

Two axial-flow Synergy Micro-Pumps as a biventricular assist device in an ovine animal model

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KEYWORDS:

left ventricular assist device;
right ventricular assist device;
biventricular support;
BiVAD;
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OBJECTIVE: This study investigated the use of 2 Synergy Micro-Pumps for full biventricular assist device (BiVAD) support. We examined right-sided and left-sided hemodynamic parameters over a range of right-sided and left-sided pump speeds in an acute, fibrillating, non-beating-heart model in sheep.

METHODS: Five juvenile sheep (43 ± 2 kg) were implanted with two Synergy Micro-Pumps (CircuLite Inc, Saddle Brook, NJ), 1 in the right (RV) and 1 in the left ventricle (LV), through a median sternotomy. The RVAD outflow graft was anastomosed end-to-side to the pulmonary artery and the LVAD outflow to the ascending aorta. After surgical implantation of both pumps, ventricular fibrillation was induced and hemodynamic parameters were measured at 9 different levels of RVAD pump speed (from 20,000 to 28,000 rpm at 1,000-rpm increments), while the speed of the LVAD was set constant at 24,000, then at 26,000, and finally, at 28,000 rpm.

RESULTS: At a fixed LVAD speed, RVAD and LVAD flow both increased identically as RVAD speed was increased. This was due to redistribution of blood volumes that resulted in resetting of pressure gradients across each pump and each vascular bed in a manner dictated by the pump pressure–flow characteristics. Results were similar with LVAD set at 24,000, 26,000, or 28,000 rpm. At the highest LVAD and RVAD speeds, flow averaged 3.1 ± 0.7 liters/min, and pressures in the right atrium, pulmonary artery, left atrium, and aorta averaged 2.2 ± 3.7 , 24.4 ± 6.5 , 22.4 ± 5.5 , and 56.6 ± 8.5 mm Hg, respectively.

CONCLUSION: BiVAD support with the 2 Synergy Micro-Pumps is feasible and able to provide full hemodynamic support in sheep. This approach holds promise for providing biventricular partial support in humans and, in particular, for full support in small adults and children.

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Left ventricular assist devices (LVADs) offer an important option for patients with end-stage heart failure. Recent technical improvements in the available devices (eg, miniaturization and increased reliability), increased surgical experience (including minimally invasive surgical approaches), and improved peri-operative and post-operative management have reduced adverse events and improved long-term survival, leading to more widespread

acceptance of LVADs by surgeons, referring cardiologists, and patients.^{1–9} As a consequence, there has been a steady increase in the number of LVAD implants in the United States and in the European Union, and this number is expected to continue to grow.¹⁰

One of the most common adverse effects of LVAD use is the development of right heart failure. As many as 30% of LVAD patients exhibit some degree of right heart failure that requires prolonged inotropic support, and as many as 5% to 10% require insertion of a right ventricular assist device (RVAD) for temporary (days to weeks) or permanent right-sided support.¹⁰ Unfortunately, our ability to predict who will need RVAD support after LVAD implant is poor, despite development of multiple risk factor scores and pre-

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operative analysis algorithms.^{11–17} However, a small number of patients, from the onset, present with a clear indication for biventricular support. Between these two scenarios, the number of patients in need of biventricular support is expected to grow.

Options for end-stage biventricular heart failure¹⁸ include the total artificial heart (TAH, eg, CardioWest; SynCardia, Tucson, AZ)¹⁹ and paracorporeal BiVADs.^{20–23} Both alternatives are associated with low survival rates and limited quality of life for surviving patients.²² Recently, encouraging results have been obtained with miniaturized LVADs used for RV support.^{23–27} However, these devices are not ideally suited for implantation in the right heart, and therefore, research on VADs remains necessary.^{28–40}

The Synergy Micro-Pump (CircuLite Inc, Saddle Brook, NJ) is the size of an AA battery, connects to the heart via an 8-mm-diameter by 20-cm-long inflow cannula, has a pumping capacity of up to ~4.25 liters/min, and is small enough to be placed in a subcutaneous pocket.^{41–43} Although clinical experience is currently limited to pumping blood from the left atrium to the subclavian artery, recent cadaveric research has indicated that this micropump can also be easily positioned as an RVAD.

The present study investigated the use of two Synergy Micro-Pumps for full biventricular assist in sheep and, in particular, to understand how performance of one micropump influences performance of the other. To simplify interpretation of results, we eliminated the confounding effects of the native RV and LV by performing all studies in fibrillating, non-beating hearts.

Materials and methods

All animals were handled according to the guidelines of the American Physiological Society. The experimental protocol was approved by the local authorities of Hannover Medical School, Hannover, Germany, and passed the Bioethical Committee of the District of Braunschweig, Germany.

Experimental protocol

Sheep were fasted for 24 hours before surgery with free access to water. After premedication with intravenous (IV) midazolam (0.2 mg/kg) and propofol (6 mg/kg), sheep were intubated and ventilated (Dräger Ventilog 2, Lübeck, Germany). Anesthesia was maintained by continuous inhalation of isoflurane, fentanyl (0.03 mg/kg IV), and animals were chemically paralyzed with atracurium (0.5 mg/kg). Ringer's solution was administered steadily to preserve homeostasis. Animals were anti-coagulated with heparin (300 IU/kg IV), and ventricular ectopy was suppressed with amiodarone (150 to 300 mg [3 to 6 mg/kg IV]). Sheep were instrumented with a central venous catheter via the left jugular vein for measuring central venous pressure, a left carotid arterial catheter for measuring systemic arterial pressure, and a Swan-Ganz catheter for measuring pulmonary artery and pulmonary capillary wedge pressures.

Five female sheep (weight 43 ± 2 kg) underwent implantation of two Synergy Micro-Pumps. A schematic of the pump is shown in Figure 1. The motor sits within the pump housing, and

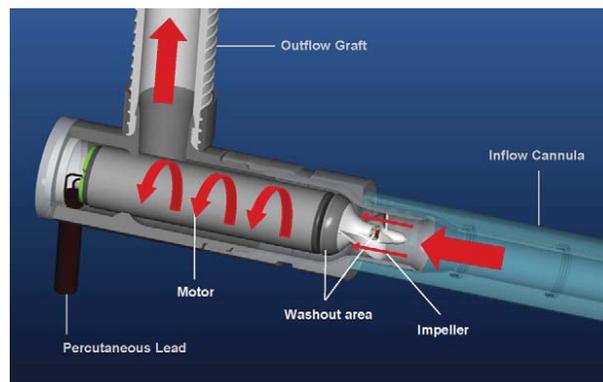


Figure 1 Schematic illustrates the path of blood through the pump.

blood is drawn into the pump housing by the impeller rotating at 20,000 to 28,000 rpm. The blood passes through narrow channels around the motor (which serves to cool the motor) and leaves the pump at a right angle to the inlet. The system's inflow cannulae were implanted in the RV and LV apices through a median sternotomy. The RVAD outflow graft was anastomosed to the pulmonary artery, and the LVAD outflow graft was anastomosed to the ascending aorta.

After implantation of both pumps and initiation of flow, ventricular fibrillation was induced and hemodynamic parameters were measured at 9 different levels of RVAD pump speed (from 20,000 to 28,000 rpm at 1,000-rpm increments) at each of 3 LVAD speeds (24,000, 26,000, and 28,000 rpm). At least 3 minutes were allowed for hemodynamic stabilization after moving from one set of RVAD and LVAD speeds to another. The overall experimental setup is illustrated in Figure 2.

Statistical analysis

Data are reported as means \pm standard deviation (SD). Calculations were performed with Statistica 6.0 software (StatSoft Inc, Tulsa, OK). Student's *t*-test was used to compare matched pairs, with $p = 0.05$ considered statistically significant.

Results

Average results from the 5 sheep with LVAD speed fixed at 24,000 rpm are shown in Figure 3. With a fixed LVAD speed, RVAD and LVAD flow increased identically and nearly linearly as RVAD speed was increased from 20,000 to 28,000 rpm in 1,000-rpm increments (Figure 3A). Flows averaged ~2.3 liters/min at with the RVAD set at 20,000 rpm and increased to ~3 liters/min with RVAD speed increased to 28,000 rpm. The main explanation for these findings is revealed by examination of the pressures at the key points of the circulation. As RVAD speed was increased, the increased flow was associated with decreases in right atrial pressure from 7 to 2 mm Hg and increases in mean pulmonary artery pressure from 14 to 31 mm Hg (Figure 3B). Concomitantly, left atrial pressure rose in parallel with pulmonary pressure. Note that there was only a 2- to 3-mm Hg transpulmonary pressure gradient, as would be expected for normal pulmonary vasculature, and that in the

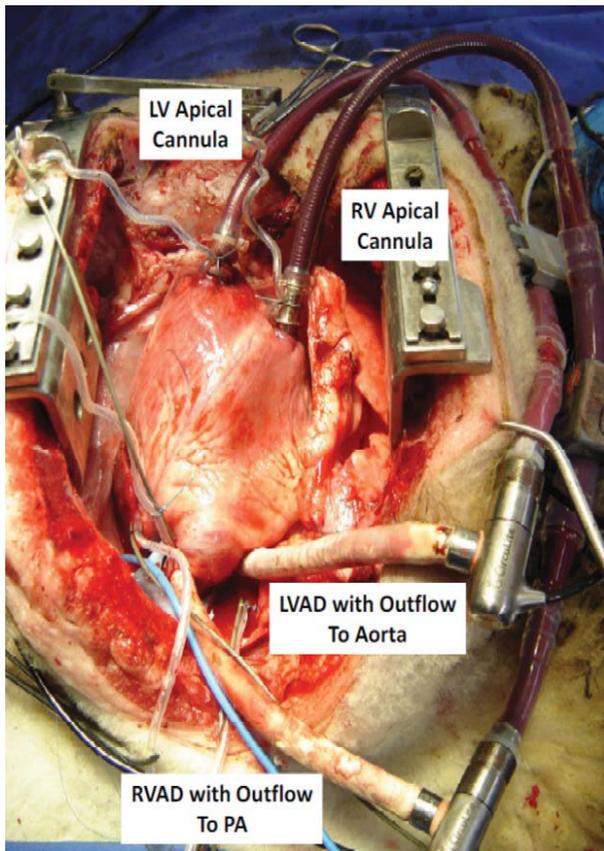


Figure 2 Intraoperative setting: 2 CircuLite Synergy Micro-Pumps were implanted into the right (RV) and the left ventricle (LV) through a median sternotomy. The RV assist device (RVAD) outflow graft was anastomosed end-to-side to the pulmonary artery (PA), and the LV assist device (LVAD) outflow to the ascending aorta. Note: The animal's head is toward bottom of the photograph, and the tail is toward the top.

case of fibrillating heart, the left atrial and ventricular pressures are nearly identical. Finally, mean aortic pressure increased slightly, from 52 to 59 mm Hg, with the increase in flow. Thus, the increase in LVAD flow, despite the constant LVAD rpm with increased rpm, can be explained by the significant decrease in the pressure gradient across the LVAD (ie, the difference between aortic and LV pressure).

The findings with LVAD speed fixed at 26,000 rpm (Figure 4) or 28,000 rpm (Figure 5) were similar to those for the LVAD speed of 24,000, except that there was a slight increase in peak flow when RVAD speed was set at 28,000. In each case, LVAD flow increased identically with RVAD flow with a decrease in the trans-LVAD pressure gradient. In summary, at the highest RVAD and LVAD speeds (both 28,000 rpm), flow averaged 3.1 ± 0.7 liters/min, and pressures in the right atrium, pulmonary artery, left atrium, and aorta averaged 2.2 ± 3.7 , 24.4 ± 6.5 , 22.4 ± 5.5 , and 56.6 ± 8.5 mm Hg, respectively.

Another way to illustrate these findings is to display RVAD and LVAD flows as a function of the respective pressure gradient across each of the VADs (Figure 6). As described above, as the RVAD flow increased, so too did LVAD flow. The increased flow for the RVAD is associated with

increased pressure gradient due to the increase in speed; however, the increase in flow for the LVAD is due to a decrease in pressure gradient. It is evident from the slopes of the pressure gradient-flow relations that these slopes are equal in magnitude but of opposite signs. This is expected, because the RVAD and the LVAD in this experiment have the same pressure-flow characteristics. With increased LVAD speed (Figure 6B and C), these relations had similar slopes, but their elevations increased; that is, at any RVAD speed, flow through the system increased as LVAD speed was increased.

Discussion

We used 2 Synergy Micro-Pumps to provide full BiVAD support in sheep during ventricular fibrillation and

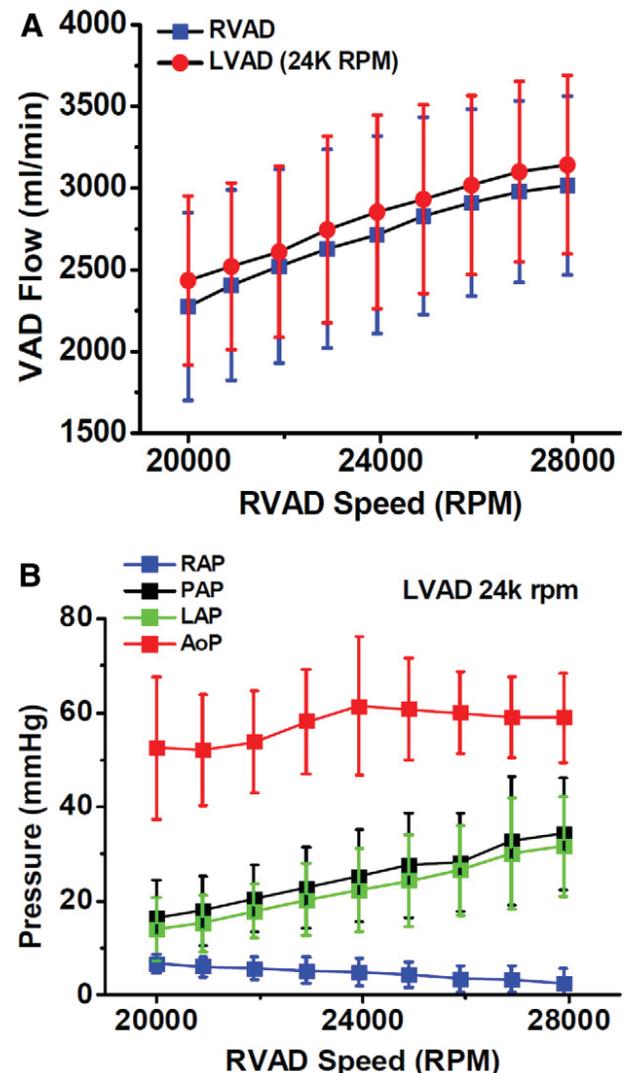


Figure 3 (A) Average results from 5 sheep with increasing right ventricular assist device (RVAD) pump speed (from 20,000 to 28,000 rpm at 1,000-rpm increments) and fixed left ventricular assist device (LVAD) speed at 24,000 rpm. (B) Mean right atrium (RAP), pulmonary artery (PAP), left atrium (LAP), and aortic (AoP) pressure at a fixed LVAD speed of 24,000 rpm. The range bars show the standard deviation.

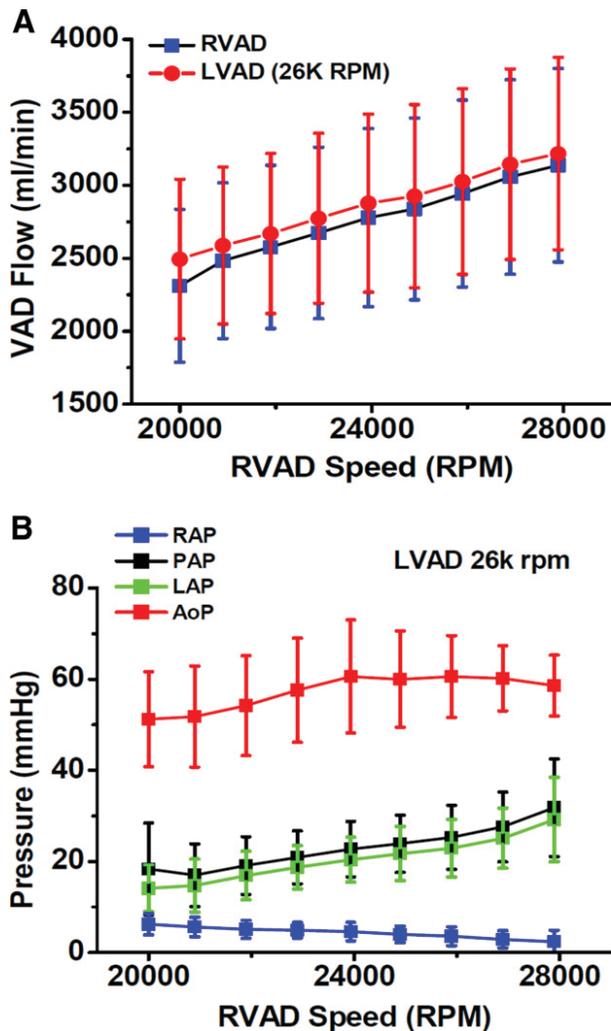


Figure 4 (A) Average results from 5 sheep with increasing right ventricular assist device (RVAD) pump speed (from 20,000 to 28,000 rpm at 1,000-rpm increments) and fixed left ventricular assist device (LVAD) speed at 26,000 rpm. (B) Mean right atrium (RAP), pulmonary artery (PAP), left atrium (LAP) and aortic (AoP) pressure at fixed LVAD speed of 26,000 rpm. The range bars show the standard deviation.

achieved an average flow rate exceeding 3 liters/min, which is approximately the normal value for sheep of the size used. The fibrillating heart model allowed us to study hemodynamics and the interactions between the 2 pumps without confounding effects of native ventricular contraction. One of the key findings was that right-sided and left-sided flow rates always equilibrated, independent of the individual pump speeds. This happened because flow through such rotational flow pumps is not fixed but is highly dependent on the pressure gradient from the pump inlet to the pump outlet. Accordingly, when flow is instantaneously changed in 1 of the pumps, the pressure gradients across both pumps readjusts (presumably due to blood volume redistribution between systemic and pulmonary circuits) such that a new equilibrium state, determined by the pump pressure-flow characteristics, is achieved in which flow rates through the 2 pumps are equal. So, at a fixed LVAD speed and a gradually in-

creasing RVAD speed, the pressure gradient *increases* from the right atrium to the pulmonary artery and this is mirrored by an approximately equal *decrease* in pressure gradient from the left atrium to the aorta. This behavior is completely predictable based on the pump flow characteristics. Thus, with 2 continuous-flow pumps (such as the Synergy Micro-Pumps) used in series in a BiVAD configuration, flow rates will equilibrate and pressures will adjust according to the pressure-flow characteristics of the pumps; the quantitative nature of that relationship are further influenced by the relative capacitances and resistances of the systemic and pulmonary vascular beds.

Although most patients with severe heart failure can be managed long-term with isolated LVAD support,¹⁰ some patients with fulminant biventricular failure require biventricular support.^{19,22} In addition, ~10% of patients presenting with end-stage heart failure require biventricular support.¹⁰ As many as 5% to 10% of patients implanted with an

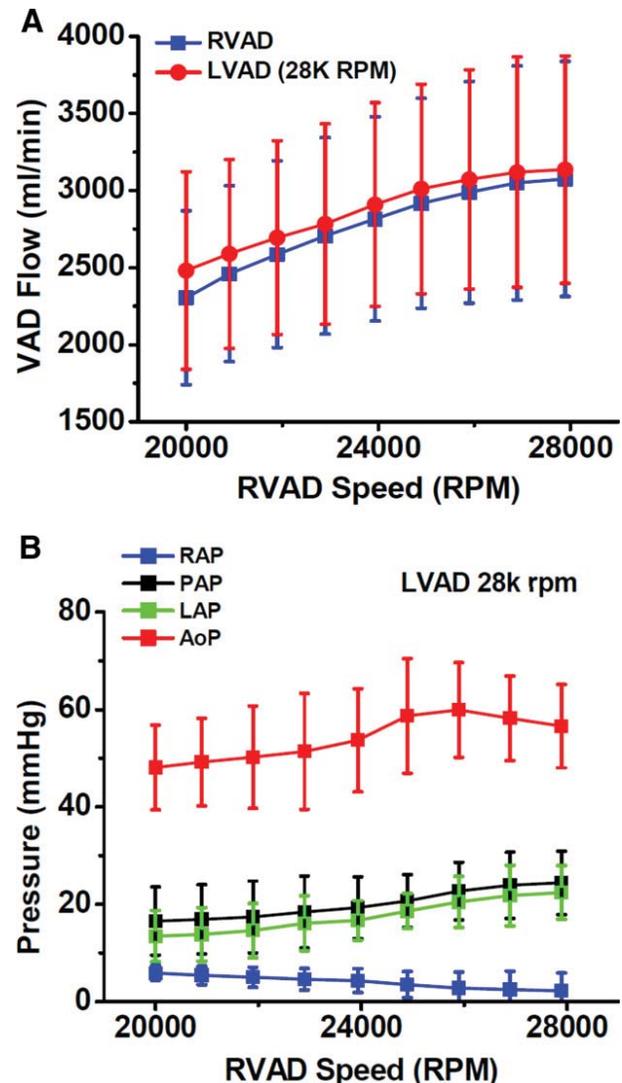


Figure 5 (A) Average results from 5 sheep with increasing right ventricular assist device (RVAD) pump speed (from 20,000 to 28,000 rpm at 1,000-rpm increments) and fixed LVAD speed at 28,000 rpm. (B) Mean right atrium (RAP), pulmonary artery (PAP), left atrium (LAP), and aortic (AoP) pressure at fixed LVAD speed of 28,000 rpm.

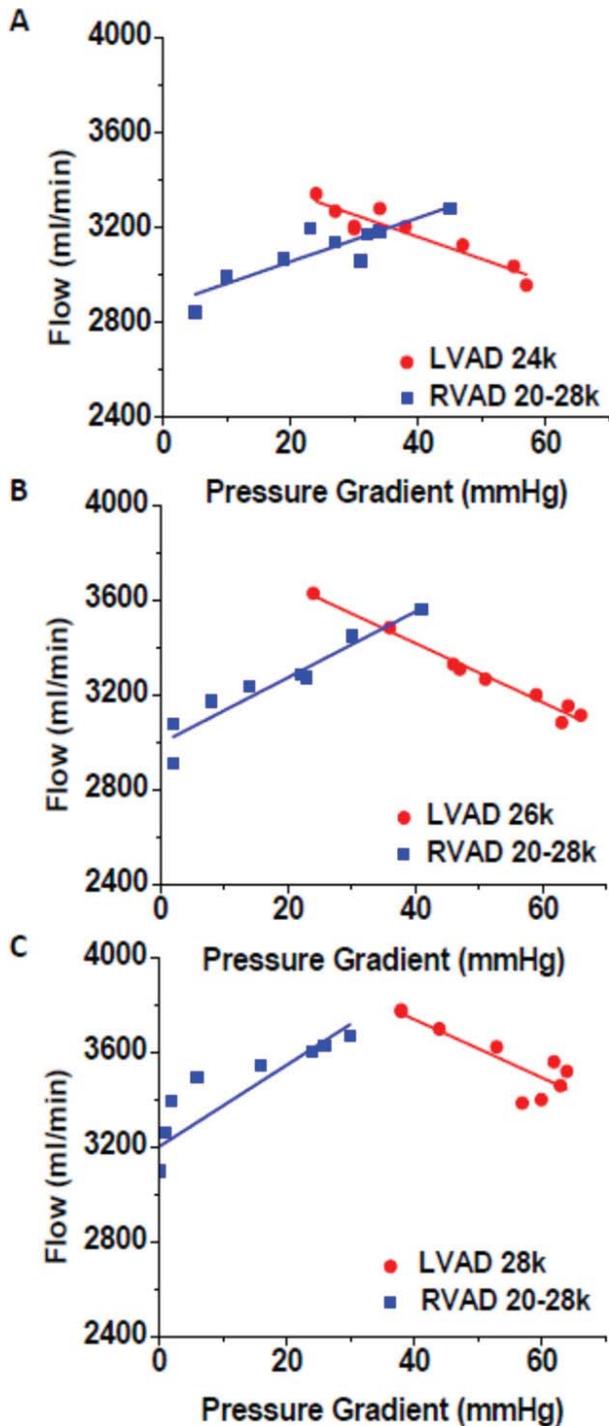


Figure 6 Example of the relationship between ventricle-to-artery pressure gradient and flow through the left ventricular assist device (LVAD) and right ventricular assist device (RVAD) for fixed LVAD speeds of (A) 24,000 rpm, (B) 26,000 rpm, and (C) 28,000 rpm. For any LVAD speed, RVAD speed is increased, and there is an increase in pressure gradient for the RVAD and a decrease in pressure gradient across the LVAD. The slopes of the respective relations, however, are equal in magnitude, but have opposite sign.

LVAD will eventually require short-term or long-term RV support. Thus, as the use of LVADs expands, there will be increased need for safe and effective long-term RV support devices.

Short-term options for patients presenting with biventricular failure include the use of paracorporeal BiVADs, and in some cases, extracorporeal membrane oxygenation.^{18,22,29} However, patient mobility is limited, and risks of infection and other adverse events that compromise outcome are quite high.¹⁰ For this reason, long-term options that allow for patient mobility with lower risks of adverse events are being sought. One option is use of a pneumatic TAH,¹⁹ which could become more widely accepted as the pneumatic drivers decrease in size and the systems become more reliable.

Another more recently explored option is biventricular support with 2 miniature continuous-flow “LV” assist devices.^{23–27} Although such devices have been designed and optimized (anatomically and physiologically) for LV assist, investigators have been able to adapt them for use on the right side. The adaptations include spacers to adjust inflow cannula depth of penetration into the RV and constrictors on the outflow graft to decrease output to the low-pressure, low-resistance pulmonary circuit. Although much effort has been devoted during the development of the TAH and extracorporeal BiVADs to balancing right-sided and left-sided output, much less is known or written about the interactions between 2 continuous-flow VADs and how they are optimally adjusted in the clinical setting.

It is also noteworthy that the approaches discussed here are not applicable to small adults and children because of size limitations. Accordingly, efforts to develop ever-smaller devices can help with these important underserved populations.

The Synergy Micro-Pump is a small (AA battery-sized) continuous-flow device designed for partial LV support.^{28,29} The inflow cannula is designed for insertion into the atrium or, with an extended titanium cage into the ventricle. In either case, the tip can be used in the respective chambers on the right or left sides without modifications. Regarding flow rates, with a pressure gradient across the pump of 70 to 80 mm Hg (a typical gradient when used for left heart support), this device can pump up to ~4.25 liters/min when set at maximal rotational speed (28,000 rpm). The flow rate increases as the pressure gradient decreases. At the minimal rotational speed of 20,000 rpm and with a pressure gradient of 30 mm Hg, which might be encountered during RV support, the pump flow is only 3 liters/min. Thus, based on anatomic and pump flow characteristics, the Synergy Micro-Pump offers an attractive option for right-sided support because of its small size, versatility of anatomic positioning, and the flow rates achievable at low pressure gradients.

The current study represents the only the first step in understanding the potential utility of the Synergy Micro-Pump as a right-sided pump or as a component of a BiVAD system. To simplify interpretation of findings, we studied hemodynamics with a fibrillating heart. However, the situation is more complicated if the native heart is beating, particularly when the pump is providing partial support for one or both sides. Then, the interactions become much more complicated, although the general principles of volume re-

distribution and establishment of pressure gradients according to pump characteristics are still valid.

Another limitation of the present study is that the pulmonary vasculature of the young healthy sheep used in the present study is not representative of most patients with chronic heart failure. In the present study, we observed a transpulmonary pressure gradient averaging only 2 to 3 mm Hg, indicative of low pulmonary vascular resistances. High pulmonary vascular resistances are common in patients, and the assumption of system linearity may not hold. This could affect the interaction between 2 pumps operating in series.

Finally, the current results are limited to acute hemodynamic effects in anesthetized animals. Factors such as baroreflexes and neurohormonal levels that exert effects over longer time periods will also have an effect on device-vasculature and device-device interactions.

Although the current study was performed with the Synergy Micro-Pump, we believe that the underlying findings would pertain to the biventricular configuration of any continuous-flow pump whose flow depends on rotational speed and pressure gradient. The concept is the same: when rotational speed of 1 pump is increased, the pressure gradients across both pumps will adjust through redistribution of volume between circulations so that the flow through the 2 pumps will equilibrate.

In conclusion, biventricular assist with the 2 Synergy Micro-Pumps is feasible and able to provide full hemodynamic support in sheep. This approach holds promise for providing biventricular partial support in humans and, in particular, for full support in children.

Disclosure statement

This research was funded by a grant to Dr Schmitto from CircuLite. Dr Burkhoff and Oliver Fey are employees of CircuLite. Dr Schmitto as well as Dr Strueber are Principal Investigators in the CircuLite European Clinical Trial.

None of the other authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

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