Validation of pulse contour derived stroke volume variation during modifications of cardiac afterload

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Background. Left ventricular stroke volume variation (SVV) or its surrogates are useful tools to assess fluid responsiveness in mechanically ventilated patients. So far it is unknown, how changes in cardiac afterload affect SVV. Therefore, this study compared left ventricular SVV derived by pulse contour analysis with SVV measured using an ultrasonic flow probe and investigated the influence of cardiac afterload on left ventricular SVV.

Methods. In 13 anaesthetized, mechanically ventilated pigs [31 (± 6) kg], we compared cardiac output (CO), stroke volume (SV), and SVV determined by pulse contour analysis with SVV measured using an ultrasonic aortic flow signal (Bland–Altman analysis). After obtaining baseline measurements, cardiac afterload was increased using phenylephrine and decreased using adenosine (both continuously administered). Measurements were performed with a constant tidal volume (12 ml kg−1) without PEEP.

Results. Neither increasing mean arterial pressure (MAP) [from 59 (7) to 116 (19)] nor decreasing MAP [from 63 (7) to 39 (4)] affected CO, SV, and SVV (both methods). Method comparison revealed a bias for SVV of 0.1% [standard error of the mean (SE) 0.8] at baseline, −1.2% (SE 0.8) during decreased and 4.0% (SE 0.7) during increased afterload, the latter being significantly different from the others (P<0.05). Thereby, pulse contour analysis tended to underestimate SVV during decreased afterload and to overestimate SVV during increased afterload. Limits of agreement were approximately 6% for all points of measurement.

Conclusions. Left ventricular SVV is not affected by changes in cardiac afterload. There is a good agreement of pulse contour with flow derived SVV. The agreement decreases, if afterload is extensively augmented.


Keywords: heart, cardiac afterload, positive end-expiratory pressure; heart, cardiac preload; heart, stroke volume variation, validation

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Cardiac preload is one determinant of cardiac output (CO). Optimizing cardiac preload is therefore crucial in the care of haemodynamically unstable patients. Numerous parameters for assessing cardiac preload and guiding fluid therapy have been suggested and extensively studied. Over the last decade, functional preload parameters such as stroke volume variation (SVV) and others have been repeatedly described to be superior when compared with cardiac filling pressures [central venous pressure (CVP) and pulmonary artery occlusion pressure], volumetric parameters [right ventricular end-diastolic volume (RVEDV) (pulmonary thermodilution)], and left ventricular end-diastolic area (transoesophageal echocardiography).1–3

†Declaration of interest. A.E.G. and D.A.R. are members of the medical advisory board of Pulsion Medical Systems. This study was exclusively supported by a research grant of the University of Munich.
An extensively studied method for monitoring functional preload is the pulse contour derived SVV.1–3 This method uses the area under the systolic portion of the arterial pressure curve for beat-to-beat determination of stroke volume (SV) (in relative values) and their variation over the respiratory cycle. Its feasibility and appropriateness in estimating cardiac preload and volume responsiveness has been reported in many clinical trials.4–7 An experimental validation of this method, however, is still lacking.

Cardiac afterload determines CO and perfusion pressure and is often altered in critically ill patients, as in sepsis or hypertensive crisis. Immediate restoration of CO and perfusion pressure is crucial to provide adequate organ perfusion and to prevent multiple organ failure from hypoperfusion. As initial haemodynamic stabilization and restoration of perfusion pressure is often performed using vasoactive agents besides fluid therapy, the influence of changes in afterload on SVV needs to be known.

Therefore, we performed this study (i) to compare left ventricular SVV derived by pulse contour analysis to an experimental gold standard method (aortic flow probe) and to investigate (ii) whether left ventricular SVV is affected by induced changes in cardiac afterload.

Methods
The study was approved by the local Governmental Commission on the Care and Use of Animals. The animals received care in compliance with the ‘Guide for the Care and Use of Laboratory Animals’ (NIH publication No. 86-23, revised 1996).

Anaesthesia
Thirteen pigs [31(±) 6 kg] were fasted overnight and premedicated with i.m. ketamine (500 mg) and azaperone (4 mg). After cannulation of a peripheral vein and pre-oxygenation, anaesthesia was induced with fentanyl (0.02 mg kg⁻¹), propofol (1.5–2 mg kg⁻¹), and atracurium besilate (2 mg kg⁻¹). The animals were intubated and lungs ventilated with 50% oxygen in air to adjust end-tidal \( P_{\text{CO}_2} \) to 35–40 mm Hg. Mechanical ventilation was performed with a tidal volume of 12 ml kg⁻¹, an inspiration to expiration ratio of 1:2, and no positive end-expiratory pressure applied. During surgery, anaesthesia was maintained with fentanyl (0.045 mg kg⁻¹ h⁻¹), midazolam (2.5 mg kg⁻¹ h⁻¹), and propofol (10 mg kg⁻¹ h⁻¹). For maintenance of anaesthesia during measurements, the rate of midazolam and propofol infusion was reduced by 30%. After surgical preparation, no further muscle relaxation was performed. Saline infusion was given at a rate of 10 ml kg⁻¹ h⁻¹ throughout the study period to maintain hydration. The animals were ventilated in a volume-controlled mode with a mechanical ventilator (Servo 900 D, Siemens, Elema, Schweden). Body temperature was kept constant using a warming pad and a warming lamp.

Surgical preparation
Animals were placed in the supine position and the jugular veins, one carotid artery, and one femoral artery were exposed. Veins and arteries were cannulated with 8.5 and 5 F introducer sheaths (Arrow, Reading, PA, USA), respectively, for catheter installation. An electronic micro-tip catheter (SPC 350, Millar Instruments, Houston, TX, USA) was introduced via a 5 F introducer sheath into the carotid artery for arterial pressure recordings. An 8 F central venous catheter (Arrow) inserted into the right external jugular vein was used for drug administration. A 5 F electronic micro-tip catheter was used for CVP recordings (only eight animals for technical reasons). A 7 F thermistor tipped pulmonary artery flotation catheter (VoLEF, Pulsion, Munich, Germany) was introduced via an 8.5 F introducer sheath in the left external jugular vein for pulmonary artery pressure recordings and thermodilution. Finally, a 4 F thermistor tipped catheter (PiCCO, PV 2015L20, Pulsion, Germany) was placed via a 5 F introducer sheath into the femoral artery for pulse contour analysis and transcardiopulmonary thermodilution.

A sternotomy was then performed and the heart exposed in the pericardial cradle. An ultrasonic flow probe (diameter 14–16 mm, Medi-Stim AS, Oslo, Norway) was placed around the ascending aorta. Afterwards, the thoracic cavity was closed airtight in multiple layers.

Before the measurements, cardiac preload was optimized by repeated bolus injections of a colloid solution (Voluven®, hydroxyethylstarch 6%, 130/0.4, Fresenius Kabi, Germany) until CO as measured with the ultrasonic flow probe did not increase any further.

Measurements
Aortic flow signal and intravascular pressures
Blood flow in the ascending aorta was measured using a precalibrated ultrasonic flow probe and a volume flowmeter (CardioMed medical volume flowmeter, CM 1008, Medi-Stim AS, Oslo, Norway). Signals were transferred to a personal computer, where vascular pressures—mean arterial pressure (MAP), CVP, and mean pulmonary artery pressure (MPAP)—were simultaneously recorded. Signals were registered over 60 s with a sample frequency of 250 Hz. Analysis of the acquired signals was performed with Flexpro software Version 6.0.18 (Weisang, St Ingbert, Germany). Systemic vascular resistance (SVR) was calculated as follows: [(MAP – CVP)/CO] × c, where c is the conversion factor (=79.9).

Left ventricular SV was calculated using the integral of the ascending aortic flow signal together with the ECG. Left ventricular SVV was defined as the variation (percentage) in flow derived SV over one respiratory cycle and
was calculated as follows: SVV (%) = \((|SV_{\text{max}} - SV_{\text{min}}|)/0.5(SV_{\text{max}} + SV_{\text{min}}))\times100\). The mean value of a registration period of 60 s was used for statistical analysis.

**Pulse contour analysis**

Online pulse contour analysis was performed using the PiCCO plus System (version 6.0) and PiCCO-VoLEF Data Acquisition Software (Pulsion, Munich, Germany). CO, SV, and SVV were continuously registered. The mean value during a recording period of 60 s, corresponding to the flow and pressure values, was used for statistical analysis.

**Thermodilution**

Thermodilution measurements were performed after three sequential central venous injections of 10 ml cold saline solution (<8°C) randomly administered throughout the respiratory cycle to assess: RVEDV (by pulmonary thermodilution) and global end-diastolic volume (GEDV) (by transcardiopulmonary thermodilution). Measurements were accepted if none of the three thermally derived CO values differed by more than 10% from the mean of those three measurements. Otherwise, an additional measurement was performed. The mean of three valid measurements was used for statistical analysis. RVEDV and GEDV were determined to confirm that no change in ventricular filling occurred throughout the study.

**Afterload modifications**

Augmentation of cardiac afterload was performed with continuous application of the \(\alpha_1\)-agonist phenylephrine (phenylephrine hydrochloride, Sigma-Aldrich, Munich, Germany) (30–120 \(\mu\)g kg\(^{-1}\) min\(^{-1}\)). The rate of phenylephrine administration was adjusted to increase MAP by approximately 100%. Once the desired pressure was achieved, the rate of phenylephrine administration was left unchanged. After a stabilization period of 10 min, measurements during increased afterload were performed. Phenylephrine was then discontinued and MAP was given 20 min to return to baseline before performing the second baseline measurement.

Cardiac afterload was reduced by continuous application of adenosine (adenosine free base, dissolved in sterile water for injection, Sigma-Aldrich, Munich, Germany) (100–200 \(\mu\)g kg\(^{-1}\) min\(^{-1}\)) to decrease MAP by 30–40%. Again, after MAP was successfully reduced, the rate of adenosine administration was left unchanged and measurements during decreased afterload were performed after 10 min of stabilization. Finally, after discontinuation of adenosine and stabilization over 20 min, the final baseline measurement was made.

**Statistical analysis**

Data were analysed using SigmaStat for Windows 3.1 (Systat Software, Inc., Germany). Normally distributed data, as tested by the Kolmogorov–Smirnov test, were analysed with a one-way analysis of variance (ANOVA) for repeated measurements. If data did not pass the test for normal distribution, Friedmann’s test was used. If the tests found significant differences, post hoc testing was performed using Tukey’s test. Statistical tests were applied separately for each intervention: increased afterload and decreased afterload (three points of measurement each); baseline I, increased afterload and baseline II for the analysis of the intervention increased afterload; and baseline II, decreased afterload and baseline III, respectively for the analysis of the intervention decreased afterload. Differences between the two methods were again compared using a one-way ANOVA for repeated measurements for the three measurements. Differences were considered significant for a \(P\)-value of <0.05. All data are presented as mean (standard deviation) unless indicated otherwise.

**Results**

**Haemodynamic data**

Thirteen animals [31(6) kg] were studied. For technical reasons, pulse contour derived SVV could not be measured in one animal during increased and another during decreased afterload. Haemodynamic data are presented in Table 1. Administration of phenylephrine increased MAP by 100% and the infusion of adenosine reduced MAP by 38%. These changes in MAP were associated with significant changes in SVR. MPAP did not change throughout the study. CO did not change after altering MAP, but decreased slightly throughout the study \((P<0.05)\).

**Thermodilution**

The results of the thermodilution measurements are presented in Table 1. Neither increasing nor decreasing cardiac afterload had any significant effect on GEDV and RVEDV. End-diastolic volumes did not change throughout the study.

**SV and SVV**

Increasing cardiac afterload had no effect on left ventricular SV and SVV derived from the aortic flow signal and pulse contour analysis. Decreasing cardiac afterload did
not influence SV and SVV measured with either flow probe or pulse contour analysis (Table 2).

**Method comparison**

**Stroke volume**

SV, as measured using the flow signal and pulse contour analysis, is compared by Bland–Altman analysis in Figure 1. Regression analysis of SV determined by the two methods showed a strong correlation of the two methods at baseline ($r^2 = 0.887, P < 0.001$) and after modifying cardiac afterload ($r^2 = 0.615, P = 0.002$ and $r^2 = 0.832, P < 0.001$, during increased and decreased afterload, respectively). However, pulse contour analysis overestimated flow derived CO at each point of measurement. A Bland–Altman analysis of flow and pulse contour derived SV found a bias between the two methods of 16.8 ml [confidence interval of the bias (CI of bias) 12–21], 17.4 ml (CI of bias 13–22), and 22.6 ml (CI of bias 19–27) during increased afterload, baseline conditions, and during decreased afterload, respectively (Fig. 1A–C). Thereby, the bias during decreased afterload (22.6 ml) was significantly higher than the bias at the other two measurement points ($P < 0.05$). The limits of agreement were 1.5 ml (lower limit) and 32.0 ml (upper limit) [standard error (SE) 3.8] during increased afterload, 3.0 and 31.8 ml (SE 3.5) at baseline II, and 9.3 and 35.9 ml (SE 3.3) during decreased afterload.

**SV variation**

Comparison of flow and pulse contour derived SVV is presented in Figure 2. Regression analysis found a significant moderate correlation of the two methods at baseline and after modifying cardiac afterload. Correlation coefficients ($r^2$) were 0.555 ($P = 0.014$), 0.434 ($P = 0.005$), and 0.467 ($P = 0.014$) during increased afterload, at baseline, and during decreased afterload, respectively. Bland–Altman analysis comparing SVV determined using flow signal and pulse contour analysis found a tight bias at baseline (0.1%, CI of mean −1.6 to 1.9) and during decreased afterload (−1.2%, CI of mean −2.8 to 0.4), but a slightly increased bias during increased afterload (4.0%, CI of means 2.2–5.9) (Fig. 2A–C). The latter differed significantly from the bias at baseline and during decreased afterload ($P < 0.05$). At baseline II, the limits of agreement were −5.7% (lower limit) and 6.0% (upper limit) (SE 1.4), during decreased afterload the limits of agreement were −6.3% and 3.9% (SE 1.3), and during increased afterload the limits of agreement were −1.8% and 9.9% (SE 1.5).

**Discussion**

This study is the first experimental validation of pulse contour derived SVV determination. It is, therefore, the main finding of our study that there is a good agreement of pulse contour derived SVV with a gold standard method. Further both left ventricular SVV derived by the aortic flow signal and by pulse contour analysis did not change, whereas cardiac afterload was modified pharmacologically.

With this pharmacological approach to cardiac afterload alteration, we were able to perform pulse contour analysis using the inferior abdominal aortic pressure signal as it is

Table 1 Haemodynamic data at baseline during increased afterload (phenylephrine infusion) and decreased afterload (adenosine infusion). HR, heart rate; MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; SVR, systemic vascular resistance; GEDV, global end-diastolic volume; RVEDV, right ventricular end-diastolic volume. Data are reported as mean values (standard deviation). Significant vs previous baseline measurement, $P < 0.05$

<table>
<thead>
<tr>
<th></th>
<th>Baseline I</th>
<th>Increased afterload</th>
<th>Baseline II</th>
<th>Decreased afterload</th>
<th>Baseline III</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HR (beats min⁻¹)</strong></td>
<td>86 (27)</td>
<td>102 (31)</td>
<td>95 (22)</td>
<td>90 (19)</td>
<td>91 (21)</td>
</tr>
<tr>
<td><strong>MAP (mm Hg)</strong></td>
<td>59 (7)</td>
<td>116 (19)</td>
<td>63 (7)</td>
<td>39 (4)</td>
<td>57 (8)</td>
</tr>
<tr>
<td><strong>MPAP (mm Hg)</strong></td>
<td>20 (4)</td>
<td>22 (5)</td>
<td>18 (4)</td>
<td>17 (4)</td>
<td>19 (3)</td>
</tr>
<tr>
<td><strong>SVR (dyne s⁻¹ cm⁻³ m⁻³)</strong></td>
<td>1746 (555)</td>
<td>3308 (808)</td>
<td>2311 (681)</td>
<td>1295 (299)</td>
<td>1893 (379)</td>
</tr>
<tr>
<td><strong>GEDV (ml)</strong></td>
<td>499 (107)</td>
<td>585 (119)</td>
<td>462 (97)</td>
<td>481 (97)</td>
<td>456 (85)</td>
</tr>
<tr>
<td><strong>RVEDV (ml)</strong></td>
<td>123 (36)</td>
<td>113 (39)</td>
<td>120 (36)</td>
<td>125 (34)</td>
<td>119 (31)</td>
</tr>
</tbody>
</table>

Table 2 Haemodynamic data derived from the aortic flow signal and pulse contour analysis at baseline during increased afterload (phenylephrine infusion) and decreased afterload (adenosine infusion). SVfp, SV derived from the aortic flow signal; SVVfp, SVV derived from the aortic flow signal; COfp, CO derived from the aortic flow signal; SVpc, SV derived by pulse contour analysis; SVVpc, SVV derived by pulse contour analysis; COpc, CO derived by transcardiopulmonary thermodilution. Data are reported as mean values (standard deviation). Significant vs previous baseline measurement, $P < 0.05$

<table>
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<th>Baseline III</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SVfp (ml)</strong></td>
<td>27 (9)</td>
<td>25 (8)</td>
<td>20 (7)</td>
<td>21 (6)</td>
<td>20 (4)</td>
</tr>
<tr>
<td><strong>SVVfp (%)</strong></td>
<td>8 (3)</td>
<td>10 (4)</td>
<td>1.8 (0.3)</td>
<td>1.8 (0.3)</td>
<td>1.8 (0.3)</td>
</tr>
<tr>
<td><strong>COfp (litre min⁻¹)</strong></td>
<td>22.2 (0.4)</td>
<td>2.4 (0.6)</td>
<td>37 (13)</td>
<td>44 (12)</td>
<td>31 (11)</td>
</tr>
<tr>
<td><strong>SVVfp (%)</strong></td>
<td>11 (4)</td>
<td>14 (4)</td>
<td>11 (4)</td>
<td>11 (2)</td>
<td>13 (5)</td>
</tr>
<tr>
<td><strong>COpc (litre min⁻¹)</strong></td>
<td>4.0 (1.0)</td>
<td>4.6 (1.0)</td>
<td>3.2 (0.7)</td>
<td>3.6 (0.7)</td>
<td>3.3 (0.7)</td>
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</tbody>
</table>
predominantly done at the bedside. Alternatively, using an aortic balloon catheter to increase cardiac afterload would have excluded the use of this vascular access. The positive inotropic effect of phenylephrine is considered to be small, and adenosine has been proved not to alter contractility in pigs. However, no measurements of contractility to prove the absence of changes in myocardial contractility after pharmacological interventions were performed in our

Fig 1 Bland–Altman analysis of SV derived by flow signal on the ascending aorta (fp) and by pulse contour analysis (pc). The bias (bias) (2 standard deviations) (limits of agreement) is represented by the horizontal lines. (a) During increased afterload (phenylephrine infusion), (b) during baseline conditions, and (c) during decreased afterload (adenosine infusion).

Fig 2 Bland–Altman analysis of SVV derived by flow signal on the ascending aorta (fp) and by pulse contour analysis (pc). The bias (bias) (2 standard deviations) (limits of agreement) is represented by the horizontal lines. (a) During increased afterload (phenylephrine infusion), (b) during baseline conditions, and (c) during decreased afterload (adenosine infusion).
model. Heart rate changed slightly during infusion of phenylephrine, but not during infusion of adenosine. Our results on RVEDV and GEDV indicate that no major changes in ventricular filling occurred after alteration of cardiac afterload and throughout the study. CO decreased slightly throughout the study, which may be attributed to an impairment of myocardial contractility in the course of the experiment. Pulse contour analysis was calibrated by transcardiopulmonary thermodilution, which comprises (in contrast to the pulmonary artery thermodilution) more than one respiratory cycle. Therefore, the random injection of thermal indicator throughout the respiratory cycle should have had a minor influence on CO and GEDV determination.

**Stroke volume**

We found a considerable, but constant off-set between flow and pulse contour derived SV independent of cardiac afterload. The correlation, however, was strong. This might be related either to the flow probe, which is pre-calibrated by the manufacturer, or to the calibration of pulse contour derived SV by transcardiopulmonary thermodilution. Pulmonary artery thermodilution has previously been reported to overestimate true CO in humans and animals. This overestimation has been observed in particular in the presence of low CO. In humans, however, a good agreement of pulse contour derived CO and CO assessed by pulmonary artery thermodilution has been reported. Therefore, the off-set observed in our study might also be related to the precalibration of the ultrasonic flow probe. In addition, it was recently reported in a small set of animals that both absolute values and proportional changes in SV derived by pulse contour analysis inaccurately reflect rapid changes in SV. However, in the present study, another algorithm for pulse contour analysis was used.

In our study, the bias between the two methods significantly increased, when afterload was decreased, though CO and preload did not change. Therefore, the overestimation of SV by the pulse contour analysis might also, to a minor degree, be related to cardiac afterload. More data are needed to confirm this result. To date, our data suggest that considering the good correlation with a gold standard (even for very low SVs) changes in CO assessed online can be used for monitoring global cardiac function in haemodynamically unstable patients.

**SV variation**

Pulse contour derived SVV has been described as a valuable estimate of fluid responsiveness in mechanically ventilated patients. One of those studies reported positively on its feasibility and ability to predict fluid responsiveness in patients with altered cardiac afterload in the course of sepsis. Nouira and colleagues reported in six dogs that other functional parameters of cardiac preload (pulse pressure variation and systolic pressure variation) decreased when norepinephrine was administered in haemorrhagic shock. However, those results are only comparable to a limited degree with ours due to the positive inotropic effects of norepinephrine, a significant decrease in heart rate after application, and the lack quantification of intravascular volume status. Thus, a systematic investigation of the influence of changes in afterload on SVV is lacking.

In the present study, neither flow nor pulse contour derived SVV changed significantly after alteration of afterload suggesting that left ventricular SVV is basically independent of cardiac afterload within the range studied in our model. The bias between the two methods was very low at baseline (0.1%) reflecting a good agreement between the two methods. As the bias decreased slightly during reduced afterload (−1.2%) and slightly increased during increased afterload (4.0%), there seems to be an afterload dependence of the agreement between the two methods. However, the limits of agreement remained stable (around ±6%), with a moderate correlation (r² from 0.44 to 0.62). These limits of agreement are, of course, only estimates of the real limits of agreement. Limits would be different in a second sample and probably tighter in a larger study population than ours.

**Conclusions**

In conclusion, we found that left ventricular SVV was not affected by changes in cardiac afterload in our experimental model. There is good agreement between pulse contour derived SVV and a gold standard comparator, whereas SV is overestimated by pulse contour analysis according to our data. However, the agreement between the two methods decreases slightly, if changes in cardiac afterload occur. According to our data, continuous measurement of pulse contour derived SVV may be used to guide fluid therapy in patients with altered cardiac afterload.

**Acknowledgement**

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