Chapter 2

Performance of three minimally invasive cardiac output monitoring systems

Rob de Wilde, Bart Geerts, Jisheng Cui, Paul van den Berg and Jos Jansen
Anaesthesia 2009; 64: 762–769
Ideally cardiac output monitoring is accurate, precise, operator-independent, rapid, non-invasive, continuous, easy to use, and cost-effective. Methods that follow changes in cardiac output may provide an early warning on changes in circulatory function or allow ‘interrogation’ of the circulation with interventions.

Cardiac output has perhaps traditionally been monitored by using a thermodilution pulmonary artery catheter (PAC) using intermittent bolus thermodilution (COtd) and this is still considered by some the best reference method. However, it may not be feasible to follow changes on interventions or applied challenges, due to its time delay [1,2]. Devices based on beat-to-beat assessment of stroke volume are better equipped to monitor changes in cardiac output and two technologies currently available are based on arterial pulse contour and transoesophageal ultrasound.

The recently introduced auto-calibrated FloTrac/Vigileo (Edwards Lifesciences, Irvine, CA, USA) is a pulse contour method for cardiac output monitoring that, in contrast to devices like the PiCCO™ (Pulsion Medical, Munich, Germany) and LiDCO™ (LiDCO Ltd, Cambridge, UK), does not require an independent calibration [3] and is thus relatively non-invasive using the pressure signal from a standard peripheral arterial line. The standard deviation (SD) of the pulse pressure is correlated to stroke volume based on the patient’s age, gender, body height and weight after an automatic adjustment related to an estimate of vascular compliance. Early validation showed conflicting results, but after the introduction of newer software (version 1.07), results became more uniform [4-8].

In some respects the Modelflow method is similar, deriving an aortic flow waveform from arterial pressure by using a three-element input impedance model. Stroke volume is integrated from the flow waveform. The parameters of the model are based on aortic pressure, gender, age, height and weight of the patient. The Modelflow (or pulse contour) method can follow beat-to-beat cardiac output changes, both after calibration by thermodilution as well as in a non-calibrated setting [9-12].

The HemoSonic monitor (HemoSonic 100, Arrow International, Reading, PA, USA) comprises an ultrasound probe with both M-mode and pulsed Doppler transducers [13,14]. The former measures (in real time) the diameter of the descending aorta while the latter measures blood velocity in the aorta. From these, aortic blood flow (ABF) is computed which in turn enables estimation of cardiac output [15].

The aim of our study was to compare the accuracy, precision and monitoring ability of cardiac output measurements by FloTrac-Vigileo, Modelflow and HemoSonic with intermittent pulmonary artery thermodilution as the reference method.
Methods

Patients and anaesthesia

After ethical approval and written informed consent, 13 patients were studied after coronary arterial bypass grafting or mitral valve reconstruction. All patients had symptomatic coronary artery disease without previous myocardial infarction but patients with a history of abnormal ventricular function, aortic aneurysm, extensive peripheral arterial occlusive disease, aortic valve pathology, and pharyngeal or oesophageal pathology were excluded. Patients with persistent postoperative arrhythmia or the necessity for artificial pacing or heart assist devices were also excluded. All patients were included in the study during their initial post-operative period in the Intensive Care Unit (ICU).

Anaesthesia during surgery and ICU stay was generally with appropriate doses of propofol, sufentanil and vasoactive medication. The lungs were mechanically ventilated (Dräger 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 fraction of inspired oxygen was maintained at 0.4 and PEEP 5 cmH₂O. During the observation period ventilator settings, sedation and vasoactive medication, when used, were unchanged.

Monitoring techniques

Before ICU admission, a radial artery was catheterized with a 20G catheter (Arrow, Reading, PA, USA) to monitor arterial pressure (Pa) and a pulmonary artery catheter (Edwards Lifesciences, Irvine, CA, USA) introduced into the right jugular vein to monitor central venous pressure (CVP), pulmonary artery pressure (PAP) and to estimate cardiac output (CO) by the intermittent thermodilution method (COtd).

COtd 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 COtd measurements were averaged [16]. Blood pressure transducers were referenced to the level of the tricuspid valve and zeroed to atmospheric pressure.

The radial artery pressure (Pa) from the radial artery catheter was also connected to a FloTrac pressure transducer (Edwards Lifesciences) with a bifurcated lead, one limb connected to the Vigileo system (Edwards Lifesciences) to measure pulse contour cardiac output (COed) and the other limb connected to a bedside monitor pressure module (Hewlett Packard model M1006A) whose output was used as the input signal to the modified Modelflow system (BMEYE, Academic Medical Center, Amsterdam, the Netherlands) to estimate pulse contour cardiac output (COMf). Detailed information about the FloTrac-Vigileo system [17] and
Modelflow system \(^{[17,18]}\) can be found elsewhere. An ultra-sound probe (HemoSonic100, Arrow, Reading, Pa, USA) to monitor aortic blood flow (ABF) was inserted through the mouth and advanced in the oesophagus to the level of the 4\(^{th}\) intercostal space and its position adjusted to obtain the highest Doppler velocity signal along with simultaneous optimal visualization of aortic wall images \(^{[12,14]}\). The final position of the probe was checked by chest X-ray, and readjusted after changes in position of the patient, if necessary. All measurements were made by the same clinician under supervision of team members experienced with HemoSonic100 cardiac output monitoring. Cardiac output (COhs) was calculated from ABF \(^{[14]}\). COtd, COed, COmf, COhs, Pa, PAP, CVP, blood temperature, heart rate (HR), were continuously recorded and stored on a personal computer for documentation and offline analysis.

**Figure 1** Different positions of the patient during the interventions. A: During supine position VT was increased with 50% and PEEP was increased with 10 cmH\(_2\)O. B: PLR, Passive legs raising is performed by maintaining the patient in a supine position and raising the legs by repositioning of the bed. C: HUT, head up tilting. During all interventions except for HUT, the heart (symbol \(♥\)) and baroreceptors (symbol \(o\)) are in-level and blood pressure transducers do not have to be re-referenced. The Doppler probe may move during PLR and HUT and a repositioning of the probe is needed.

**Study protocol**
Measurements were carried out within 2 h of arrival in ICU and after hemodynamic stabilization post-surgery. Characteristics and treatment data of each patient were collected. During ‘Baseline 1’ (Figure 1) a series of measurements of HR, MAP, CVP, PAP, COtd, COed, COmf, and COhs were obtained. To change cardiac output, four interventions were applied. First, the tidal volume setting of the ventilator was increased by 50% for 5 minutes. Then 2 minutes later, the same series of measurements were repeated (‘VT-series’). Then, 5 minutes after values returned to baseline another series of measurements were performed (‘Baseline 2’). Next, positive airway pressure (PEEP) was increased by 10 cmH\(_2\)O for 5 minutes, and after 2 minutes the next series of measurements was taken (‘PEEP-series’).
Then, 5 minutes after return from increased PEEP, a ‘Baseline 3’ series of measurements was carried out. Next, passive leg raising was performed from the supine position by lifting both legs at a 30° angle and holding them there for 5 minutes: 2 minutes later, with legs still elevated the series of measurements were repeated (‘PLR-series’). Five minutes after return from passive leg raising, ‘Baseline 4’ measurements were performed. Lastly, a head up tilt was induced by raising head of the bed to 30°: 2 minutes later a series of measurements (‘HUT-series’) were made. Five minutes after return from HUT, during, the last series of (‘Baseline 5’) measurements were performed.

**Statistical analysis**

After confirming a normal distribution of data with the Kolmogorov–Smirnov test, agreement between COed, COf, COhs and COTd as well as agreement in changes in cardiac output was evaluated with Bland-Altman statistics. The agreement between COf or COed or COhs and COTd was computed as the bias (i.e., accuracy) and precision (i.e., standard deviation), with the limits of agreement (LOA) computed as the bias ±2SD [19]. The coefficient of variation was computed as [COV=100×(SD/mean)]. We also applied the method of Myles and Cui [20], and used a random effects model to calculate precision and limits of agreement. We included the effects of intervention (VT, PEEP, PLR and HUT) as a covariate in order to get a more precise estimate of the residual within-subject variation. Differences in cardiac output were analysed further with factorial ANOVA, and there were three factors; monitoring method (fixed factor, four levels); intervention (fixed factor, eight levels, repeated) and subjects (random factor, 13 levels). If ANOVA indicated a statistically significant (p<0.05) result in cardiac output between baseline and intervention, a post-hoc test (Tukey-HSD in multiple comparison, LSD in pairwise comparison) was used to identify the significant effect. The ability of the monitors to measure the change in cardiac output change (ΔCO) due to our interventions was calculated by subtracting the averaged cardiac output values during the relevant baselines from the mean cardiac output during the intervention (both as absolute and percentage changes). We regarded a ‘positive trend’ as being when the change in value of the new monitor was in the same direction as those found for COTd, whereas, a ‘negative trend’ was one where these changed in opposite directions. Ideally, only positive scores should be present. These scores were analysed using 2x2 tables and presented as percentages. Separate scores were counted for changes when thermodilution cardiac output values differed by at least a clinically relevant 5 and 10%.

**Results**

We included 13 cardiac surgical patients, 11 after coronary arterial bypass grafting and 2 after mitral valve reconstruction. A total of hundred seventeen paired CO data sets with COTd,
COed, COmf and COhs were obtained during 5 baselines periods and, VT, PEEP, PLR and HUT interventions. Averaging the baseline value before and the baseline value after the intervention resulted in 104 paired values for statistical evaluation. The data were normally distributed. Mean COtd was 5.28 L·min⁻¹ (range 2.57 to 8.61 L·min⁻¹). The coefficient of variation for averages of three thermodilution measurements equally distributed over the ventilatory cycle was 5%.

**Agreement of methods with thermodilution cardiac output**

Figure 2 shows Bland-Altman plots for difference between COtd and COed, COmf or COhs. Bias between COtd and COmf and between COed and COmf was 0.33 and 0.30 L·min⁻¹ respectively which was significantly different from the bias between COtd and COhs (-0.41 L·min⁻¹, p < 0.001). From Figure 2 it is observable that the distribution of errors is different among the methods. COmf has best precision (0.69 L·min⁻¹) and smallest range of the limits of agreement (-1.08 to 1.68 L·min⁻¹, 26%, Figure 2B) whereas values of precision and limits of agreement for COed and COhs are larger (-1.47 to 2.13, 34%, Figure 2A and –2.62 to 1.80 L·min⁻¹, 44%, Figure 2C, respectively).

**Figure 2** Bland-Altman plots of the difference of cardiac output (CO) values between conventional thermodilution (COtd) and three minimal invasive methods (n = 104). In panel A, COed, CO by auto-calibrated FloTrac-Vigileo system. In panel B, COmf, CO by non-calibrated Modelflow method. In panel C, COhs, CO by HemoSonic 100 ultrasound system. Solid line represents the bias, dotted lines absolute limits of agreement and dashed-dotted lines the limits of agreement in percentage.
Result based on the random effects model of Myles and Cui [20] are shown in Figure 3. The residual within-subject standard deviation was substantially smaller after adjustment for baseline. For example, the original within-subject standard deviation was 0.41 and 0.79 for COtd and COed, respectively. After adjusting for the relevant covariates, the within-subject standard deviation reduced to 0.21 and 0.20, respectively. This reduced the width of the 95% limits of agreements accordingly (Figures 2 and 3). Bias and precision of both, the original and modified Bland-Altman methods are presented in Table 1.

**Figure 3** Modified Bland-Altman plots of the difference of cardiac output (CO) values between conventional thermodilution (COtd) and three minimal invasive methods, based on a random effects model (n = 13). In panel A, COed, CO by auto-calibrated FloTrac-Vigileo system. In panel B, COmf, CO by non-calibrated Modelflow method. In panel C, COhs, CO by HemoSonic 100 ultrasound system. Solid line represents the bias, dotted lines absolute limits of agreement and dashed-dotted lines the limits of agreement in percentage.
**Table 1**: Comparison of bias and precision between the original and modified Bland-Altman methods.

COtd, intermittently thermodilution cardiac output (reference method); COed, CO measured with FloTrac-Vigileo; COmf, CO measured with non-calibrated Modelflow; COhs, CO measured with HemoSonic 100.

<table>
<thead>
<tr>
<th>Method</th>
<th>Bias L·min⁻¹</th>
<th>Precision L·min⁻¹</th>
<th>Error (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Classical Bland-Altman statistics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COed – COtd</td>
<td>0.33</td>
<td>0.90</td>
<td>34</td>
</tr>
<tr>
<td>COmf – COtd</td>
<td>0.30</td>
<td>0.69</td>
<td>26</td>
</tr>
<tr>
<td>COhs – COtd</td>
<td>-0.41</td>
<td>1.11</td>
<td>44</td>
</tr>
<tr>
<td><strong>Modified Bland-Altman statistics (Random effects model)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COed – COtd</td>
<td>0.33</td>
<td>0.69</td>
<td>25</td>
</tr>
<tr>
<td>COmf – COtd</td>
<td>0.30</td>
<td>0.64</td>
<td>24</td>
</tr>
<tr>
<td>COhs – COtd</td>
<td>-0.41</td>
<td>1.07</td>
<td>42</td>
</tr>
</tbody>
</table>

**Effects of intervention on CO**

The effects of the four applied interventions on our measures are shown in Table 2. Increasing tidal volume did not result in a change in cardiac output with any method. Other interventions did, however, change CO. With Factorial ANOVA the main effects on cardiac output values related to the measurement techniques was \(F = 23.73, p < 0.001\), and related to the interventions was \(F = 13.85, p < 0.001\). Differences between methods were consistent across all interventions \(F = 0.19, p = 1.000\).

As expected, cardiac output changes by all three methods correlate significantly \((p \leq 0.001)\) with cardiac output changes by COtd (COed v COtd, slope 1.46, CI95% 1.07 to 1.81; COmf v COtd, slope 0.82, CI95% 0.61 to 0.101; COhs v COtd, slope 0.88, CI95% 0.62 to 1.15). COed significantly overestimates the change (compared with COtd) but changes in COmf and COhs were similar to COtd.

Regarding direction of change, the score for agreement was 86% for COmf and 81% for COed and COhs. These scores greatly improve if clinically irrelevant changes of <5% or <10% are excluded from counting. For a 5% threshold, agreement is found in 96%, 85% and 93% with COmf, COed and COhs respectively. For a 10% threshold, these values are 100%, 89% and 100% respectively.
Figure 4 Bland-Altman plots with percentage changes in cardiac output in three minimal invasive methods and percentage changes by conventional thermodilution. For abbreviations see Figure 2. Solid line presents bias and dotted lines limits of agreement.

The Bland-Altman plots for changes in cardiac output with LOA are shown in Figure 4. Bias between change COtd and change COed, change COmf or change COhs is not significantly different (-3.03, -3.28, and -2.01 % respectively). COed (-29.59 to 23.52 %) has the largest range of the limits of agreement in contrast to COmf (-17.23 to 10.67 %) and COhs (-20.28 to 16.27%), respectively changes between COed and COtd clearly depends on the level of averaged change of COed and COtd (Figure 4A).
Table 2 Changes in cardiac output (CO) related to increase of tidal volume, increase of PEEP, passive leg raising and head up tilt intervention. COtd, intermitted thermodilution cardiac output; COed, CO measured with FloTrac-Vigileo; COmf, CO measured with non-calibrated Modelflow; COhs, CO measured with HemoSonic 100; CO difference is difference between CO intervention and CO baseline. Results of post-hoc analysis, pairwise comparison (LSD) of cardiac output differences related to interventions, factorial ANOVA (F = 13.85, p < 0.001).

<table>
<thead>
<tr>
<th>CO Baseline</th>
<th>CO Intervention</th>
<th>CO difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD) L- min⁻¹</td>
<td>Mean (SD) L- min⁻¹</td>
<td>in %</td>
</tr>
<tr>
<td>Increased tidal volume</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COtd</td>
<td>5.28 (1.28)</td>
<td>5.28 (1.44)</td>
</tr>
<tr>
<td>COed</td>
<td>5.72 (0.88)</td>
<td>5.89 (1.47)</td>
</tr>
<tr>
<td>COmf</td>
<td>5.75 (1.38)</td>
<td>5.43 (1.48)</td>
</tr>
<tr>
<td>COhs</td>
<td>4.81 (0.93)</td>
<td>4.75 (0.98)</td>
</tr>
<tr>
<td>Increased PEEP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COtd</td>
<td>5.37 (1.35)</td>
<td>4.66 (1.47)</td>
</tr>
<tr>
<td>COed</td>
<td>5.99 (0.93)</td>
<td>4.61 (1.51)</td>
</tr>
<tr>
<td>COmf</td>
<td>5.71 (1.45)</td>
<td>4.88 (1.47)</td>
</tr>
<tr>
<td>COhs</td>
<td>4.86 (0.89)</td>
<td>4.17 (1.04)</td>
</tr>
<tr>
<td>Passive leg raising</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COtd</td>
<td>5.39 (1.33)</td>
<td>5.79 (1.37)</td>
</tr>
<tr>
<td>COed</td>
<td>5.61 (0.93)</td>
<td>5.07 (0.97)</td>
</tr>
<tr>
<td>COmf</td>
<td>5.73 (1.44)</td>
<td>5.97 (1.46)</td>
</tr>
<tr>
<td>COhs</td>
<td>5.11 (0.74)</td>
<td>5.56 (0.76)</td>
</tr>
<tr>
<td>Head up tilt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COtd</td>
<td>5.34 (1.20)</td>
<td>5.16 (1.21)</td>
</tr>
<tr>
<td>COed</td>
<td>5.78 (1.06)</td>
<td>5.33 (1.35)</td>
</tr>
<tr>
<td>COmf</td>
<td>5.81 (1.31)</td>
<td>5.38 (1.30)</td>
</tr>
<tr>
<td>COhs</td>
<td>5.14 (1.13)</td>
<td>4.55 (1.01)</td>
</tr>
</tbody>
</table>

Discussion
Our main finding is that only Modelflow yields limits of agreement (26%) that are below the 30% criteria for limits of agreement for a theoretically acceptable alternative to thermodilution cardiac output [21]. Monitoring changes or trends in cardiac output can, however, be performed reasonably well with the non-calibrated Modelflow and HemoSonic (the auto-calibrated FloTrac-Vigileo performs less well in this regard).
Any error in our reference method (COtd) might influence the comparison between cardiac output by thermodilution and FloTrac-Vigileo, Modelflow or HemoSonic. Individual thermodilution cardiac output estimates show substantial scatter (10-15%) in value even under stable haemodynamic and ventilatory conditions [22]. An average of at least three measurements – over the respiratory cycle – is advised to obtain cardiac output estimate with acceptable precision [11,16] (this can require injections to be performed by a motor driven syringe under computer control) [23].

The results of the present study did not show conflicting results with respect to the results of previous reports, obtained with either the FloTrac-Vigileo system version 1.07 [4-8], the non-calibrated Modelflow method [11,12] or Hemosonic 100 system [24,25]. Myles and Cui [20] criticized in a recent editorial the use of standard Bland-Altman analysis to compare methodologies (such as ours in this study) where repeated measurements are used. We feel, however, that multiple observations in a patient really only apply when taken under the same experimental conditions. Where conditions are changing with time, it seems valid to take several observations and then assess response over time. Nonetheless, we took the precaution of applying both the ‘classical’ Bland-Altman statistics [19] and the random effects model proposed by Myles and Cui [20]. The differences in results of analysis are presented in the Figures 2 and 3. For all three methods the limits of agreement of the classical Bland-Altman analysis are larger than with the random effects model. This can be explained by the removal of within patient variation in cardiac output. Especially the difference between COed and COtd (Figure 2A) decreased considerably with the random effects model (Figure 3A). This is account for the overestimation of changes in cardiac output by the FloTrac-Vigileo system (Figure 4A).

Passive leg raising as an intervention in combination with oesophageal ultra-sound blood flow measurement has been used to identify those patients that likely beneficially respond to fluid challenge with an increase in cardiac output [26-28]. Monnet at al. [27] demonstrated that the HemoSonic device could reliably predict such responders. Our data suggests that this may also be the case with FloTrac-Vigileo and Modelflow.

One concern was that during passive leg raising (or even head up tilt), the oesophageal probe position may change. We were careful to reposition the probe regularly to obtain an optimal signal. However, the position of baroreceptors in relation to the heart is also changed by these manoeuvres and this may influence arterial blood pressure by auto-regulation (Figure 1). We would expect this effect to be constant across all methods and not bias any particular device.
Conclusions
The non-calibrated Modelflow method showed best performance in estimation of cardiac output. Changes in cardiac output by thermodilution were also tracked well by the non-calibrated Modelflow and also by the HemoSonic device, whereas the auto-calibrated FloTrac-Vigileo overestimated the changes in cardiac output. Directional changes in cardiac output by thermodilution were detected with a high score by all three methods. Encouraged by the simplicity of setup procedure and advantage for the patient, we suggest future work focuses on the Modelflow system.
References


