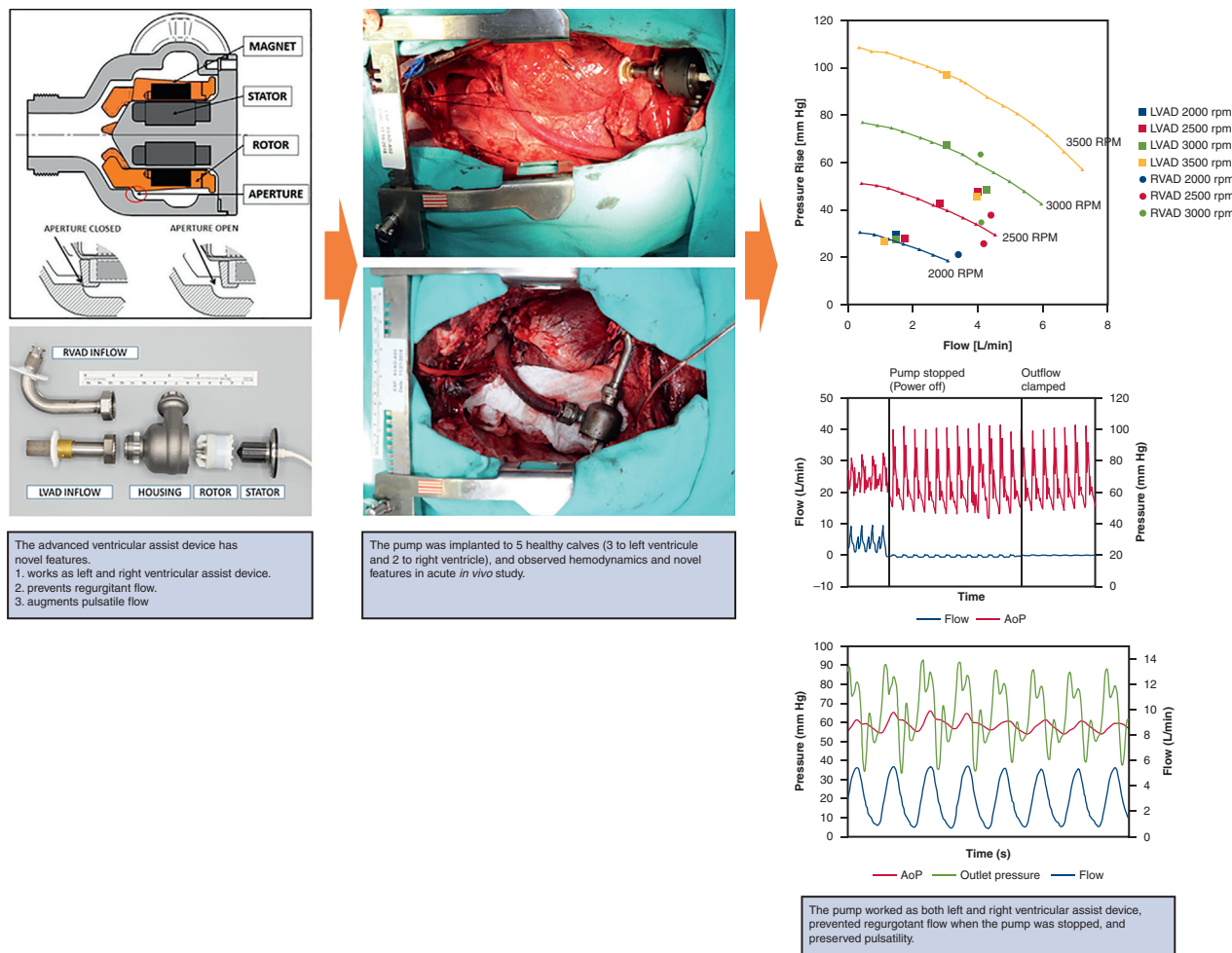
FIGURE 7. The Advanced ventricular assist device is a universal pump designed to be used as a left, right, and biventricular ventricular assist device and also has features to preserve arterial pulsatility and prevent regurgitant flow while the pump is off. We report here the first acute animal study of the universal Advanced ventricular assist device implanted through a median sternotomy in calves (n = 5). The pump kept the hemodynamics stable as both left (n = 3) and right (n = 2) heart support, had a regurgitant flow shut-off feature and offered potential pulse augmentation. *LVAD*, Left ventricular assist device; *RVAD*, right ventricular assist device; *AoP*, aortic pressure.

There are some limitations to this study. First, healthy animals were used in these experiments. The ventricular cavity of the healthy calves appeared to be of smaller dimensions, and in the end-systolic phase, the ventricles were fully ejected. The pump should be more resistant to suction events than existing pumps, because when suctions occur, the pump aperture automatically closes and lowers the flow, reducing the suction on the tissue. Second, the pump is designed to be fully implanted in the chest and intended to fit in the pericardial space. The long inflow cannula is designed for in vivo studies with normally hypertrophic hearts in calves and enables us to adjust the pump position easily during acute animal study.[25] Third, the pump showed lower pulsatility augmentation than in the in vitro study. Some factors could affect the results, such as the length of the outflow conduit, compliance

difference, or preload sensitivity of the native heart. To enhance pulsatility, the outflow conduit should be as short and wide as possible.

In conclusion, we report here the first acute animal study of the universal Advanced ventricular assist device intended for right, left and biventricular support (Figure 7). The pump kept the hemodynamics of calves stable with up to 4.3 L/min as both an LVAD and an RVAD, and a regurgitant flow shut-off feature and potential pulse augmentation. The pump development is ongoing; further device assessments would include more thorough performance analysis and biocompatibility testing in a chronic model.

Conflict of Interest Statement
Fukamachi and Horvath are the device co-inventors. Horvath is a consultant for the Cleveland Clinic and may

receive future royalties. Kuban disclosed patents on loosely related devices. Sale disclosed a financial relationship with St. Jude. All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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