A monitoring and physiological control system for determining aortic valve closing with a ventricular assist device†

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OBJECTIVES: Real-time monitoring of the aortic valve function and the loading state of the left ventricle (LV) during mechanical circulatory support is essential. Therefore, we developed a system that determines accurately the aortic valve closing moment based on integrals derived from the pump inlet pressure and the pump power [pressure-power area (PPA)].

METHODS: A Deltastream diagonal pump was implanted in 10 healthy Rhoen sheep. Changes in ventricular volume and pressure in different assist levels were measured by a conductance catheter placed in the LV and were correlated with intrinsic pump signals, motor power, voltage and current. Measurements were obtained in the state of normal as well as decreased left ventricular contractility induced by β-blockers.

RESULTS: Complete datasets were obtained in seven animals. The PPA-feedback signal reached its maximum at the speed of aortic valve closing. This was validated by pressure-volume (PV)-catheter measurements both at the baseline and in the state of decreased contractility. In both cases, zero-crossing occurred at the point of aortic valve closing speed.

CONCLUSIONS: With this trial, we deliver the experimental basis for the development of an automatic feedback controller that would allow periodic speed changes in accordance with the loading state of the native ventricle and the opening state of the aortic valve. This would deliver real-time data to treating physicians and enable the establishment of a standard weaning protocol.

Keywords: Heart assist devices • Aortic valve • Patient monitoring

INTRODUCTION

It is well known that in cases of dilated cardiomyopathy, mechanical unloading by the means of mechanical circulatory support may reverse or at least ameliorate the effects of volume and pressure overload, which trigger pathological remodelling of the heart [1]. In fact, numerous trials describe the regression of cardiomyocyte hypertrophy, the upregulation of SERCA-2a expression, the restoration of β-adrenergic responsiveness and a faster cellular relaxation [2–4]. However, it is still unclear in which subset of patients this reverse remodelling, once taking place on the cellular and genetic level, actually translates into myocardial recovery and prevention of side-effects of continuous blood flow. Real-time monitoring of the loading state of the ventricle is therefore essential. For this reason, we developed this system, which accurately determines the aortic valve’s closing moment based on integrals derived from the pump inlet pressure (PInP) and the pump power [pressure-power area (PPA)].

MATERIALS AND METHODS

Animal model

Ten healthy female Roehn sheep (weight 55–85 kg) were used in the study according to the guidelines of the German Animal
Anaesthesia and surgical preparation

Anaesthesia was performed according to a standard institutional protocol. General anaesthesia was induced with 20 mg/100 kg xylazine (Narcoyl® 2 ad us. vet. Intervet Swissmedic, 20 mg/ml) and 6–10 mg/kg propofol (Propofol MCT 1%, 50 ml, Fresenius Kabi Deutschland GmbH, Bad Homburg, Germany) and maintained with 1.5–2% isoflurane (Forene®, Abbott GmbH & Co. KG, Wiesbaden, Germany) in oxygen (50–100%) and fentanyl (0.005 mg/kg/h). Roncuronium (Esmeron® 10 mg/ml, N.V. Organon, Oss, Netherlands) 100–150 mg i.v. was administered as a muscle relaxant. Heparin (Heparin-Na 25000 Rati®, Ratiopharm GmbH, Ulm, Germany) was administered intravenously (10 000–15 000 IU) with a targeted activated clotting time of 400 s. Systemic pressure was obtained through an arterial tubing line placed in the left carotid artery.

Surgical procedure

We performed a lateral thoracotomy at the fifth intercostal space. For better exposure, we removed the fifth rib. Following excision of the pericardium, we placed the pressure-volume (PV)-conductance catheter (Millar® Venti-CATH-510S, 5 Fr, Millar Instruments, Inc., Houston, TX, USA), CD-Lecycom (CA-71x3-PL, 7 Fr, Zoetermeer, Netherlands) into the LV. Calibration of the PV catheter was performed regularly. Left ventricular support was facilitated by a Deltastream diagonal pump (DP3, Medos Medizintechnik GmbH). The inflow cannula [Medos ventricular assist device (VAD) Cannula—32, 36, 42, 51 Fr] was inserted on the beating heart into the left ventricular cavity through the apex and the outflow cannula (Medtronic 18–22 Fr) was inserted into the ascending aorta.

Pump performance

The DP3 was controlled by a custom-made controller box using a 4Q maxon converter and a Simulink program. We defined two assist levels (ALS) of the pump based on rotational speed and opening state of the aortic valve: 0% AL was defined as the lowest rotational speed at which backflow through the pump was inhibited and 100% AL as the rotational speed at which the aortic valve stayed permanently closed. We determined the 0 and 100% ALS in each trial by increasing the pump speed within 30 s from 2000 rpm (0% AL) to the rotational speed at which suck-down of the LV occurred (100% AL). In a second step, measurements were started at an AL of 50–60% and rotational speed was stepwise increased by 250–500 rpm every 2 min until left ventricular suckdown occurred.

Data acquisition and analysis

Changes in ventricular volume and pressure were measured by a conductance catheter placed in the LV. Left ventricular pressure (LVP) was furthermore measured by a pressure sensor implanted in the inlet cannula of the DP3 pump. Measurements were obtained in the state of normal left ventricular contractility and in the state of decreased left ventricular contractility as induced by metoprolol (Beloc® i.v. 5 mg/5 ml, AstraZeneca GmbH, Wedel, Germany) or esmolol (Brevibloc® 100 mg/10 ml, Baxter, Germany) that led to a decrease in maximal LVP to 50% of the baseline (Table 1). Aortic pressure, pulmonary artery pressure, central venous pressure and PiNP were measured by Datex.

Aortic flow (AoQ), which was used to define the point of complete aortic valve closing, and pulmonary artery flow were measured by a Transonic PAU-series 2-channel 402p system with two Transonic PAU-series sensors (Transonic Systems, Inc., Ithaca, NY, USA) attached to the ascending aorta (diameter 20, 22 or 24 mm) and to the main pulmonary artery (diameter 18, 20, 22 or 24 mm). The pump flow [ventricular assist device flow (VADQ)] was measured by a Transonic 1-channel H9CSC143, T110R with a Transonic PAX series sensor (Transonic Systems, Inc., Ithaca, NY, USA), attached to the outflow graft. The intrinsic pump signals, motor power, voltage and current were measured by a power analyzer (WT 1800, Yokogawa, Japan). The communication and control module for the pump speed and the corresponding data acquisition was developed in Simulink (MathWorks, Natick, MA, USA) and performed by Powerlab (ADInstruments, Dunedin, New Zealand) or by dSpace signal-processor system (dSpace, Paderborn, Germany). All signals were acquired at a sampling frequency of 2 kHz. Data analysis was performed by Labchart7 (ADInstruments, Dunedin, New Zealand) and a custom-made software using Matlab (MathWorks, Natick, MA, USA).

RESULTS

We obtained complete data in 7 animal trials. Table 1 lists animal weight, the β-blocker used to facilitate a 50% decrease in contractility and pump speed at which 100% AL was achieved.

The work of the native ventricle is typically estimated by pressure-volume loops (PVLs). Figure 1A demonstrates a PVL for a single cardiac cycle from one of our animal trials. In Fig. 1B and C, time is indicated by the colours red, blue, black and green drawing the PVL counterclockwise.

For real-time monitoring of the aortic valve and in order to determine the point at which the aortic valve is permanently closed, we developed a new method based on the pressure–power area (PPA) diagram of the VAD. The PPA is defined as the area calculated by integration of one closed loop (corresponding to one cardiac cycle) in a diagram plotting LVP over the motor power. Figure 1D shows a typical PPA diagram for a single cardiac cycle of the same animal trial. In contrast to the PVL, the PPA diagram is drawn clockwise as indicated by the arrows.

<p>| Table 1: Animal trial, weight, β-blocker used to facilitate a 50% decrease in contractility and pump speed at which 100% AL was achieved |
|----------------|----------------|----------------|</p>
<table>
<thead>
<tr>
<th>Animal trial number</th>
<th>Weight (kg)</th>
<th>β-Blocker used</th>
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<tr>
<td>1</td>
<td>70.7</td>
<td>Beloc®</td>
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<tr>
<td>2</td>
<td>55.2</td>
<td>Brevibloc®</td>
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<tr>
<td>3</td>
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<td>Brevibloc®</td>
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<tr>
<td>4</td>
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</tr>
<tr>
<td>5</td>
<td>71.6</td>
<td>Brevibloc®</td>
</tr>
<tr>
<td>6</td>
<td>85.0</td>
<td>Brevibloc®</td>
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<tr>
<td>Motor speed (rpm) for 100% AL baseline/β-blocked case</td>
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<td>4600/2900</td>
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<td>4700/3300</td>
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Figures 2A and B show typical steady-state measurements of PVLs and PPAs taken from a real-time measurement of an animal trial. In each cardiac cycle, measurements were performed for 2 min at different motor speeds indicated in the figure by different colours. For each cardiac cycle, the PVL and the PPA were calculated and averaged at each motor speed.

**Figure 1:** Relation between left ventricle (LV) pressure load and pump power consumption/LV volume changes. (A) pressure-volume loop (PVL) diagram of a single cardiac cycle, timeline indicated by red, blue, black and green; the loop rotates counterclockwise as indicated by the arrows in the figure. (B) LV pressure of a single cardiac cycle. (C) LV volume of a single cardiac cycle. (D) pressure-power area (PPA) diagram defined by our method of a single cardiac cycle; the motor power rotates clockwise as indicated by arrows in the figure; the motor power augments during emptying of the LV (afterload related) and decreases during LV filling.

**Figure 2:** Typical steady-state measurements of a PVL and PPA taken from a real-time measurement of an animal trial. Cardiac cycles are measured for 2 min at a defined motor speed indicated by the different colours. For each cardiac cycle, PPA and PVL are calculated and averaged for each motor speed. (A) Steady-state measurement of PVL diagram, (B) steady-state measurement of PPA diagram, (C) PVL area gradient with rpm increase and (D) PPA gradient with rpm increase.
The resulting PVL and PPA gradient are shown in Fig. 2C and D, respectively.

We observed that by increasing the motor speed, the area of PVL was reduced and by reaching the suction point, it became almost zero. In contrast, we observed that the feedback variable PPA increased and finally reached a maximum at a motor speed after the aortic valve permanently closed. The permanent closing of the aortic valve was defined as zero AoQ measured during one cardiac cycle.

The same measurements were then performed in the state of decreased contractility. The PPA-feedback variable reached its maximum after the aortic valve permanently closed but in contrast to normal contractility, at a lower motor speed (see Table 1).

In the next step, we implemented an improved protocol. In combination to the stepwise increasing motor speed, square waves pulses with small amplitude (250–500 rpm) and low frequency (<0.05 Hz) were applied around the current mean motor speed (Fig. 3). We calculated in real-time the PPA derivative (ΔPPA), which was defined as the difference of mean PPA for the high- and the low-speed periods of the applied square wave pulses.

We found that, regardless of contractility, the ΔPPA signal always changed from positive to negative after the point of permanent aortic valve closing. Figure 4 illustrates typical measurements in the state of normal contractility. As the pump flow (VADQ: in red) increased, the AoQ (in blue) decreased (Fig. 4A), the maximum of the PPA-feedback variable was reached after the point at which permanent aortic valve closing had taken place (Fig. 4B) and at the same time the ΔPPA signal changed from positive to negative (Fig. 4C).

**DISCUSSION**

Current management of left ventricular mechanical support resembles a blind flight in a foggy sky. The opening state of the aortic valve is considered to be crucial. However, echocardiographic examinations deliver solely a snapshot in time, thus real-time identification of the optimal pump speed setting would promote myocardial recovery and ameliorate side-effects of continuous blood flow such as aortic leaflet fusion [8, 9] and thrombus formation [10]. Furthermore, maintenance of a certain degree of pulsatility seems to have beneficial effects on the coagulation system [6]. For these reasons, we developed a physiological control system based on the PPA-feedback signal that enables real-time monitoring of left ventricular contractile state and OLIVU during left ventricular assist device assistance.

Since all sensors, regardless of the chosen material, are susceptible to significant drift and hematocrit changes, we focused on pump power as an alternative to commercial sensors. The PPA-feedback signal proved to have a peak after the permanent aortic valve closing. This was validated by PV catheter measurements both at the baseline and under the state of decreased contractility. Similarly, in the improved protocol, the ΔPPA signal changed from positive to negative after the aortic valve closing point was reached. Therefore, our method provides the possibility to determine the motor speed range at which the VAD should be operated in order to promote cardiac recovery.

According to PV catheter measurements, an increase in pump speed resulted in a decrease in LVP and left ventricular end-diastolic volume. This effect was profound as the aortic valve closed and the volume of the heart decreased dramatically.

With this trial, we aimed to deliver the experimental basis for the development of an automatic feedback controller that would allow periodic speed changes in accordance with the loading state of the native ventricle and deliver real-time data to treating physicians. The presented method promises to enable an operational speed modulation that, on the one hand, is significant enough to provoke a relevant response of the system, while on the other hand, maintains the overall performance of the pump. When implementing the presented method, it is important that the frequency of the speed modulation is low enough so that multiple heartbeats can occur within a single high-speed and low-speed period.

Further research, including simulations of different physiological states in a Mock Heart Circulation Loop, is now being conducted in order to develop more sophisticated control algorithms.
and practically implement our findings in the clinical setting. The PPA-feedback signal can provide physicians with real-time information about the loading state of the ventricle and the opening state of the aortic valve during mechanical circulatory support. In addition, the PPA-feedback signal could also supply clinicians with information about ventricular function that is normally obtained by PVLs such as end-systolic and end-diastolic pressure-volume relationships. This would allow the operation of the VAD at a speed that sufficiently unloads the ventricle, but at the same time preserves a certain degree of contractility, overcoming the risk of myocardial atrophy and therefore promoting myocardial recovery. Furthermore, information about the contractile state of the ventricle and the opening state of the aortic valve would enable the establishment of a standard weaning protocol in cases of myocardial recovery.

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Conflict of interest: none declared.

REFERENCES


APPENDIX. CONFERENCE DISCUSSION

Dr S. Clark (Newcastle upon Tyne, UK): This is obviously a very important issue and a very elegant solution that you've described. Where do you see the next stage of future development in this going forward in clinical terms?

Dr Spiliopoulos: We are currently in the early stages of research. Our aim is to develop in the mid-term a micro- and microcontroller for continuous flow pumps. The microcontroller would enable an intermittent pulsatile function of the pump by adapting its rotation speed, and the macrocontroller would deliver information about left ventricular function and weaning potential. And that's the thing we want to have for the future.

Dr Clark: And if I understood correctly, you're going to have a continual flux in motor speed or rotational speed?

Dr Spiliopoulos: Yes.

Dr Clark: Did you look at any impact that that would have on component wear and power consumption?

Dr Spiliopoulos: To be honest, the analysis of the data is still ongoing. That's a question I cannot give an answer to right now. But what I can say is that we can now determine precisely and in real-time the point of aortic valve closing. Furthermore, we have observed that pressure-power loops correlate directly with conventional pressure volume loops of the left ventricle. Finally by measuring the variation of left ventricular pressure over time, we eliminate the well-known problem of sensor drift. That means measurements are reliable.

Dr Clark: And you were monitoring aortic valve closure very carefully in this study.

Dr Spiliopoulos: Yes.

Dr Clark: But what about the degree of aortic valve opening because that's obviously a very important issue as well. Not just that the aortic valve can open but to what degree it opens.

Dr Spiliopoulos: Certainly, I agree with that, but since we are at the early stage of research, this is an issue that we have not yet examined.