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ORIGINAL ARTICLE

Asymmetric speed modulation of a rotary blood pump affects ventricular unloading

Tohid Pirbodaghi[a,*], Alberto Weber[b], Shannon Axiak[c], Thierry Carrel[b] and Stijn Vandenberghe[a]

[a] ARTORG Cardiovascular Engineering, University of Bern, Bern, Switzerland
[b] Cardiac Surgery Department, Inselspital University Hospital, Bern, Switzerland
[c] Department of Veterinary Anesthesia, University of Bern, Bern, Switzerland

* Corresponding author. ARTORG Cardiovascular Engineering, University of Bern, Murtenstrasse 50, Postfach 44, 3010 Bern, Switzerland. Tel: +41-31-6322700; fax: +41-31-6329766; e-mail: pirbodaghi@artorg.unibe.ch (T. Pirbodaghi).

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Abstract

OBJECTIVES: Rotary blood pumps (RBPs) running at a constant speed are routinely used for the mechanical support of the heart in various clinical applications, from short-term use in heart-lung machines to long-term support of a failing heart. Their operating range is delineated by suction and regurgitation events, leaving limited control on the cardiac workload. This study investigates whether different ratios of systolic/diastolic support are advantageous over a constant-speed operation.

METHODS: In order to effectively control the load on the heart, this study aimed at developing a pulsatile control algorithm for rotary pumps to investigate the impact of pump speed modulation during systole and diastole on the left ventricle unloading. The CentriMag^{TM} RBP with a modified controller was implanted in four sheep via a left thoracotomy and cannulated from the ventricular apex to the descending aorta. To modulate the pump speed synchronized with the heartbeat, custom-made real-time software detected the QRS complex of the electrocardiogram and controlled the pump speed during systole and diastole. Four different speed modulations with the same average speed but different systolic and diastolic speeds were compared with the baseline and the constant speed support. Left ventricular (LV) pressure and volume, coronary flow and pump flow were analysed to examine the influence of the pump speed modulation.

RESULTS: Pulsatile setting reduces the cardiac workload to 64% of the baseline and 72% of the constant speed value. Maximum unloading is obtained with the highest speed during diastole and high-pulse amplitude. End-diastolic volume in the pulsatile modes varied from 85 to 94% of the baseline and 96 to 107% of the constant speed value. Consequently, the mechanical load on the heart can be adjusted to provide assuagement, which may lead to myocardial recovery. The higher pump speed during systole results in an increase in the pulse pressure up to 140% compared with the constant speed.

CONCLUSIONS: The present study is an initial step to more accurate speed modulation of RBPs to optimize the cardiac load control. To develop future control algorithms, the concept of high speed during diastole having a maximal unloading effect on the LV and high speed during systole increasing the pulse pressure is worth considering.

Keywords: Rotary blood pumps • Speed modulation • Systole and diastole • Pulsatile flow • *In vivo* study

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INTRODUCTION

The advent of ventricular assist devices (VADs), which are utilized to partially or completely support the left or right ventricle, has revolutionized the treatment of patients with end-stage heart failure. Nowadays, VADs based on rotary blood pumps (RBPs) for mechanical circulatory support have gained widespread acceptance and usage due to features like small size, lower anticoagulation requirements, higher quality of life and long-term durability. These pumps offer an appealing alternative to the first-generation VADs based on positive displacement pumps, and their field of application may vary from short-term support in cardiopulmonary bypass to long-term mechanical support of patients with end-stage heart failure. In contrast to positive displacement pumps and the native heart, RBPs provide non-physiological blood flow due to the typical use of a constant speed in clinically available devices. Non-pulsatile haemodynamics may have significant implications for vital organs during acute and chronic cardiac support [1, 2]. Studies on the effect of continuous flow for long-term support show that non-pulsatile flow increases the risk of adverse events such as gastrointestinal bleeding [3, 4], peripheral vasculature stiffening and haemorrhagic strokes [5, 6]. Furthermore, a continuous low level of support may result in backflow during diastole, and conversely a continuous high level of support may lead to a collapse of the ventricle, indicating that synchronized speed modulation may broaden the range of applicable speeds of RBPs.

In the literature, there are few reports describing the attempts to modulate the rotary pump's speed, which only focus on asynchronous speed modulation [7], mathematical modelling [8–10] and *in vitro* investigation of pump speed modulation using sinusoidal waveforms [11]. A promising application of VADs, besides their usage in the bridge-to-transplantation and destination therapy, is the bridge-to-myocardial recovery [12, 13]. Although the mechanism of functional recovery of a failing heart is not completely understood, cardiac unloading by assist devices has been suggested as a mechanical tool to promote recovery [14, 15]. We hypothesized that a synchronized speed-modulated pump could yield better control over the heart device interaction, and it might provide pathways to heart recovery and device weaning. Furthermore, to overcome the aforementioned limitations of RBPs and effectively control the load on the heart, the main objective of this study was to modulate the speed of a centrifugal RBP and investigate the effect of pump speed variation during systole and diastole on cardiac unloading. We have examined different levels of support during systole and diastole (comparable with co-pulsation and counter-pulsation) to investigate whether the systolic duration of modulated pulses matters.

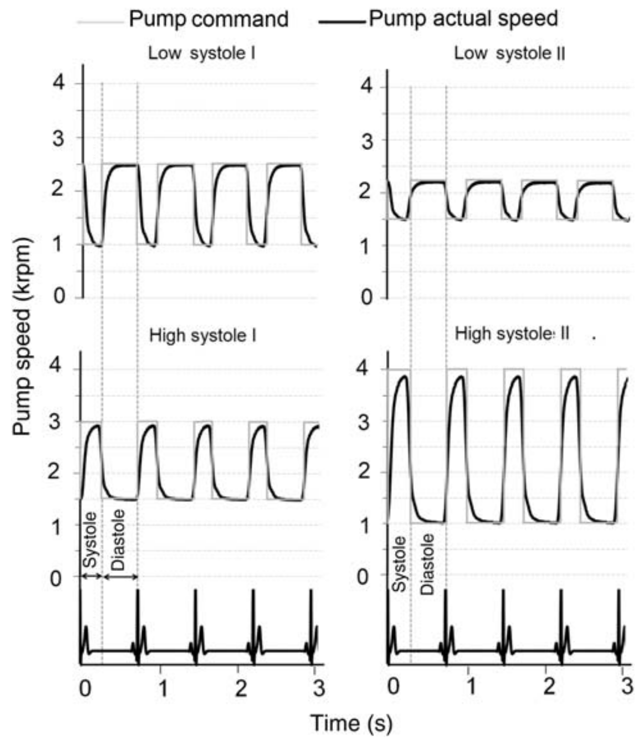

Figure 1: Pump command speed and actual pump speed derived from the motor's Hall sensors; systole starts at the beginning of the QRS complex and last for one-third of the heart cycle and the rest of the heart cycle is considered as diastole.

METHODS

Pulsatile speed pattern of rotary blood pump

The CentriMag^{TM} RBP (Levitronix GmbH, Zürich, Switzerland) is a magnetically levitated centrifugal-flow pump designed to provide haemodynamic support for the periods of up to 30 days during extracorporeal procedures. This pump is based on a bearing-less motor technology and operates without mechanical bearings or seals, which results in minimal friction in the blood path. It is composed of a disposable pump head and a reusable motor that works with a direct drive yielding firm control over the speed. A Levitronix industrial controller was modified and tuned to run with the CentriMag pump. This modified proportional-integral controller yields a direct speed control via analogue voltage and feedback of the actual speed. The control algorithm used to modulate the pump speed was written in LabVIEW (National Instruments, Austin, TX, USA) and communicates in real time via a data acquisition system (c-RIO-9074, National Instruments) with the pump controller, while continuously receiving the animal's electrocardiographic (ECG) signal using a patient monitor (Datex-Ohmeda Division, Instrumentarium Corp., Helsinki, Finland). The programme detects the QRS complexes in the ECG signal using a peak detector algorithm based on the Pan-Tompkins technique [16] and then produces the pump control signal in synchrony with the heart rate. Figure 1 presents different levels of pump command speed during systole and diastole. All the pump speed scenarios have the same mean speed (2000 rpm), and therefore, the number of pump impeller revolutions per each heartbeat is equal. Moreover, this figure shows the actual pump speed derived from the motor's Hall sensors, demonstrating how well the pump can follow the command speed. Pump systole starts at the beginning of the QRS complex and is defined as one-third of the heart cycle, which is based on the length of the previous cycle, while the rest of the heart cycle is considered as diastole.

Surgical preparation and instrumentation

The CentriMag^{TM} RBP was implanted in four healthy female sheep (56–83 kg). All animals received humane care in compliance with the Guide for the Care and Use of Laboratory Animals (National Academy of Sciences, 1996), and the study was approved by the Swiss Federal Veterinary Office. After premedication and induction of anaesthesia, the animals were intubated and anaesthesia and analgesia were maintained with isoflurane in oxygen (1.6%) and fentanyl (5–10 µg/kg/h). A left thoracotomy was used to enter the thorax and expose the left ventricular (LV) apex and the descending aorta (used as a surrogate for the very short ascending aorta). The animals were heparinized to maintain the whole-blood activated clotting time of >400 s. For the surgical implantation of pump inflow, LV apical cannulation was performed using a modified 32 Fr angled venous cannula (DLP 67532, Medtronic Inc., Minneapolis, MN, USA), and a 22 Fr arterial cannula (EOPA 77522, Medtronic) was placed in the descending aorta. The inlet/outlet cannulation was kept short (30 ± 5 cm) in order to simulate the implantable VADs. Following pump priming and the connection of the cannulas to the inlet/outlet ports, pump operation commenced. Coronary flow (CF) and pump flow (PF) were measured using ultrasonic flow probes (Transonic Systems Inc., Ithaca, NY, USA) on the left main coronary artery (8PAU) and the outlet cannula of the pump (9PXL). Fluorescence-based optical sensors (Foxy AL-300) and portable spectroscopes (NeoFox, Ocean Optics, Dunedin, FL, USA) were placed in the coronary sinus and the left carotid artery to measure continuous venous and arterial oxygen partial pressure, respectively. The hemi-azygous vein was ligated to prevent blood mixing in the sinus. Aortic pressure, LV pressure and volume were acquired by a dual pressure 7 Fr admittance catheter (Scisense Inc., London, Ontario, Canada) inserted in the LV via the right carotid artery. Oxygen saturation was measured via pulse-oximetry on the tail. The actual speed of the pump impeller was monitored via an analogue output at the pump controller from the motor's Hall sensors. All signals were acquired using an iWorx data recorder (model 416) and Labscribe data acquisition software (iWorx, Dover, NH, USA) at a sampling rate of 200 Hz. The cRIO-9074 was used to generate analogue voltages to command the pump speed. Prior to recording, the admittance catheter was soaked in warm saline and its pressure signal zeroed to atmosphere. All pressure sensors were calibrated with a PXCAL medical pressure calibrator (Edwards Lifesciences Inc., Irvine, CA, USA) over their expected range.

Study protocol

The study protocol was performed chronologically as follows:

(i) First, baseline measurements, including haemodynamic data (ECG, LV pressure and volume, CF and PF, arterial and venous oxygen partial pressure), were recorded. Baseline is defined as the condition in which the pump is switched off and its inlet cannula is clamped.
(ii) Then, a series of LV pressure–volume (PV) loops were measured during inferior vena cava occlusion at the baseline. These loops were used to derive the volume-axis intercept, V0 in the PV plane for the LV data.
(iii) After that, four different rotational speeds during systole and diastole (Fig. 1) as well as a 2000-rpm constant speed were prescribed for the pump speed (the order of the waveforms was randomized for all sheep).
(iv) Finally, another BL measurement was done to compare with the first BL and control the stability of the animal during the experiment.

After the termination of the study, the animal was euthanized with potassium chloride and the heart was excised to weigh the left ventricle.

Myocardial oxygen consumption

In contrast to many other species, the left and right coronary arteries of sheep exclusively perfuse their respective ventricles, without overlap from left to right. Venous blood from the right ventricular myocardium drains directly into the atrium, whereas the LV venous blood drains into the coronary sinus together with blood from the hemi-azygous vein. Since we ligated the latter, the measurement of the coronary blood flow in the main stem captures the whole flow going through the LV and the measurement of the arterial and coronary sinus pO_2 results in a difference that is exclusively caused by the oxygen consumption of the LV [17]. Myocardial oxygen consumption (MVO_2) is then calculated as the product of this difference and the CF and is expressed in ml/min per 100 g tissue. It is defined as follows [18]:

$$MVO_2 = (AO_2 - VO_2) \times \frac{\text{mean CF}}{\text{LV mass}} \times 100 \qquad (1)$$

where AO_2 and VO_2 are the oxygen contents in the arterial blood and coronary sinus blood, respectively, expressed in ml O_2/dl and can be calculated as:

$$\frac{A}{V} O_2 = \left(\frac{1.35 \times Hb \times SO_2}{100\%}\right) + (pO_2 \times 0.0031) \qquad (2)$$

where Hb represents the haemoglobin concentration (gram per 100 ml), SO_2 the oxygen saturation and pO_2 the oxygen partial pressure measured by NeoFox sensors.

Statistical analysis

One-way analysis of variance was performed to assess the effect of the pump speed on the LV unloading and haemodynamic parameters. In addition, Tukey's *post hoc* test was utilized to compare different pump speed patterns with each other as well, with the baseline and constant speed groups using GraphPad Prism 5.0 (GraphPad Software, San Diego, CA, USA). Probability values of <5% ($P < 0.05$) were considered to be statistically significant.

RESULTS

Table 1 lists the characteristics and energetic parameters of the sheep at the baseline that are averaged over 25 heart cycles. Stroke work (SW) correlates to the energy that LV transfers to the blood and pressure–volume area (PVA) is the total energy consumed by the LV to contract [19].

The average ventricular PV loops over 25 heart cycles are shown in Fig. 2 for sheep #1 as a typical example. The lower pump speed during systole leads to smaller PV loops compared with the baseline and the constant speed, while the higher speed during systole has a slight effect on the size of loops. 'Low systole I' has the smallest (surface area) PV loop.

In Fig. 3, PF patterns are compared (for sheep #1). It is observed that 'high systole II' results in backflow (−1.8 ± 0.06 l/min) through the pump, while for the other pump speed patterns, there is always a positive flow. For low pump speeds during systole, the minimum PF (2.09 ± 0.05 and 3.12 ± 0.11 l/min for low systole I and II, respectively) is remarkably higher compared with the high speed during systole. For the constant

Table 1: Characteristics and energetic parameters of the sheep at baseline

Sheep number	Weight (kg)	LV weight (g)	HR (bpm)	SW (mmHg ml)	PVA (mmHg ml)	CF (ml)
1	56	173	93 ± 1.3	2081 ± 203	4171 ± 221	305 ± 26
2	68	195	72 ± 0.9	4383 ± 31	6625 ± 138	176 ± 23
3	69	166	52 ± 1.4	2301 ± 156	3790 ± 232	–
4	83	204	67 ± 1.8	4389 ± 125	7896 ± 118	–

Values are the mean ± SD, with the average over ∼25 cardiac cycles. HR: heart rate; SW: stroke work; PVA: pressure volume area; CF: coronary flow.

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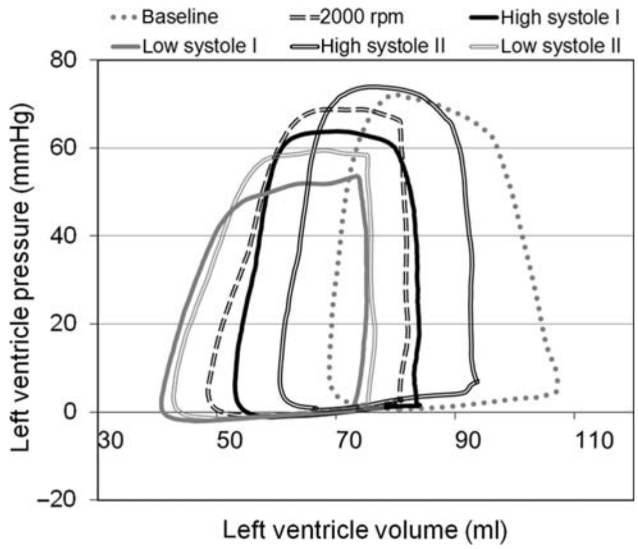

Figure 2: Variation of PV loops due to different pump speed patterns in sheep #1 as a typical example.

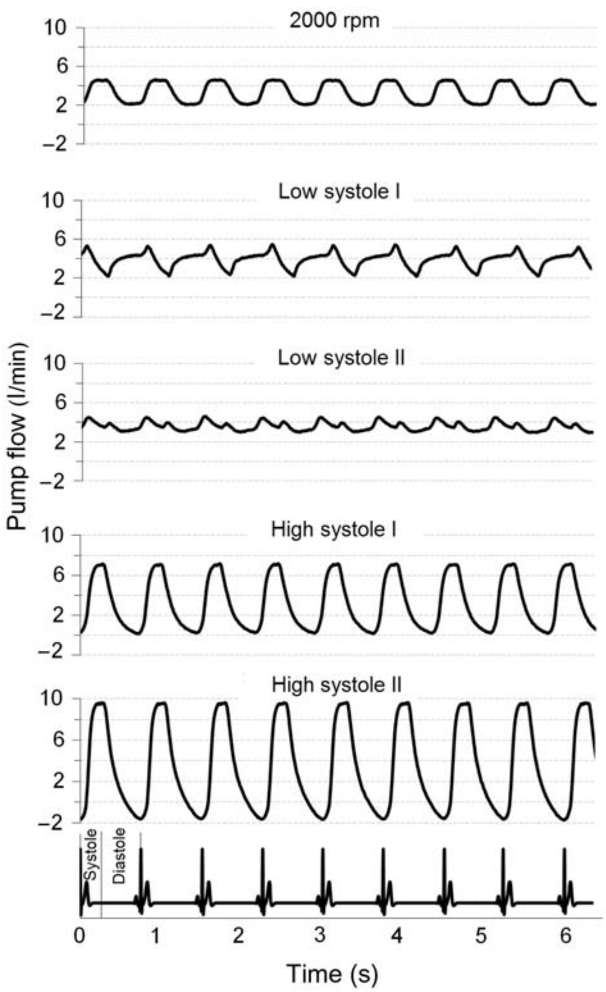

Figure 3: Variation of PF patterns due to different pump speeds.

speed (2000 rpm) support, the pulsatility in PF is completely caused by the beating heart.

The effect of different pump speed patterns on SW, PVA and end-diastolic volume (EDV) is depicted in Fig. 4. The values are

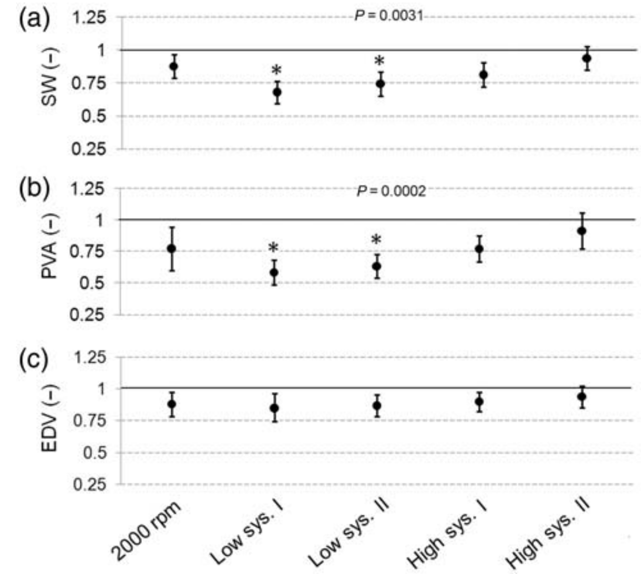

Figure 4: Comparison of SW, PVA and EDV due to different applied waveforms to the pump, the values are the average of all animal data and have been non-dimensionalized by their respective baseline values (solid line represents the baseline value), **P* < 0.05 vs baseline.

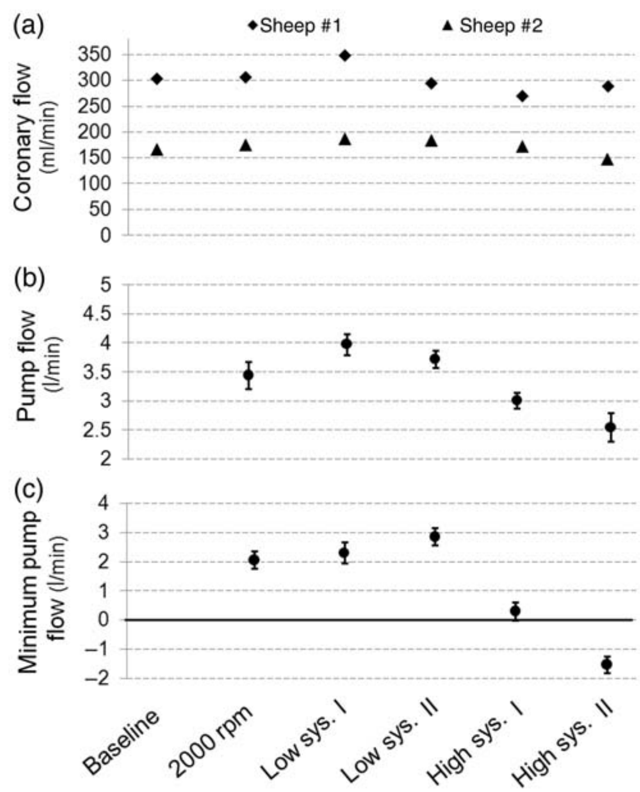

Figure 5: Variation of mean CF, mean PF and mean minimum PF over 25 heart cycles due to different pump speed patterns.

the average of all animal data and have been non-dimensionalized by their respective baseline values. In order to assess the unloading of the heart due to pump speed variation, Fig. 4a and b compare SW and PVA, indicating that a higher speed during diastole can decrease the cardiac workload more than a constant speed. Low systole I has the smallest SW (64% of

Table 2: Diastolic arterial pressure, mean pulse pressure and LV myocardial oxygen consumption due to pump support for sheep #1

	Baseline	2000 rpm	Low systole I	Low systole II	High systole I	High systole II
Diastolic arterial pressure (mmHg)	59.39 ± 1.83	66.82 ± 1.14	69.08 ± 1.64	66.05 ± 1.49	55.27 ± 1.65	49.38 ± 1.70
Mean pulse pressure (mmHg)	35.8 ± 7.57	24.1 ± 6.92	23.3 ± 4.86	22.7 ± 7.58	28.9 ± 11.65	33.6 ± 15.05
Venous pO_2 (mmHg)	52.36	50.82	49.77	47.84	50.86	47.57
Arterial pO_2 (mmHg)	131.30	122.04	104.23	113.66	112.90	110.68
MVO_2 (ml oxygen use/100 g myocardium/min)	42.56	39.62	34.21	34.43	33.21	30.11

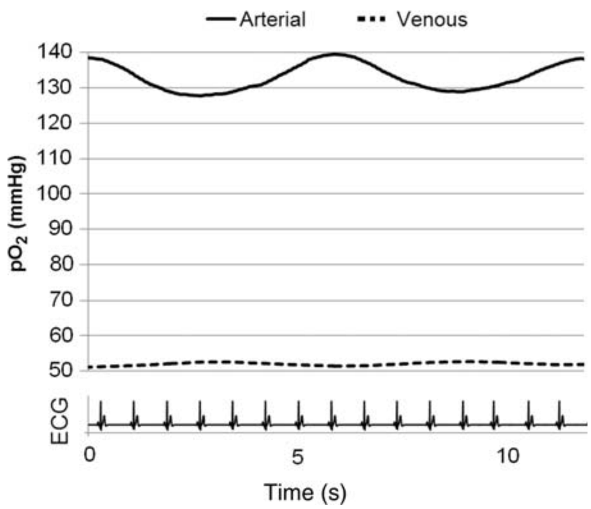

Figure 6: Variation of the oxygen partial pressure in arterial and venous blood due to breathing at the baseline.

the baseline value and 72% of the constant speed) and PVA (58% of the baseline value and 77% of the constant speed). SW can be controlled between 64 and 93% (high systole II) of the baseline value, thereby controlling the heart load by only changing the pump speed pattern; meanwhile, the mean speed remains the same at 2000 rpm. Figure 4c illustrates that EDV in the pulsatile modes varied from 85 to 94% of the baseline and 96 to 107% of the constant speed value.

The effect of different pump speed patterns on mean CF over 25 heart cycles is illustrated in Fig. 5a for sheep #1 and #2. Due to surgical complications, the CF probe could not be reliably placed on sheep #3 and #4. Low systole I results in a higher mean CF compared with other pump speeds. Figure 5b and c show the variations in the mean PF and the minimum PF. High systole II has the lowest (2.55 ± 0.34 l/min) and low systole I has the largest (3.95 ± 0.11 l/min) mean PF. It is important to notice that while all the waveforms have the same mean speed, high systole II has a negative minimum PF (−1.73 ± 0.14 l/min) indicating a backflow through the pump.

Table 2 lists the diastolic arterial pressure (the mean of the arterial pressure during diastole only) and the pulse pressure due to pump support. Low systole I has the highest diastolic arterial pressure and high systole II has the highest pulse pressure. A higher pump speed during systole results in an increase in the pulse pressure up to 140% compared with the constant speed support. Moreover, this table compares the myocardial oxygen consumption between different pump speed patterns and baseline for sheep #1, where low systole I has the lowest oxygen consumption value.

Figure 6 illustrates the variations in the oxygen partial pressure in arterial and venous blood due to breathing at the baseline. It should be mentioned that data are only for one animal and serve as an illustration of the new technique to calculate the myocardium oxygen consumption.

DISCUSSION

This study confirms that a synchronized RBP can effectively control the cardiac load and broadens the range of applicable pump speeds. Also, it is in line with the findings of Maybaum et al. [15], who demonstrated the importance of the synchrony relationship between the heart and the assist device for ventricular unloading and myocardial recovery. In addition, the pump speed modulation using different levels of support during systole and diastole offers additional control modalities of haemodynamics. Providing a pulsatile flow together with the other advantages of rotary pumps is of great importance to advanced heart failure patients and might be useful for the perfusion of other vital organs.

To modulate the PF, the controllers of some commercially available pumps (e.g. Jarvik 2000, Medos Delta stream DP3, Heartware HVAD) include the Lavare cycle in which the pump speed is intermittently and asynchronously varied to allow better washing and prevent clot formation. It should be mentioned that in our study, we focused on the pump speed variation during systole and diastole synchronized with ECG to investigate its effect on the cardiac load control.

Considering the effect of pump speed patterns on LV unloading, it is observed that a higher level of pump support during diastole unloads the LV significantly more than constant speed, which confirms the results published in Pirbodaghi et al. [21]. The higher the pump speed during diastole, the less the LV can fill (more volume of blood goes through the pump, Fig. 5b), and according to the Frank-Starling law of the heart, the LV will generate less work. Low systole I (1000 rpm during systole and 2500 rpm during diastole) has the highest unloading effect on the LV (64% of the baseline SW and 72% of the constant speed SW; 56% of the baseline PVA and 77% of the constant speed PVA). As a result, high speed during diastole unloads the heart the most.

Although the pump speed during systole for this speed is low (1000 rpm), PF is always positive. Backflow through the pump, as is the case with high systole II, increases the load on the heart, which is potentially dangerous for a weakened heart. The backflow is caused by the high pressure difference between aorta and LV during diastole and clearly requires a high speed to be overcome. Consequently, its prohibition is an important issue in the selection of the pump speed pattern. Another important point that should be considered in the interaction between the heart and the assist device is its effect on heart perfusion. The results show that the low systole I (with high speed in diastole) increases the mean CF. This could be partially due to the fact that low systole I has the highest diastolic arterial pressure (Table 2), which can force more blood inside the coronary artery. Higher CF is likely to be beneficial for the myocardium due to the impact of myocardial blood flow for heart recovery and device weaning. The data show that low systole I has the lowest oxygen consumption value, and the results are in agreement with those published by Voitl *et al*. [20], which demonstrated that the myocardial oxygen consumption can be reduced by mechanical assistance. As a result, it can be concluded that this speed pattern (in general low pump speed during systole and high pump speed during diastole) is the best option for the modulation of the pump speed.

The results should be interpreted with caution, since an intact animal model does not accurately reflect the clinical picture of humans with heart failure. Regardless of this limitation, however, our study demonstrates the feasibility of pulsing RBPs and provides a useful initial step towards the clinical implementation of speed-modulated rotary pumps. In the present study, we focused on the effect of heart-pump synchronization and different levels of support during systole and diastole on the cardiac load control. We indeed believe that the pulsing of RBPs has a substantial potential for heart failure bridging to recovery that needs to be explored, and further studies are required to validate this and assess the importance of different prescriptive parameters.

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Conflict of interest: none declared.

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