Chapter 3

A comparison of stroke volume variation measured by the LiDCOPLUS and FloTrac-Vigileo

Rob de Wilde, Bart Geerts, Paul van den Berg and Jos Jansen
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Since the introduction of continuous cardiac output measurement by arterial pulse contour analysis, real time measurement of stroke volume (SV) stroke volume variation (SVV) and pulse pressure variation (PPV) during mechanical ventilation have evolved in clinical practice. Most studies have shown SVV and PPV to be good indicators of fluid responsiveness [1-3]. However, in two separate publications [4,5] Pinsky advised caution in the clinical use of SVV based on the fact that beat-to-beat SV by the pulse contour technique has not been validated to monitor rapid changes in SV, such as occurs within a single breath. This is further complicated by the use of different algorithms to calculate SV and SVV by different monitoring systems. In this light, a clinical validation study on SVV seemed important. The aim of our study was to compare SVV estimates by the LiDCOplus system (SVVli) (LiDCO Ltd. Cambridge, UK) with SVV estimates by the FloTrac-Vigileo system (SVVed) (Edwards Lifesciences, Irvine, CA, USA) in post operative cardiac surgery patients. To induce changes in SVV we applied five different interventions to the patients. These interventions were: increase of tidal volume, increase of positive end-expiratory pressure (PEEP), a head up tilt procedure, passive leg raising and fluid loading. In between these interventions patients returned to the baseline condition prior to undertaking the next intervention.

Methods
After approval of the study protocol by the University Medical Ethics committee, fifteen patients were studied after coronary arterial bypass grafting with or without mitral valve repair. The study was conducted according to the principles of the Helsinki declaration and written informed consent was obtained from all patients the day prior to surgery. Patients were only selected if they were scheduled to receive a pulmonary artery catheter and a radial artery cannula for peri-operative monitoring and care. All patients had symptomatic coronary artery disease without previous myocardial infarction and were on β-adrenergic blocking medication. Patients with a history of abnormal ventricular function, aortic aneurysm, extensive peripheral arterial occlusive disease, or postoperative valvular insufficiencies were not considered for this study. Patients with postoperative severe arrhythmia or a requirement for artificial pacing or cardiac assist devices were also excluded. The final inclusion of the patients was during their initial post-operative period in the ICU. In the operating room, the radial artery was catheterized with a 20G catheter (Arrow, Reading, PA, USA) to monitor arterial pressure and a pulmonary artery catheter (Edwards Lifesciences, Irvine, CA, USA) was introduced into the right internal jugular vein to monitor central venous pressure (CVP), pulmonary artery pressure (PAP) and to estimate cardiac output (CO) by the intermittent thermodilution method (COtd). Anaesthesia during surgery and the ICU-stay was maintained with propofol (2.5 mg·kg⁻¹·h⁻¹), sufentanil (0.06-0.20 mg·kg⁻¹·h⁻¹) and vasoactive medication according to
institutional standards. The lungs were mechanically ventilated (EVITA 4, Dräger AG, Lübeck, Germany) in a volume-control mode with settings aimed to achieve normocapnia with a tidal volume of 8-12 ml·kg\(^{-1}\) and a respiratory frequency of 12-14 breaths·min\(^{-1}\). The administered fraction of inspired oxygen was 0.4 with PEEP of 5 cmH\(_2\)O. During the observation periods, sedation and vasoactive medication, when used, were unchanged.

**Measurements**

Measurements started in the postoperative period. The radial artery pressure, derived via the radial artery catheter was measured with a FloTrac pressure transducer (Edwards Lifesciences). Of the bifurcated cable, one limb was connected to the Vigileo system (Edwards Lifesciences, software version v1.07) to measure pulse contour cardiac output and SVVed and the other limb was connected to a bedside monitor pressure module (Hewlett Packard model M1006A, Hewlett Packard Company, Palo Alto, CA, USA) of which the output signal was used as input to the LiDCOplus (LiDCO Ltd, Cambridge, UK) pulse contour system to deliver cardiac output, pulse pressure variation (PPVli) and SVVli. Detailed information about both pulse contour techniques can be found in recent literature \[6-9\]. Radial artery pressure, PAP and CVP were recorded online on computer disk for documentation and offline calculations. Radial artery pressure, PAP and CVP transducers were referenced to the intersection of the anterior axillary line and the 5\(^{th}\) intercostal space. After changes in position of the patient the transducers were re-referenced. Airway pressure was measured at the proximal end of the endotracheal tube with an air-filled catheter connected to a pressure transducer. Airway pressure was balanced at zero level against ambient air.

CO\(_{td}\) measurements were performed with an automated system under computer control and measured in triplicate (10 ml saline solution at room temperature) in 2 minutes, with the measurements equally spread over the ventilatory cycle. These three individual CO\(_{td}\) measurements were averaged \[10,11\].

We calibrated the LiDCOplus system with thermodilution cardiac output measurements at the start of the observation period. The FloTrac-Vigileo system used its internal auto-calibration. From the beat-to-beat cardiac output values with the LiDCOplus and FloTrac-Vigileo system, stroke volume (SVli and SVEd), stroke volume variation (SVVli and SVVEd) and pulse pressure variation (PPVli) were determined. SVV and PPV were calculated over 20-second periods of radial artery pressure data.

**Study protocol**

Measurements were carried out within 2 hours of arrival in ICU and after hemodynamic stabilization. Characteristics and treatment data of each patient were collected. During the
‘Baseline-1’ period, a series of measurements of HR, COtd, PPVli, SVVli and SVVed were obtained. To change SVV, five interventions were applied. First, the tidal volume setting of the ventilator was increased by 50% for 5 minutes. Two minutes after onset of the increase tidal volume challenge, the same series of measurements were repeated (‘VT-series’). Then, 5 minutes after the ventilation values were returned to baseline another series of measurements were performed (‘Baseline-2’). For the second intervention, positive airway pressure (PEEP) was increased by 10 cmH\textsubscript{2}O for 5 minutes, and after 2 minutes at the increased PEEP the next series of measurements was obtained (‘PEEP-series’). Five minutes after return from increased PEEP to baseline, a ‘Baseline-3’ series of measurements was carried out. For the third intervention, passive leg raising was performed from the supine position by lifting both legs at a 30° angle and holding them there for 5 minutes. Two minutes after the onset of leg raising the series of measurements were repeated (‘PLR-series’). Five minutes after return from passive leg raising, ‘Baseline-4’ measurements were performed. For the fourth intervention, a head-up-tilt was performed by raising head of the bed to 30°. After 2 minutes of head-up-tilt the next series of measurements were made (‘HUT-series’). Five minutes after return from head-up, the last series of baseline measurements were performed (‘Baseline-5’). Lastly, the fifth intervention, a fluid loading with 500 ml Hydroxyethyl Starch (HES 130/0.4) over 15 minutes, was undertaken. Five minutes after ending fluid loading the last series of measurements were made (‘FL-series’). Fluid loading was only performed in eight patients. In the other patients it was not indicated. The study protocol lasted about 75-90 minutes following which sedation was stopped and weaning procedures were started. During the protocol we encountered no adverse events. All patients were discharged from the intensive care unit on the first postoperative day.

Statistical analysis

After confirming a normal distribution of data with the Kolmogorov–Smirnov test, differences between SVVed and SVVli during baseline and interventions were analyzed using a paired t-test. Calculations of bias and precision and limits of agreement between SVVed and SVVli were performed using Bland and Altman analysis \cite{12} in which bias was the difference between SVVli and SVVed and precision the standard deviation (SD) of this difference. The upper and lower limits of agreement were calculated as the bias ±2SD. The coefficient of variation was calculated as 100% · SD/mean. The percentage limits of agreement were calculated as twice the coefficient of variation. The differences in precision between the two methods were tested by using correlated variances in paired samples \cite{13,14}. Repeatability of SVVli and SVVed was calculated using the data from the baseline measurements. A p-value of less than 0.05 was considered statistically significant. Unless otherwise stated, data are presented as mean ± SD.
Results
Fifteen postoperative cardiac surgery patients were included. Patient demographics were; male to female ratio of 12:3, mean age 66 (range 55 to 82) years, and mean body surface area (BSA) 1.98 ± 0.20 m². Only eight patients received fluid loading. A total of 136 paired data sets were obtained. The data was normally distributed. COtd ranged from 2.6 to 7.7 with an average of 5.0 ± 1.1 L·min⁻¹. Heart rate ranged from 54 to 92 (average 75 ± 8 min⁻¹). SVVli ranged from 1.4 and 26.8% (average 8.7 ± 4.6%), SVVed from 2.0 to 26.0% (average 10.2 ± 4.7%) and PPVli from 1.9 to 25.3 (average 8.8 ± 4.7%).

Figure 1 Bland-Altman plot, representing agreement between stroke volume variation (SVV) by the LiDCO system (SVVli) and by Edwards FloTrac-Vigileo system (SVVed). The solid line represents the bias and the dotted lines the limits of agreement, dashed lines the limits of agreements in percentage.

Agreement of SVVli and SVVed
The error diagram for difference between SVVli and SVVed is shown in Figure 1. Bland-Altman statistics are indicated in the Figure by bias and limits of agreement. The bias is significantly different from zero, at 1.5 ± 2.5%, < 0.001, (95% confidence interval 1.1 to 1.9). The upper and lower limits of agreement are 6.4 and – 3.5%. The coefficient of variation for the differences between SVVli and SVVed was 26% giving a relatively large range for the percentage limits of agreement of 52%.
Interventions

Data on COtd, HR, PPVli, SVVli, SVVed and the differences between SVVli and SVVed for the different interventions and baseline conditions are shown in Table 1. With Factorial ANOVA the main effects on SVV values related to the measurement techniques was \( F = 14.49, p = 0.02 \), and related to interventions was \( F = 8.29, p < 0.001 \). Differences between SVV measurement methods were consistent across all observations \( F = 1.54, p = 0.142 \).

Table 1 Differences in cardiac output (CO), heart rate (HR), pulse pressure variation (PPV) and stroke volume variation (SVV) at interventions. The interventions are; increase of tidal volume with 50\% (VT); increase in PEEP with 10 cmH\(\text{2}\)O (PEEP); passive leg raising (PLR); head-up tilt (HUT) and fluid loading (FL); Method of measurement: CO thermodilution (COtd), PPV LiDCO system (PPVli), SVV LiDCO system (SVVli), SVV FloTrac-Vigileo system (SVVed). Statistic analysis paired t test (*).

<table>
<thead>
<tr>
<th>Intervention</th>
<th>COtd (L min(^{-1}))</th>
<th>Heart rate (min(^{-1}))</th>
<th>PPVli (%)</th>
<th>SVVli (%)</th>
<th>SVVed (%)</th>
<th>Coefficient of variation (%)</th>
<th>SVV difference</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline 1</td>
<td>4.9 ± 1.0</td>
<td>76 ± 7</td>
<td>7.9 ± 4.3</td>
<td>7.8 ± 3.4</td>
<td>9.4 ± 3.9</td>
<td>1.6 ± 1.7</td>
<td>20</td>
<td>0.003</td>
</tr>
<tr>
<td>VT</td>
<td>4.9 ± 1.0</td>
<td>78 ± 9</td>
<td>11.2 ± 5.6</td>
<td>10.6 ± 5.8</td>
<td>12.9 ± 6.5</td>
<td>2.3 ± 2.9</td>
<td>24</td>
<td>0.009</td>
</tr>
<tr>
<td>Baseline 2</td>
<td>5.1 ± 0.9</td>
<td>74 ± 8</td>
<td>7.5 ± 3.6</td>
<td>7.6 ± 3.0</td>
<td>8.5 ± 3.3</td>
<td>1.0 ± 2.4</td>
<td>30</td>
<td>0.134</td>
</tr>
<tr>
<td>PEEP</td>
<td>4.3 ± 1.1</td>
<td>75 ± 8</td>
<td>12.4 ± 5.8</td>
<td>12.4 ± 5.6</td>
<td>13.3 ± 5.0</td>
<td>0.9 ± 2.4</td>
<td>19</td>
<td>0.171</td>
</tr>
<tr>
<td>Baseline 3</td>
<td>5.2 ± 0.9</td>
<td>75 ± 7</td>
<td>7.7 ± 3.7</td>
<td>7.6 ± 2.9</td>
<td>8.9 ± 3.4</td>
<td>1.7 ± 1.9</td>
<td>34</td>
<td>0.010</td>
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<tr>
<td>PLR</td>
<td>5.4 ± 1.0</td>
<td>74 ± 8</td>
<td>6.5 ± 3.3</td>
<td>5.9 ± 2.8</td>
<td>8.7 ± 3.1</td>
<td>2.9 ± 3.2</td>
<td>44</td>
<td>0.004</td>
</tr>
<tr>
<td>Baseline 4</td>
<td>5.2 ± 1.0</td>
<td>75 ± 8</td>
<td>8.5 ± 3.9</td>
<td>8.3 ± 4.2</td>
<td>10.0 ± 4.1</td>
<td>1.7 ± 1.9</td>
<td>21</td>
<td>0.004</td>
</tr>
<tr>
<td>HUT</td>
<td>4.9 ± 1.0</td>
<td>75 ± 9</td>
<td>9.7 ± 5.0</td>
<td>10.8 ± 4.5</td>
<td>11.6 ± 8.3</td>
<td>0.8 ± 2.9</td>
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<td>0.287</td>
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<tr>
<td>Baseline 5</td>
<td>4.9 ± 1.3</td>
<td>75 ± 11</td>
<td>8.6 ± 4.0</td>
<td>9.0 ± 6.1</td>
<td>10.1 ± 5.4</td>
<td>1.2 ± 1.9</td>
<td>20</td>
<td>0.009</td>
</tr>
<tr>
<td>FL</td>
<td>5.6 ± 1.2</td>
<td>74 ± 12</td>
<td>6.7 ± 4.0</td>
<td>5.9 ± 2.9</td>
<td>6.5 ± 3.3</td>
<td>0.7 ± 1.0</td>
<td>15</td>
<td>0.095</td>
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</table>

One-way ANOVA statistics showed no significant difference between five baseline measurements for CO \( F = 0.203, p = 0.936 \), HR \( F = 0.094, p = 0.984 \), PPVli \( F = 0.184, p = 0.946 \), SVVli \( F = 0.254, p = 0.906 \) and SVVed \( F = 0.390, p = 0.815 \), indicating no significant effects over time.

On average, the tidal volume challenge showed no change in COtd and an increase in PPVli, SVVli and SVVed. During the PEEP challenge we observed a decrease in COtd and an increase of PPVli, SVVli and SVVed. Passive leg raising resulted in increased COtd and decreased PPVli, SVVli and SVVed. The head-up challenge resulted in a decreased COtd.
and increased PPVli, SVVli and SVVed. Fluid loading increased COtd and decreased PPVli, SVVli and SVVed. Heart rate did not change significantly during study interventions. The most significant result was the difference between SVVli and SVVed for the different interventions (Table 1). We considered the results obtained during the five baseline observations as repeated measures. Analysis of these repeated measurements showed the following coefficients of variation: SVVli = 21%, SVVed = 22% (no difference between SVVli and SVVed, \( = 0.024, = 0.779 \)), and PPVli = 23%.

**Discussion**

We found SVVli and SVVed to differ significantly. With percentage limits of agreement of 52% we conclude that the LiDCOplus and FloTrac-Vigileo devices are not interchangeable. Furthermore, the determination of SVVli and SVVed appeared to be ambiguous as can be concluded from the high value of coefficients of variation (21 and 22%) for repeated measures. These findings underline Pinsky’s warning to be careful in the clinical use of SVV by pulse contour techniques, and to be restrained in using SVV (as a solitarily variable) in the management of individual patients.

The significant mean difference between SVV measured by the LiDCO and FloTrac-Vigileo device is most probably not caused by the calculation of SVV because both systems use a similar computation i.e. \( \text{SVV} = 100 \cdot \frac{(\text{SVmax} - \text{SVmin})}{\text{SVmean}} \) (where \( \text{SVmax} \) is the maximum, \( \text{SVmin} \) is the minimum and \( \text{SVmean} \) is the mean stroke volume). Therefore it is most likely explained by the difference in the calculation of \( \text{SVmin} \), \( \text{SVmax} \) and \( \text{SVmean} \) by the two systems. The main difference in computation of SV is based on the correction for individual arterial compliance. The LiDCO system uses a pressure dependent correction for compliance based on Remington’s equations whereas the FloTrac-Vigileo uses Langewouter’s equations. There is a large similarity between the computations of SV (Figure 2). With both systems these equations lead to a diminished SV at higher pressure levels compared to lower pressure levels with the same arterial pressure curve. However, this correction for compliance may differ between the two systems. A difference in calibration between the two systems has no influence on SVV, indeed, assuming a calibration constant \( k \), leads to \( \text{SVV} = 100 \cdot \frac{(k \cdot \text{SVmax} - k \cdot \text{SVmin})}{k \cdot \text{SVmean}} \). With \( k \) in the nominator and denominator the calibration factor is ruled out in the determination of SVV.
In a recent paper Hofer et al. [17] compared the FloTrac-Vigileo and the PiCCOplus system (Pulsion Medical Systems, Munich, Germany) for assessment of SVV to predict fluid responsiveness. The authors found SVV measured by the PiCCO system to be higher than the SVV by the FloTrac-Vigileo system. Besides this bias, we calculated from their Bland-Altman analysis percentage limits of agreement of approximately 40% between the two systems. The authors concluded that there was similar performance of the two investigated systems in terms of predicting fluid responsiveness although the SVV threshold level in predicting fluid responsiveness by the PiCCO system (12.1%) differed from the FloTrac-Vigileo system (9.6%). The differences in absolute SVV values were explained by the difference in signal detection sites (radial artery for FloTrac-Vigileo system and femoral artery for PiCCO system) as well as difference in signal analysis techniques. In our study we can exclude the influence of different detection sites because we used the same site for both techniques, i.e. the radial artery. Thus the difference between SVVli and SVVed was most probably related to differences in signal analysis. We did not calculate receiver operating curves to calculate differences in thresholds for predicting fluid responsiveness because we consider our number of fifteen patients too low. However, we expect different threshold levels for the LiDCO and FloTrac-Vigileo system as well.

A wide range for the percentage limits of agreement (approximately 40%) can also be observed in the study by de Castro et al. [18], in which SVV measured by the PiCCOplus system was compared with SVV measured by aortic Doppler echocardiography.
Given these margins of error, we conclude that none of the above mentioned systems is interchangeable with the other. It seems that the calculation of SVV is prone to propagation of errors [18]. This is supported by the high coefficients of variation for repeated measures, SVVli of 21% and SVVed of 22%, observed in our study. As the errors in the measurements of SVVli and SVVed are not completely independent we cannot estimate the coefficient of variation for the difference between the two techniques from the coefficients of variation of both systems [19]. The coefficient of variation for the difference may vary between 1% and 43%. In our study we observed a coefficient of variation for the difference of 26%, which lies within this range.

Nevertheless the changes in SVV induced by our interventions were in agreement with what was clinically expected (Table 1). During the increase in tidal volume we observed, in comparison to baseline, no change in cardiac output but an increase in SVV. A similar increase in SVV to the increase of tidal volume was observed by Kim and Pinsky [20] in a well controlled animal study. During both the increased PEEP and head-up-tilt manoeuvres, CO decreased and SVV increased. Following both passive leg raising and fluid loading we observed an increase in CO and decrease in SVV with both systems. However, the difference between SVVli and SVVed fluctuated considerably.

Despite these shortcomings, SVV still seems a variable of considerable interest. Several authors have shown that SVV can predict the effects of fluid loading on cardiac output, albeit using different thresholds (ranging from 9.5 to 12.5%) to separate responder and non responders [17,21-23]. Although there is no reason to doubt the general principle of SVV as a predictor of fluid responsiveness, we conclude from our results that some caution in the use of SVV in individual patients is justified. Indeed, based on Bland-Altman analysis for repeated measurements for SVV with percentage limits of agreement, the value of SVV may differ by up to 40% between measurements. Thus an initial observed SVV of 10% may subsequently change to 14% or 6% without any change in the patient’s condition. This has important clinical implications: to improve cardiac output, a SVV of 14% may favour fluid loading, whereas a SVV of 6% may favour the use of catecholamines.

Conclusions
In this study, SVV measurements made by the LiDCOplus system (SVVli) and by the FloTrac-Vigileo system (SVVed) differed significantly. With percentage limits of agreement of 52% the two methods did not agree and should not be used interchangeably. Furthermore, the determination of SVVli and SVVed appeared to be ambiguous as illustrated by the high values of their respective coefficient of variation (21% and 22%) for repeated measures. These findings limit clinical usefulness in individual patients and limit the comparability of results on fluid loading responsiveness from different studies.
References
