Effects of Thoratec pulsatile ventricular assist device timing on the abdominal aortic wave intensity pattern

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1Institute for Dynamic Systems and Control, ETH Zurich, Zurich, Switzerland; 2Department of Cardiology, University Hospital Bern, Bern, Switzerland; 3Department of Clinical Veterinary Medicine, University of Bern, Bern, Switzerland; and 4ARTORG Center for Biomedical Research, University of Bern, Bern, Switzerland

Submitted 5 February 2014; accepted in final form 18 August 2014

Jahren SE, Amacher R, Weber A, Most H, Flammer SA, Traupe T, Stoller M, de Marchi S, Vandenberghe S. Effects of Thoratec pulsatile ventricular assist device timing on the abdominal aortic wave intensity pattern. Am J Physiol Heart Circ Physiol 307: H1243–H1251, 2014. First published August 22, 2014; doi:10.1152/ajpheart.00085.2014.—Arterial waves are seen as possible independent mediators of cardiovascular risks, and the wave intensity analysis (WIA) has therefore been proposed as a method for patient selection for ventricular assist device (VAD) implantation. Interpreting measured wave intensity (WI) is challenging, and complexity is increased by the implantation of a VAD. The waves generated by the VAD interact with the waves generated by the native heart, and this interaction varies with changing VAD settings. Eight sheep were implanted with a pulsatile VAD (PVAD) through ventriculooaortic cannulation. The start of PVAD ejection was synchronized to the native R wave and delayed between 0 and 90% of the cardiac cycle in 10% steps or phase shifts (PS). Pressure and velocity signals were registered, with the use of a combined Doppler and pressure wire positioned in the abdominal aorta, and used to calculate the WI. Depending on the PS, different wave interference phenomena occurred. Maximum unloading of the left ventricle (LV) coincided with constructive interference and maximum blood flow pulsatility, and maximum loading of the LV coincided with destructive interference and minimum blood flow pulsatility. We believe that noninvasive WIA could potentially be used clinically to assess the mechanical load of the LV and to monitor the peripheral hemodynamics such as blood flow pulsatility and risk of intestinal bleeding.

METHODS

Animals. This study was approved by the Commission of Animal Experimentation of the Canton of Bern, Switzerland (No. 52/09). Eight adult, female, mixed breed sheep (59 – 83 kg) were implanted with a Thoratec PVAD (Thoratec, Pleasanton, CA) via left thoracotomy as described in detail previously (3). A custom-made cannula was inserted in the LV apex of the beating heart, and an outflow graft was anastomosed end-to-side on the aorta. Figure 1 shows a schematic of the PVAD implantation. The sheep were premedicated with intramuscular midazolam (0.2 mg/kg) and methadone (0.2 mg/kg), and anesthesia was induced with intravenous midazolam (0.2 mg/kg), ketamine (3.5 mg/kg), and propofol (1 – 3 mg/kg). After orotracheal intubation, anesthesia was maintained with a minimal concentration of 1.6% isoflurane in oxygen and fentanyl (5 µg/kg, followed by 5–10 µg·kg⁻¹·h⁻¹ infusion). Neuromuscular blockade was provided by rocuronium (0.15–0.6 mg/kg), and the lungs were mechanically ventilated. An orogastric tube was placed to decompress the rumen, and the rectal temperature was maintained between 36 and 38°C with a circulating warm air blanket. Autologous blood transfusion with a cell saver (AutoLog; Medtronic, Minneapolis, MN) was used in the event of severe intraoperative blood loss. To create a broader range of hemodynamic conditions, pharmacological interventions were additionally performed in each sheep with continuous rate intravenous infusions of phenylephrine (bolus, 1.25–2.25 µg/kg; maintenance,
EFFECTS OF PVAD TIMING ON THE AORTIC WI PATTERN

Fig. 1. Schematic overview of the pulsatile ventricular assist device (PVAD) implantation. A custom-made cannula was inserted into the left ventricular (LV) apex of the beating heart, and an outflow graft was anastomosed end-to-site on the descending aorta. Flow probes were mounted on the inlet and outlet cannulas of the PVAD to measure PVAD inflow and outflow, respectively; a pressure transducer was mounted on the PVAD driveline to measure the driveline pressure (pneumatics) of the PVAD.

The cardiac support protocol consisted of actuating the PVAD by a Medos pneumatic driver (Medos Medizintechnik, Stolberg, Germany) in external trigger mode with a 35% systolic period. This external trigger was provided by a cRIO-9074 real-time controller (National Instruments, Austin, TX) that applied a square wave pulse to the Medos driver. The duration of the PVAD systole of 1 cardiac cycle (double arrow, “R-R 100%”) between the R wave of the ECG and the onset of PVAD systole. The duration of the PVAD systole was set to 35%.

The cardiac support protocol was repeated for each hemodynamic state induced in each sheep.

In addition to the surgical method described previously (3), a cut-down of the left groin was performed and a vascular access port inserted into the femoral artery. A 5-F guiding catheter was inserted through the guide and positioned with the tip at the level of the vertebral artery, and confirmed by X-ray visualization. The pressure and velocity signals produced by the wire were routed through a Volcano ComboMap monitor to a National Instruments cDAQ data acquisition system, where they were recorded with custom LabView software together with duplicates of arterial pressure, ECG, and PVAD trigger signal to enable later synchronization with the iWorx recorded data. In the first four sheep, recycled Combowires were used, and these sheep were needed for training and tuning of the measurement protocols. The final instrumentation setup for the study was therefore only available in the remaining four sheep.

Table 1. Overview of the signal quality of all available data sets

<table>
<thead>
<tr>
<th>Sheep</th>
<th>Data Set 1</th>
<th>Data Set 2</th>
<th>Data Set 3</th>
<th>Data Sets Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Poor pressure and velocity signals</td>
<td>Poor pressure and velocity signals</td>
<td>OK</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
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<tr>
<td>8</td>
<td>OK</td>
<td>OK</td>
<td>OK</td>
<td>1, 2, 3</td>
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</table>

Protocol data were recorded such that, in total, 12 data sets were available with the final instrumentation (3 data sets in 4 sheep). Each data set consisted of data records of the 10 different PS and the 2 baselines (12 data records) of the cardiac support protocol. The data sets were postprocessed, and due to either strongly arrhythmic behavior or poor Doppler signal quality, 5 of 12 data sets were excluded from this study. A total of 7 data sets from 3 different sheep were thus available for further analysis, as indicated in Table 1.

A section of stable heart beats (range 14–34 beats, median 36 beats) was selected for each data record, and for each of these sections, a single representative average heart beat was calculated. All data were processed using MATLAB (R2012b; The MathWorks, Natick, MA). Figure 3 illustrates the terminology used to describe the recorded data.

The total WI was calculated as (20)

\[ I = \frac{dP \cdot dU}{dI} \]

where \( I \) is the total WI (W/m²), \( P \) is the abdominal aortic pressure (Pa), and \( U \) is the abdominal aortic blood flow velocity (m/s).
was separated into its forward (+) and backward (−) components by

\[
dP_\pm = \frac{1}{2}(dP \pm \rho c dU)
\]

\[
dU_\pm = \frac{1}{2}(dU \pm \frac{dP}{\rho c})
\]

\[
dI_\pm = dP_\pm \cdot dU_\pm,
\]

where \( \rho \) is the blood density (kg/m\(^3\)) and \( c \) is the wave speed (m/s). The value of the product of \( \rho \) and \( c \) was calculated as the slope of the linear section of the pressure-flow velocity loop at the beginning of systole (20) for each baseline. The mean value of \( \rho c \) for the two baselines of each data set was calculated and used for all calculations. Figure 4 shows a representative WI pattern of a baseline. The backward components of the total WI (\( dI_\pm \)) represent the waves reflected in the periphery and are not discussed in the current report.

Indexes for local pressure pulsatility were calculated, as well. The energy equivalent pressure (EEP), representing the total hemodynamic energy normalized by the displaced volume and thus expressed as a pressure, is calculated as (23)

\[
EEP = 7.5 \times 10^{-3} \left( \frac{P \cdot U dt}{U dt} \right) \text{ (mmHg)},
\]

where the factor \( 7.5 \times 10^{-3} \) converts the pressure (from Pa to mmHg). The surplus hemodynamic pressure (SHP) is the difference between EEP and the local mean arterial pressure (MAP\( l \), mmHg):

\[
SHP = EEP - MAP \text{ (mmHg)}.
\]

SHP is equal to zero if there is no pulsatility and the flow velocity is constant.

In addition to the parameters described above, the stroke work [SW (J)] of the LV was calculated as the area of the pressure-volume loop, the assistance ratio (AR) was calculated as the ratio between the volumetric outflow rate of the PVAD and the pulmonary artery flow (used as a measure for cardiac output), and the PVAD stroke volume [PVAD SV (ml), the volume ejected from the PVAD per PVAD cycle] was calculated by integration of the outflow rate of the PVAD.

Statistical analyses were performed using SPSS Statistics 21.0 (IBM, Armonk, NY). Analysis of variance (ANOVA) was performed for each calculated parameter to test if there was a statistically significant dependency on the PS. This indicator of the data set and an indicator of the sheep were entered into the ANOVA model to account for individual variability. Additionally, if the ANOVA was found to be significant for the PS, pairwise \( t \)-tests with Bonferroni correction were performed to see for which PS the parameters were significantly different from baseline. A \( P \) value <0.05 was considered statistically significant for both tests mentioned above.

RESULTS

The seven data sets provided a broad range of hemodynamic conditions. The heart rate in these seven data sets varied between 81 and 119 beats/min with a mean of 95 beats/min, the MAP varied between 44 and 86 mmHg with a mean of 56 mmHg, and the cardiac output varied between 4.4 and 7.6 l/min with a mean of 5.7 l/min.

Influence of the PVAD on the hemodynamics. The PVAD interacts with the heart and the cardiovascular system and influences the hemodynamic parameters. This interaction was found to be statistically significant by ANOVA performed for EEP, SHP, AR, PVAD SV, and SW. Figure 5 shows the distribution of EEP, SHP, AR, PVAD SV, and SW for all 7 data sets for the 10 different PS. Pairwise \( t \)-tests were performed to identify phase shifts (PS) where the parameters EEP, SHP, and SW were significantly different from baseline. Table 2 summarizes these results. The AR and PVAD SV were significantly different from baseline for all PS because the baseline has zero AR and zero PVAD SV. The PVAD filling depends on the PS because it is influenced by the amount of overlap between the PVAD filling period and the LV ejection period. PVAD filling was found to correlate strongly with PVAD SV (\( R^2 = 0.95 \)), and thus PVAD flow. Consequently, the AR is PS dependent due to the balance between the LV ejection and the PVAD filling.

Influence of the PVAD on the wave intensity. The implantation of a PVAD makes the WIA more complex due to the

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**Fig. 3.** Overview of the terminology used to describe the measured data. Each data set consists of 12 data records characterized by a PVAD setting (baseline or a specific PS), obtained from 1 of 4 sheep. For each sheep, 3 data sets were recorded, giving a total of 12 data sets.

**Fig. 4.** A representative wave intensity (WI) pattern of a baseline (sheep 8, data set 2), highlighting the 2 characteristic forward-traveling waves of the LV (9, 19): a compression wave at start of LV ejection followed by a decompression wave at end ejection. The WI is normalized to the peak magnitude (PM) of the LV compression wave.

**Fig. 5.** A representative wave intensity (WI) pattern of a baseline (sheep 8, data set 2), highlighting the 2 characteristic forward-traveling waves of the LV (9, 19): a compression wave at start of LV ejection followed by a decompression wave at end ejection. The WI is normalized to the peak magnitude (PM) of the LV compression wave.
addition of two dominant forward-traveling waves: a PVAD compression and decompression wave at start and end of PVAD ejection, respectively. Figure 6 shows the WI of the baseline and the measurements with a supported LV for different PS (sheep 6, data set 1), together with the pressure in the ascending and abdominal aorta. Clearly, the PVAD waves interfere with the native LV waves and change the WI pattern. The pressure waveform in the abdominal aorta is different and deformed compared with the pressure waveform in the ascending aorta. Different interference phenomena can be observed for the range of PS, due to the varying occurrence time of the PVAD waves in the cardiac cycle.

The wave interference phenomena occur when one of the PVAD waves arrives at the measurement site simultaneously with one of the LV waves. Figure 7 depicts a summary of the arrival times of the two dominant forward-traveling waves of the LV and of the PVAD in the abdominal aorta for different PS. For PS = 0 (copulsation) and 10%, constructive interference occurred between the compression waves and decompression waves of the LV and the PVAD. Figure 8 shows this constructive WI pattern for a PS between 0 and 15%. For PS = 40 and 50% (counterpulsation), destructive interference occurred between the LV decompression wave and the PVAD compression wave. Figure 9 shows this destructive WI pattern for a PS between 40 and 50%. For PS = 70 and 80%, destructive interference occurred between the LV compression wave and the PVAD decompression wave. Figure 10 shows this destructive WI pattern for a PS between 70 and 80%.

The intensity and energy of a wave is characterized by its peak magnitude (PM) and the area under the curve (AC), respectively, and both parameters are influenced by the PS. These influences on PM and AC were found to be statistically significant for all of the wave types analyzed by ANOVA: LV compression wave, LV decompression wave, PVAD compression wave, and PVAD decompression wave. Figure 11 shows the distribution of PM and the AC for these 4 waves for all data sets for the 10 different PS. Pairwise t-tests were performed to identify PS where the PM and the AC were significantly different from baseline. Table 2 summarizes these results. For the rest of the PS, the PM and the AC were not significantly different from baseline. For the PM and the AC of the PVAD waves, all PS were significantly different from baseline because there are no PVAD waves in the baseline.

Table 2. Statistical significance of differences in hemodynamic parameters, LV wave PM, and LV wave AC compared with baseline as a function of PS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PS, %</th>
<th>0</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>50</th>
<th>60</th>
<th>70</th>
<th>80</th>
<th>90</th>
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<td>SHP</td>
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<td>PM LV Comp.</td>
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<td>AC LV Comp.</td>
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<td>AC LV Decomp.</td>
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Statistical significance of differences are indicated for the hemodynamic parameters, left ventricular (LV) wave peak magnitude (PM), and area under the curve (AC) compared with baseline as a function of phase shift (PS), determined by pairwise t-test with Bonferroni correction. Open circles indicate that the change was significantly lower than baseline, whereas a cross indicates that the change was significantly higher than baseline. A \( P \) value < 0.05 was considered statistically significant. Comp., compression; Decomp., decompression.
DISCUSSION

The goal of this study was to investigate the effect of mechanical circulatory support on wave travel in the arteries. The abdominal aorta was chosen for the measurements because patients with PVADs typically do not suffer from gastrointestinal bleeding, whereas patients on continuous-flow VADs show a high incidence of such complication (8, 11, 22). Consequently, abdominal WI patterns under PVAD support should yield insight into what type of hemodynamic disturbance is acceptable in that region. We have analyzed WI patterns in the abdominal aorta at various PVAD settings. The WI pattern in arteries of unsupported patients has been shown to be relatively consistent with two main forward-traveling waves (10, 20), a compression wave at the beginning of LV ejection and a decompression wave following the deceleration of LV ejection, as can be seen in Fig. 4. The first of these two main peaks is shown to represent the contraction of the LV, and the second peak is shown to represent the early diastolic relaxation of the LV. These two peaks might be important parameters to define the circulatory state of a heart failure patient (19, 24). The in vitro WI pattern of a PVAD has been shown to be similar to this pattern (13), with a compression

Fig. 6. Overview of the WI and pressures (P) measured in sheep 6 (data set 1). Left column shows the WI in the abdominal aorta from the baseline (top) and from 10 different PS (below); middle column shows the pressure in the ascending aorta; and right column shows the pressure in the abdominal aorta. The vertical lines in left column represent the start of the LV compression wave (solid black), the start of the LV decompression wave (solid gray), the start of the PVAD compression wave (dashed black), and the start of the PVAD decompression wave (dashed gray), respectively. The WI is normalized to the PM of the LV compression wave of the baseline.
wave at the beginning of PVAD ejection and a decompression wave following the deceleration at the end of PVAD ejection.

The in vivo WI pattern in the abdominal aorta with an implanted PVAD is a combination of the two patterns mentioned above. Instead of one, there are two wave sources interacting with each other. Although the arrival times of the LV waves in the abdominal aorta are quite constant, the PS changes the arrival times of the PVAD waves (Fig. 7). The arrival times of the PVAD decompression wave, and thus the related interference phenomenon between this wave and the LV waves, depend on the duration of PVAD systole. In the current study, the length of PVAD systole is 35% of the cardiac cycle. Depending on the PS, different interference phenomena occur between the LV waves and the shifting PVAD waves, which alter the WI pattern. Constructive interference occurs

![Fig. 7](http://example.com/fig7.png)

**Fig. 7.** Arrival time scheme of the compression and decompression waves of the LV and the PVAD in the abdominal aorta. The measured arrival times of the LV waves (black crosses, compression wave; gray crosses, decompression wave) are approximated as horizontal lines (black line, compression wave; gray line, decompression wave), and the measured arrival times of the PVAD waves (black circles, compression wave; gray circles, decompression wave) are approximated linearly increasing with PS (black dashed line, compression wave; gray dashed line, decompression wave). The length of LV ejection is indicated with a double arrow and equals the vertical distance between the solid lines. The length of PVAD systole is indicated with a double arrow and equals the vertical distance between the dashed lines. The boxes indicate the intersections between the arrival times of the LV waves and the arrival times of the PVAD waves (black box, constructive interference; gray box, destructive interference). In the area around these intersections, interferences occur due to coexistence of an LV wave and a PVAD wave. Comp., compression; decomp., decompression.

![Fig. 8](http://example.com/fig8.png)

**Fig. 8.** A representative WI pattern for constructive interference between the compression waves and decompression waves of the LV and the PVAD (sheep 8, data set 2), which occurs at PS = 0–15%. Two strong waves are seen due to constructive interference: one compression wave, and one decompression wave. The compression wave is the addition of the LV and PVAD compression waves, and the decompression wave is the addition of the LV and PVAD decompression wave. The WI is normalized to the PM of the LV compression wave of the baseline.

![Fig. 9](http://example.com/fig9.png)

**Fig. 9.** A representative WI pattern for destructive interference between the LV decompression wave and the PVAD compression wave (sheep 6, data set 1), which occurs at PS = 40–50%. The WI is normalized to the PM of the LV compression wave of the baseline.
when the compression waves of the LV and the PVAD, or the decompression waves of the LV and PVAD, arrive at the same time (Fig. 8). Destructive interference occurs when the decompression wave of the LV arrives at the same time as the compression wave of the PVAD (Fig. 9) or when the compression wave of the LV arrives at the same time as the decompression wave of the PVAD (Fig. 10). Because the wave speed is the same for all waves, the WI interference pattern observed for forward-traveling waves at one measurement site will be similar, but shifted in time, at all other measurement sites in the artery. Therefore, each PS is related to a specific forward WI pattern.

In addition to a specific forward WI pattern, each PS is related to the hemodynamics and the PVAD filling (Fig. 5), as well as the PM and the AC of the LV and PVAD waves (Fig. 11). For PS = 0 (copulsation), 10, and 20%, maximum unloading of the LV (minimum SW), minimum AR, and maximum arterial flow pulsatility (maximum EEP and SHP) occur. For these PS, the PVAD filling starts in the isovolumetric relaxation phase or during early diastole of the LV and continues during LV diastole. The PVAD thereby drains blood from the LV, preventing proper LV filling and decreasing the end-diastolic volume. Therefore, the LV gets unloaded (minimum SW), and the AR is at the minimum value because the LV can eject blood into the aorta before the PVAD filling occurs. Additionally, AR might be affected by the cannula dimensions or type. The maximum EEP and SHP are results of the constructive interference (in part or total) between the LV and PVAD compression and decompression waves, which leads to maximum PM and AC of these waves. For PS = 40, 50, and 60% (counterpulsation), maximum AR and PVAD SV and minimum arterial pulsatility (minimum EEP and SHP) occur. For these PS, the LV systole occurs simultaneously with PVAD diastole, and the LV ejects blood into the PVAD instead of the aorta. Therefore, PVAD filling is maximized and only a small part of the total cardiac output is ejected through the aortic valve, leading to a maximum AR and minimum PM of the LV compression wave. The minimum EEP and SHP are results of the deconstructive interference (in part or total) between the LV decompression wave and the PVAD compression wave, which leads to minimum PM and AC of these waves. For PS = 70 and 80%, maximum loading of the LV occurs. For these PS, the PVAD ejects during the last part of LV filling and LV isovolumetric contraction, which results in an increased LV pressure required to open the aortic valve. Because the PVAD fills during the last part of LV systole and isovolumetric relaxation, it empties the LV further before LV filling. Additionally, destructive interference occurs between the LV compression wave and the PVAD decompression wave. For PS = 30 and 90%, no interference occurs and the hemodynamic parameters lie between the values seen for copulsation and counterpulsation. The variation in PM of the LV and PVAD waves for each PS depends on both the intensity of the individual waves and the interference occurring between them. Because of the interference between the waves, the individual waves cannot be separated from each other for all PS.

Arterial WIA is a method to monitor the relation between individual hemodynamics for each PVAD setting. As shown previously (3) and in the current study, maximum unloading of the LV is seen for copulsation (PS = 0–20%) and might be used for bridging the most severe phase of cardiac dysfunction. Figure 8 shows the corresponding WI pattern in the abdominal aorta for maximum unloading. Maximum loading of the LV is seen for PS = 70–80%. Figure 10 shows the corresponding WI pattern in the abdominal aorta for maximum loading. Our data shows that a stepwise increase of the PS from 0 to 80% gradually withdraws mechanical support from the LV.

Blood flow pulsatility in the abdominal aorta depends on the PS of the PVAD. Figure 5 shows that blood flow pulsatility in terms of SHP reached its maximum value for the PS corresponding to copulsation and maximum unloading of the LV (PS = 0–20%), whereas it reached its minimum for the PS corresponding to counterpulsation (PS = 40–60%). At these PS, the LV and PVAD waves seem to add or cancel each other in the peripheral circulation, resulting in a high or a low blood flow pulsatility, respectively. Blood flow pulsatility in VAD patients is important with respect to end-organ perfusion and adverse events such as gastrointestinal bleeding or peripheral vascular stiffening (8, 9, 11, 29). Therefore, the long-term use of the PS between 40 and 60% should probably be avoided in PVADs until solid clinical data on safety and efficacy for various PS are available.

Current clinical developments indicate that destination therapy is the preferred strategy of ventricular assistance in heart failure treatment (6). Therefore, it seems crucial to refine the latest generation of VADs to allow the operator to take control of the PS.
over the VAD-ventricle synchrony, and hence the hemodynamic interaction. This control might result in reduced complication rates and improved clinical outcomes, because the LV loading conditions and the peripheral pulsatility can be adapted to the individuals’ needs. WIA monitoring, invasive or noninvasive, may play an important role in the monitoring of the effect of each VAD setting. Perfusion-related complications with PVADs are notably less than with continuous-flow VADs (8), and the WIA results obtained in the current study can therefore be considered as a reference set of what should be accomplished with the new designs of continuous-flow VADs, which can handle more complicated physiological control via speed modulation (2).

One limitation of the WIA performed in the current study is that reflected waves were neglected, which may have led to small errors in the wave speed approximation (1). Reflected waves contain lower energy levels than the original forward waves. Therefore, their detection is prone to errors and would add even more complexity to the analysis without adding value to the interpretation. A second limitation of the WIA is that the reservoir method (31, 30) was not performed. This method takes the volume-related static pressure changes caused by vessel compliance into account and subtracts them from the WIA such that waves can be more sensitively detected. The reservoir method is based on the assumption that there are no backward waves in the diastolic phase of the heart cycle, which is not true for a PVAD-supported heart (depending on the PS). Additionally, the reservoir method is validated for pressures in the ascending aorta and might not be valid in the abdominal aorta. A third limitation of the current study is that WIA was performed at only one location in the arterial tree. A fourth limitation is that the length of the PVAD outflow graft varied with sheep size, creating small shifts in the arrival time of the PVAD waves at the anastomosis site, which to some degree influence the abdominal WI pattern.

In conclusion, the use of WIA is promising and may play a future role in guiding VAD settings for achieving maximal LV unloading or gradual reloading and for optimizing end-organ perfusion. Further development of noninvasive WIA (e.g., in the brachial, femoral, or carotid artery) will further enhance VAD tuning to patients’ needs, which should be demonstrated with outcome-oriented clinical studies.

ACKNOWLEDGMENTS

We thank the staff from the Surgical Research Unit, Department of Clinical Research, University of Bern, as well as Kathrin Maurer from the Department of Veterinary Anesthesia, University of Bern, for assistance with the experiments and Brigitta Gahl for assistance with the statistical analyses. We are further grateful to Bitmedical GmbH and Medtronic Switzerland for providing cannulas and cell saver disposables and to Vascutek Switzerland for providing BiPlex grafts.

Part of these results were presented at the American Society for Artificial Internal Organs 58th Annual Conference in San Francisco, CA, June 2012.
REFERENCES


