Withstanding the flow

*Human cardiovascular control during postural challenges*

Truijen, J.

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Chapter 3

THE EFFECT OF HEMODYNAMIC AND PERIPHERAL VASCULAR VARIABILITY ON CARDIAC OUTPUT MONITORING: THERMODILUTION AND PULSE CONTOUR CARDIAC OUTPUT DURING CARDIOTHORACIC SURGERY


Anaesthesia, 2018
Chapter 3

ABSTRACT

Background
While hemodynamic variability interferes with the assumption of constant flow underlying thermodilution (TD) cardiac output (CO) calculation, variability in arterial physiology may affect pulse contour CO methods. We compared noninvasive finger arterial pressure (NAP) based continuous CO (Nexfin®, BMEYE, Amsterdam, the Netherlands) with TD CO during cardiothoracic surgery and determined the impact of cardiovascular variability on either method.

Methods:
NAP CO was compared with TD CO at four grades (A-D) of cardiovascular variability. Grade A data was defined as heart rate (HR) and mean arterial pressure (MAP) variability <5% and absence of arrhythmias (implying stable flow), and Physiocal® interval (as measure of variability in finger arterial physiology) >30 beats. Grade B included all levels of HR/MAP variability and arrhythmias (Physiocal <30 excluded). Grade C included all Physiocal intervals (HR/MAP variability >5% and arrhythmias excluded). Grade D included all data. Comparison results were quantified as percent errors.

Results
Measurements in twenty-seven patients undergoing coronary artery bypass surgery were analyzed. Before extracorporeal circulation, the percent error was 23% (N=14 patients) in grade A, 28% (N=20) in grade B, 32% (N=22) in grade C, and 37% (N=26) in grade D with a significant increase in variance (p=0.035). Bias did not differ between grades. After extracorporeal circulation (N=27), percent errors became larger but were not different between grades.

Conclusions
Variability during cardiothoracic surgery affected the comparison between TD and NAP CO. When main sources of variability impacting the compared methodologies were included, the percent errors were large. Future CO methodology comparison studies should report hemodynamic variability.
Reductions in central blood volume by hemorrhage, positioning of the patient, anesthesia and positive pressure ventilation can be corrected by fluid therapy, while early recognition is essential. Consequently, also patients undergoing moderate risk surgery may benefit from continuous hemodynamic monitoring for optimization of arterial flow. This led to a trend towards less invasive and continuous methods to determine cardiac output (CO) or stroke volume (SV) in order to guide fluid therapy during surgery and in the intensive care setting. So-called “minimally invasive” SV or CO monitoring typically needs arterial pressure (AP) only. Presently continuous CO can be derived from noninvasive AP (NAP) wave as well as from invasive AP (IAP) with pulse contour methods.

Validation of minimally- or noninvasive continuous CO is generally based on a comparison with conventional intermittent thermodilution (TD) based estimates of CO. However, the Stewart (1893)-Hamilton (1932) equation that is incorporated in the TD device to compute CO from the dilution curve is valid for constant blood flow only. Since this is generally not the case - ventilation induced variability is even commonly quantified by “stroke volume variation” - errors are introduced and averaging of repeated measurements is required. Still, in order for this averaging to be effective, the estimates should be taken from an otherwise stationary flow. Thus, a comparison of a continuous CO method and discontinuous TD CO using averaging of multiple values can only be reliably performed under conditions of constant hemodynamics as evidenced by, at least, stability of heart rate (HR) and mean AP (MAP). Hemodynamic variability or arrhythmia obviously interfere with this requirement thus violating the basic assumptions that allow application of the Stewart-Hamilton equation to calculate CO.

The input for pulse contour CO methods are accurately measured arterial pressures. Since characteristics of the shape of the arterial pressure wave are analyzed, the signal should not be over- or underdampened. NAP measurements, using a finger cuff, are automatically calibrated by Physiocal, which regularly checks for the “unloaded volume” of the artery enclosed by the cuff. When changes in vascular tone are detected, a subsequent Physiocal is scheduled within a shorter time interval. Thus, the Physiocal interval is related to variability in the arterial physiology at the measurement site.

This study tested the hypothesis that variability in hemodynamics and peripheral vasculature physiology during cardiothoracic surgery impact the comparison of discontinuous TD CO and continuous CO. As a secondary aim, we examined the hypothesis that NAP vs. invasive AP (IAP) as basis for CO measurement introduces errors.

METHODS

High risk patients undergoing coronary artery bypass surgery with a clinical indication for invasive CO monitoring were included after obtaining written informed consent. Patients with a cardiac shunt, valvular disease, or rhythm disorder were excluded. The study was approved by the Medical Ethics Committee of the Academic Medical Center of the University of Amsterdam, Amsterdam, the Netherlands (NL18810.018.07), and complied with the provisions of the Declaration of Helsinki. This manuscript adheres to the applicable Equator guidelines.
Chapter 3

Measurements

Thermodilution CO (TD CO) was determined with a Swan-Ganz catheter (type 931HF75, Edwards Lifesciences, Irvine, CA) connected to a COM-2 apparatus (Baxter Healthcare Corporation, Edwards Critical Care Division, Irvine, CA). Injectate (10 ml bolus of 5% glucose solution) was drawn through an ice-filled container (CO-SET+, Edwards Lifesciences, Irvine, CA) and injected by a computer-controlled pneumatic power injector (Broszeit Medizintechnik, Werl, Germany) over a period of 2 seconds.\(^7\) With this approach the consistency of injected volume and linearity of injection rate was ensured, the injection time reduced and transfer of heat to the syringe by direct hand contact avoided. A priming injection to cool the tubing was followed by four injections of cooled (<10°C) glucose solution.\(^7\) The computer-controlled injections were precisely timed and equally distributed over the ventilatory cycle determined from airway pressure.\(^154, 177\) Each set of four TD CO determinations was averaged to obtain one single value. Automatically generated markers indicated the precise timing of the TD injections. TD curves were checked visually before acceptance.

Noninvasive AP (NAP, Nexfin\textsuperscript{®} monitor, Edwards Lifesciences BMEYE, Amsterdam, The Netherlands\(^116\)) measurements, based on the volume-clamp method using a finger cuff as proposed by Peñáz,\(^53\) were regularly and automatically calibrated with Physiocal\textsuperscript{®}, the physiological calibration developed by Wesseling \textit{et al.}\(^107, 178\) Finger AP was reconstructed to brachial pressures in real time.\(^2, 109, 179\) Invasive AP (IAP) was measured in the radial artery with a 20 G catheter (Ref RA-04020; Arrow International Inc., Reading, PA) and a pressure transducer (Pressure Monitoring Set, Edwards Lifesciences, Irvine, CA, USA) positioned at heart level and connected to a module (HPM1006A; Hewlett Packard, Palo Alto, CA) mounted in a patient monitoring system (Philips Medical Systems, Andover, MA). The resonance frequency of the arterial catheter-manometer system was checked with the fast flush technique.\(^77, 180\) NAP and IAP waveforms were measured ipsilaterally and sampled at 200 Hz.

Continuous CO was determined from NAP (NAP CO) and IAP (IAP CO) with Nexfin CO-trek\textsuperscript{®}.\(^10\) This pulse contour method calculates beat-to-beat stroke volume by dividing the area under the systolic part of the AP curve, i.e. pulsatile systolic area (PSA), by the aortic input impedance (Z\textsubscript{in}). PSA is the time-integral of the AP wave above diastolic pressure and between aortic valve opening and closing as determined by upstroke and incisura.\(^7\) For the calculation of the PSA, brachial artery pressure is reconstructed from finger and radial AP with dedicated reverse filters.\(^112\) Dividing the PSA by the Z\textsubscript{in} instantaneously gives SV; for each beat, Z\textsubscript{in} is determined from a three-element Windkessel model.\(^349, 151\) The used model incorporates the nonlinear effect of MAP and the influence of age, height, weight and gender of the subject on aortic mechanical properties.\(^179\) CO is calculated from SV times HR. Beat-to-beat values of NAP CO respectively IAP CO were averaged over 30 s for each of the 4 periods of the TD CO determinations.
Statistical Analysis

Hemodynamic variability was ascertained from IAP during the 4 TD determinations and expressed as:

\[
100\% \left( \frac{\text{maximal difference between any of the 4 values and their average}}{4 - \text{value} - \text{average}} \right)
\]

Presence of variability was considered to impact TD measurements (for a theoretical evaluation of the errors in TD CO see the Supplemental Content, section “Factors affecting thermodilution cardiac output measurement”). Variability in the physiology underlying the NAP measurement was detected based on the Physiocal interval. A Physiocal interval larger than 30 beats is considered to indicate acceptable NAP measurement. Detection of changes in vascular tone reduces the interval to maintain accuracy (for a theoretical evaluation of NAP CO errors, see the Supplemental Content, section “Factors affecting noninvasive pulse contour cardiac output measurement”). To ensure good quality AP recordings, for IAP it was required that the catheter-manometer system had an adequate dynamic response. For NAP, a pulse pressure <20 mm Hg was considered a dampened pressure based on earlier findings (see Supplemental Content, section “Factors affecting noninvasive pulse contour cardiac output measurement.”) Clinical measurements (JT, YSK) and statistical analysis (BEW) were performed by separate researchers.

NAP CO was compared with IAP CO to determine whether the noninvasive method introduces variability (some notes on assessing of agreement of methodologies are given in the Supplemental Content, section “Considerations on comparison of cardiac output methods”). The data after extracorporeal circulation (“after pump”) were considered to contain additional variability since peripheral AP may be less representative of central pressure. Moreover, the temperature drift caused by the warming of the subject may render TD CO erratic.

The AP CO and TD CO methods were evaluated for agreement of both the absolute and tracking values, i.e. quantifying the ability to follow CO changes. Data are presented as average ± standard deviation (SD) and minimum and maximum are given. AP CO – TD CO differences are called “absolute” while “tracking” are the AP CO – TD CO differences after removal of the bias in a subject. To remove the subject’s bias, a factor is calculated from the average TD CO values divided by the average AP CO values. Additionally, tracking was assessed by concordance analysis, in which the average of the TD CO values and AP CO values is subtracted from the values of a subject. Data in a zone of ± 0.5 l. min⁻¹ around the origin were excluded. Bland-Altman analysis was performed showing mean bias and 95% limits of agreement (LOA, ± 1.96 SD). Percent error for absolute and tracking values is calculated as:

\[
100\% \frac{1.96 \text{ SD}}{\frac{\text{AP CO} + \text{TD CO}}{2}}
\]
The range of CO in an individual is quantified by within-subject variability, expressed as the SD of a subject’s averages of TD CO and AP CO. The within-subject precision is calculated as the SD of AP CO – TD CO differences.\textsuperscript{120} This within-subject precision, and also the within-subject percent error that can be calculated from it, allow separating out precision in the individual from the precision determined over the group data. Group data is calculated from the SD over the individual averages of AP CO – TD CO differences and expressed as subject-averaged percent error. The averaged data of each individual with horizontal and vertical error bars showing the within-subject variability and precision are also given in Bland-Altman plots.\textsuperscript{2}

The influence of hemodynamic and peripheral vascular variability on the NAP vs. TD CO comparison was classified as follows: grade A data was defined as having HR and MAP variability <5%, no arrhythmias and Physiological interval >30 beats; Grade B included all levels of HR/MAP variability and arrhythmias to evaluate the impact of hemodynamic variability, while Physiological interval <30 beats was excluded. Grade C included all Physiological intervals to evaluate the impact of peripheral vascular variability, while HR/MAP variability >5% and arrhythmias were excluded. Grade D included all data. Biases were compared by analysis of variance; variances were compared with Bartlett’s test.

For data management, statistical analyses and plotting, Microsoft Office Excel 2007 (Microsoft Corporation, Redmond, WA), SPSS 19 (IBM SPSS Statistics 19, IBM Corporation, Somers, NY), and Sigmaplot 11 (Systat Software Inc., Chicago, IL) were used.

**RESULTS**

Twenty-eight patients undergoing coronary artery bypass surgery were included, of whom one was excluded due to a dampened NAP (Figure 3.1). The resonance frequency of the arterial catheter-manometer system ranged from 15-25 Hz. In total data from 27 patients (25 men, Table 3.1) were analyzed. Blood pressure was variable during surgery (Table 3.1, Figure 3.2). In these patients, 157 series of TD CO were determined in the periods before- and after pump (Figure 3.3). Before pump, in one patient no TD CO measurements were performed (Figure 3.3) due to technical issues, so 26 patients were available with a total of 91 data points.

---

**Figure 3.1**

Flow diagram of patient inclusion.
### Table 3.1 Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Average ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65 ± 9</td>
<td>46 – 83</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>175 ± 8</td>
<td>158 – 189</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>85 ± 18</td>
<td>62 – 130</td>
</tr>
<tr>
<td>Body mass index (kg m(^2))</td>
<td>29 ± 5</td>
<td>23 – 41</td>
</tr>
<tr>
<td>Mean arterial blood pressure (mm Hg)</td>
<td>70 ± 7</td>
<td>28 – 163</td>
</tr>
<tr>
<td>SD on mean arterial blood pressure (mm Hg)</td>
<td>11 ± 3</td>
<td>4 – 18</td>
</tr>
<tr>
<td>Heart Rate (bpm)</td>
<td>66 ± 11</td>
<td>27 – 150</td>
</tr>
<tr>
<td>SD on Heart Rate (bpm)</td>
<td>11 ± 4</td>
<td>5 – 25</td>
</tr>
</tbody>
</table>

Twenty seven patients, 25 men and 2 women. The "SD on mean arterial blood pressure" and “SD on Heart Rate” give an indication of the variability within the subjects over the measurements.

Grade A data was available in 14 patients (Table 3.2, Figure 3.4) before pump; percent error was 23% for NAP CO versus TD CO which increased to 28% for grade B (20 patients, Table 3.2, Figure 3.4) and to 32% for grade C (22 patients, Table 3.2, Figure 3.4). In grade D the percent error of NAP CO became 37% (26 patients, Table 3.2 and Figure 3.4). Biases in NAP CO versus TD CO were not different between the grades, but variance was increased (p=0.035). Comparing NAP CO with IAP CO within the grades, biases were different but all smaller than 0.5 l. min\(^{-1}\) while variance was equal in each case. Variance for tracking was in each instance smaller than the variance of the absolute values. The NAP CO tracking percent error remained between 11 and 13% in all grades and was not affected by variability (Table 3.2). The within-subject percent errors of 12-13% were all smaller than the group (subject-averaged) percent error of 21-38% (Table 3.3), indicating that group errors contain systematic errors leading to underrate the precision of the individual CO data. Within-subject variance was not different between grades.
Table 3.2 Cardiac output comparison; effects of potentially confounding conditions (before pump)

<table>
<thead>
<tr>
<th>Grade A (N = 14, n = 25)</th>
<th>TD CO [l. min⁻¹]</th>
<th>AP CO [l. min⁻¹]</th>
<th>AP CO – TD CO [l. min⁻¹]</th>
<th>Percent error [%]</th>
<th>Concord. [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute</td>
<td>NAP CO</td>
<td>4.57 ± 0.89 (2.68, 6.33)</td>
<td>0.07 ± 0.53 (–0.71, 1.10)</td>
<td>23</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>IAP CO</td>
<td>4.08 ± 0.77 (2.50, 5.71)</td>
<td>–0.42 ± 0.63 (–1.33, 0.65)</td>
<td>29</td>
<td>100</td>
</tr>
<tr>
<td>Tracking</td>
<td>NAP CO</td>
<td>4.50 ± 1.12 (2.48, 6.66)</td>
<td>(0) ± 0.29 (–0.68, 0.50)</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IAP CO</td>
<td>4.50 ± 1.14 (2.48, 6.71)</td>
<td>(0) ± 0.25 (–0.45, 0.44)</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Grade B (N = 20, n = 51)</td>
<td>NAP CO</td>
<td>4.45 ± 0.95 (2.68, 6.42)</td>
<td>0.15 ± 0.63 (–1.07, 2.15)</td>
<td>28</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>IAP CO</td>
<td>4.02 ± 0.81 (2.50, 5.74)</td>
<td>–0.28 ± 0.67 (–1.54, 1.47)</td>
<td>31</td>
<td>100</td>
</tr>
<tr>
<td>Tracking</td>
<td>NAP CO</td>
<td>4.29 ± 1.09 (2.36, 6.83)</td>
<td>(0) ± 0.28 (–0.78, 0.71)</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IAP CO</td>
<td>4.29 ± 1.11 (2.33, 6.93)</td>
<td>(0) ± 0.25 (–0.67, 0.62)</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Grade C (N = 22, n = 40)</td>
<td>NAP CO</td>
<td>4.49 ± 0.84 (2.68, 6.33)</td>
<td>0.06 ± 0.72 (–1.49, 1.55)</td>
<td>32</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>IAP CO</td>
<td>4.07 ± 0.68 (2.50, 5.71)</td>
<td>–0.35 ± 0.72 (–1.79, 1.02)</td>
<td>33</td>
<td>100</td>
</tr>
<tr>
<td>Tracking</td>
<td>NAP CO</td>
<td>4.43 ± 1.04 (2.48, 6.66)</td>
<td>(0) ± 0.26 (–0.68, 0.50)</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IAP CO</td>
<td>4.43 ± 1.04 (2.48, 6.71)</td>
<td>(0) ± 0.21 (–0.45, 0.44)</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Grade D (N = 26, n = 91)</td>
<td>NAP CO</td>
<td>4.46 ± 0.93 (2.68, 7.43)</td>
<td>0.24 ± 0.82 (–1.58, 2.82)</td>
<td>37</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td>IAP CO</td>
<td>4.09 ± 0.76 (2.50, 6.27)</td>
<td>–0.13 ± 0.85 (–1.89, 1.67)</td>
<td>40</td>
<td>100</td>
</tr>
<tr>
<td>Tracking</td>
<td>NAP CO</td>
<td>4.22 ± 1.05 (2.36, 6.83)</td>
<td>(0) ± 0.27 (–0.81, 0.71)</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IAP CO</td>
<td>4.22 ± 1.07 (2.33, 6.93)</td>
<td>(0) ± 0.22 (–0.67, 0.62)</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

Cardiac output (CO) values for thermodilution (TD CO) arterial pressure (AP) based pulse contour CO, from noninvasive (NAP CO) and invasive (IAP CO) AP and their differences: AP CO – TD CO, expressed as average ± SD (minimum, maximum). N = number of patients, n = number of data points. Grade A data: data pairs not included in case of >5% variability in heart rate, >5% variability in mean arterial pressure, arrhythmia or a Physiocal interval <30 beats during the TD CO. Effect of variability, grade B data: data pairs with variability in heart rate / mean arterial pressure >5% or arrhythmia included; grade C data: data pairs with Physiocal interval <30 beats included; grade D, all data. For percent error and concordance (Concord.) see Methods.
In the combined before and after pump data (Supplemental Content, section “After pump period analyses”), biases were not different between grades and not different from before pump; variance was larger than before pump but not different between grades. Within-group comparisons of NAP CO and IAP CO revealed different biases but variance was equal in each case. Variances for tracking were smaller than the variances of the absolute values. The within-subject variance increased compared to the before pump period. NAP and IAP showed similar percent errors after pump.

**Figure 3.2** Invasive (IAP, red) and noninvasive (NAP, green) arterial pressures of 27 patients. Both recordings demonstrate the variability that was present during surgery. During the pump period, in some cases the Nexfin could not find sufficient pulsatility and continuously performed restarts; this is visible as “blocks” such as in patients 6, 10 and 22.
### Table 3.3 Within-subject cardiac output variability and precision (before pump)

<table>
<thead>
<tr>
<th>Group (subject-averaged)</th>
<th>Within-subject variability [l.min⁻¹]</th>
<th>Within-subject percent error [%]</th>
<th>Within-subject precision [l.min⁻¹]</th>
<th>Group (subject-averaged) percent error [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade A (N = 14, n = 25)</td>
<td>TD CO &amp; NAP CO 0.32 ± 0.25 12</td>
<td>0.28 ± 0.21 21</td>
<td>TD CO &amp; IAP CO 0.36 ± 0.23 11</td>
<td>0.22 ± 0.18 30</td>
</tr>
<tr>
<td>Grade B (N = 20, n = 51)</td>
<td>TD CO &amp; NAP CO 0.33 ± 0.26 13</td>
<td>0.29 ± 0.13 31</td>
<td>TD CO &amp; IAP CO 0.34 ± 0.25 12</td>
<td>0.25 ± 0.10 35</td>
</tr>
<tr>
<td>Grade C (N = 22, n = 40)</td>
<td>TD CO &amp; NAP CO 0.37 ± 0.26 13</td>
<td>0.28 ± 0.19 33</td>
<td>TD CO &amp; IAP CO 0.37 ± 0.22 9</td>
<td>0.20 ± 0.17 35</td>
</tr>
<tr>
<td>Grade D (N = 26, n = 91)</td>
<td>TD CO &amp; NAP CO 0.34 ± 0.22 13</td>
<td>0.29 ± 0.15 38</td>
<td>TD CO &amp; IAP CO 0.34 ± 0.24 12</td>
<td>0.24 ± 0.09 41</td>
</tr>
</tbody>
</table>

*Within-subject variability describes the range of CO in an individual; the within-subject precision is a measure of precision in an individual. The within-subject percent error is calculated from the within-subject precision. Group (subject-averaged) percent error assesses the precision of the comparison over the group, after averaging the individual values for each subject. Grade A data: data pairs not included in case of >5% variability in heart rate, >5% variability in mean arterial pressure, arrhythmia or a Physiocal interval <30 beats during the TD CO. Effect of variability, grade B data: data pairs with variability in heart rate, mean arterial pressure >5% or arrhythmia included; grade C data: data pairs with Physiocal interval <30 beats included; grade D, all data. For the calculations see Methods.*
Figure 3.3 Cardiac output (CO) based on invasive (IAP CO, red) and noninvasive (NAP CO, green) arterial pressures (AP) of all 27 patients. One minute running averages were used for plotting. The thermodilution (TD) CO values, each averaged over 4 shots, are shown as small boxes. No TD CO measurements were performed during the pump period; in patient 26 no TD measurements were performed in the period before the pump.
Figure 3.4 Cardiac output (CO) comparisons of thermodilution (TD CO) and invasive (red) and non-invasive (green) arterial pressure based CO (AP CO) of the period before pump. Grade A data (A1-A6): data pairs not included in case of >5% variability in heart rate, >5% variability in mean arterial pressure, arrhythmia or a Physiocal interval <30 beats during TD CO. Effect of variability: grade B data including of data pairs with variability in heart rate / mean arterial pressure >5% or arrhythmia (B1-B6); grade C data including data pairs with Physiocal interval <30 beats (C1-C6); grade D, all data (D1-D6).

Scatter plot for absolute values (A1-D1), scatter plots for tracking (A2-D2; data only shown when more than one comparison was available) and the concordance plots (A3-D3) with an exclusion zone of ± 0.5 l. min⁻¹. Bland-Altman plots of the absolute values (A4-D4), for tracking (A5-D5) and of the subject-averaged values (A6-D6), with error bars indicating within-subject variability (horizontal) and within-subject precision (vertical). Dashed lines: 95% confidence intervals.
**DISCUSSION**

This study demonstrated that the comparison of NAP based CO and TD CO is affected by the hemodynamic and physiologic variability that occurs during cardiothoracic surgery. Percent errors are small for grade A with data acceptable for TD (low variability in HR, MAP and arrhythmia) and for NAP (low variability in finger arterial physiology). The larger percent errors in grade D including all data are more representative of observational studies; with percent errors ranging from 20% to 50% in the recent literature.\(^{134, 159, 185, 186}\)

The impact of variability of hemodynamics and of peripheral vascular physiology on the used CO methods is dissimilar. Arrhythmia and changes in HR and MAP violate the basic assumption of constant blood flow which is required for calculation of TD CO with the Stewart-Hamilton equation.\(^{125, 176}\) The model-based pulse contour method makes no assumptions about hemodynamic stability, but noninvasive continuous AP based CO calculation relies on peripherally measured pressure which may be insufficiently representative of central pressure.\(^{187}\) The findings in this study are in line with the hypothesized impact of sources of variability on the NAP vs TD CO comparison. The NAP and IAP CO based comparisons showed similar variabilities.

Recent studies comparing CO from noninvasive continuous AP with other clinically available methods in intensive care units brought forth disparate results. While the authors in general welcome the fact that continuous CO can be obtained with a finger cuff as only interface with the patient, concerns were raised about reliability, particularly in critically ill patients.\(^{185}\) The investigators suggest that severe vasoconstriction may have been the cause (Supplemental Content, section “Factors affecting noninvasive pulse contour cardiac output measurement”). In case of peripheral vascular decoupling measurements with a pulmonary artery catheter would seem clinically indicated.

The reference method that we used, the pulmonary artery TD technique is considered the clinical standard for cardiac output monitoring in critically ill patients.\(^{188}\) However, due to the invasive and complex nature of pulmonary artery TD it is reserved for patients at high risk of hemodynamic instability. The benefits of inserting a Swan-Ganz catheter should outweigh the risks of this procedure.\(^{81, 83}\) Moreover, the pulmonary artery TD CO measurement is an indirect procedure that has to be judged critically with regard to accuracy. Its accuracy is enhanced by averaging three or four determinations over various phases of the respiratory cycle, to eliminate the influence of respiration on cardiac output.\(^{154, 177}\) Nonetheless, arrhythmias or variability in HR or mean AP will degrade TD CO determinations.\(^{176}\)

Assessment of fluid responsiveness demands accurate CO tracking rather than absolute accuracy of a single CO determination.\(^{134}\) Moreover, the hemodynamic variability associated with central hypovolemia, and considerable stroke volume / pulse pressure variation\(^{189}\) renders TD CO less reliable. Nonetheless the tracking of changes in CO by pulse contour methods or TD is hardly influenced by any of the respective variabilities. This can be explained by the analysis method for tracking, in which the averages of the available determinations for both methods were set equal. In this way the bias is annihilated but also random errors are reduced to a certain extent; what remains are the changes around the average value. Tracking errors were approximately half of the errors found in the absolute values, in accordance with earlier studies.\(^{190-192}\)
Some limitations need to be acknowledged when interpreting the current findings. First, data were collected as clinically available and no interventions were planned to influence the accuracy or precision of the comparison. However, the analysis allowed us to separate out several factors known to influence either NAP or TD CO, giving insight in the respective errors and practical implications for use of continuous and intermittent methods. Second, non-invasive measurements were performed on the side of the intra-arterial cannula which may have influenced the pressure transfer to the finger. Finally, the data of one patient was not used due to insufficient quality of the NAP measurement. Like invasive measurements, which may exhibit dampening or overshooting of the pressure waves, non-invasive measurements may be unreliable and should be judiciously used as any measurement.

In conclusion, the comparison of TD and AP CO is affected by several factors that are frequently encountered in clinical practice. The accuracy of TD is impacted by hemodynamic variability and the AP CO is influenced by variability in peripheral vascular physiology. Small errors can be reached in well-controlled studies, and in studies with hemodynamically stable patients. Comparison of CO methods in clinical practice will likely have larger errors. Studies to compare CO methods should report hemodynamic variability to allow a meaningful interpretation of the results.
SUPPLEMENTAL CONTENT

Factors affecting thermodilution cardiac output measurement

Thermodilution (TD) cardiac output (CO) is considered the clinical “gold” standard to validate other methods of CO monitoring, however, it is not without errors. Therefore, with the TD method as the reference, the inherent TD errors should be acknowledged. In the following, we will discuss and delineate three main sources of error, which will all be expressed as percent errors (95% CI).

Technical limitations in acquisition and processing of the thermal signal

TD CO calculation has to deal with practical aspects such as determining a Stewart-Hamilton description from the measured thermal dilution curve, which usually not behaves ideally. The curve needs to be truncated (to avoid inclusion of recirculation) and extrapolated. Also, assumptions need to be made to account for the loss of indicator before, during or after injection. This depends on temperature and volume of the injectate, on injection site and type of catheter, and is rolled up into the computation constant. The technical limitations related to imposing a model on actual physiology can be designated as instrument errors. Errors due to catheter positioning or due to using the TD method when contraindicated (tricuspid regurgitation, septum defect) are not discussed here.

A recent study used a continuous flow rig to create optimal measurement circumstances and applied the best possible reference method (ultrasonic transit time flow probe) to determine the instrument errors in the TD method. Random errors (variations between readings) and systematic errors (differences related to 2 types of catheters and 3 monitoring systems) were addressed separately. The systematic precision errors (95% CI) ranged from 11.6% to 26.7%; the random errors ranged from 5.8% to 10.0% for triplicate 5-ml, ice-cooled injections. The overall instrument related percent errors (square root of the summed squares) thus ranged from 13.0% to 28.1%.

Operator related variability in conducting bolus TD measurements

Operator-related sources of error include inappropriate or inconsistent injectate temperature, varying volume of the injectate and speed / regularity of injection. When comparing CO measurements by manual vs. automated injection to simultaneous direct Fick CO, Stawicki et al. showed a 13.3% larger percent error for the manual method. Others reported similar CO for manual vs. automated injections notwithstanding significant variation in injection time, flow rate and consistency with manual injection. We will here assume that operator errors range from 0% to 13.3%.

Physiological variability violating assumptions made in the TD algorithm

For the measurement of CO with thermodilution two main assumptions are made. First, the Stewart-Hamilton equation assumes that actual flow or CO is constant over the period that a dilution curve is measured. One source of modulation is caused to the ventilation-related modifications of preload, which can be expressed as stroke volume variation (SVV) and is used to assess preload dependency. The Stewart-Hamilton equation assumes SVV to be
Chapter 3

0%, while in reality it may be 20% on average in cardiac surgery patients\textsuperscript{177} or even larger, particularly in the pulmonary circulation.\textsuperscript{193} An approach to compensate for respiration related errors is to repeat the measurements three or four times throughout the ventilation cycle to average out the variations in stroke volume and baseline temperature. The error component amounts to 35.0% (95% CI) in single boluses and 20.2% in triplicate measurements when evenly distributed over the respiratory cycle.\textsuperscript{154} A carefully controlled study under very stable post-surgical circumstances showed that, under the assumption of a mean bias of zero, this procedure can reduce the physiological variability related precision error from 27.8% to 14.4% to (95% CI) for a triplicate TD CO average.\textsuperscript{177}

The commonly executed averaging approach, however, relies on yet another important assumption: that the three or four samples used to average out the ventilatory modulation are taken from an otherwise stationary process, in other words that the cardiac output showed no drifts up or down. Slower baseline changes of actual CO during the measurements (such as caused by surgery or pharmacological interventions), HR changes and arrhythmia render an approach of averaging multiple measurements unreliable. In the carefully controlled study mentioned above,\textsuperscript{177} this was achieved by obtaining measurements during deliberately established quiet pre- and post-surgical periods without patient manipulation. In daily practice OR situations, however, the assumption of stable CO during the 3 – 4 TD CO measurements is unrealistic, and therefore also the idea that averaging will significantly reduce the errors related to ventilator modulation of CO.

Second, the Stewart-Hamilton equation assumes that the baseline temperature in the right atrium on which the cold injectate bolus is superimposed, is constant over the period that a dilution curve is measured. However, depending on the phase of the ventilation, variation in the admixture between blood from the superior and inferior caval veins, which have slightly different temperatures, results in cyclic baseline fluctuations influencing the area under the dilution curve and thus the computation of CO.\textsuperscript{176} Also rapid changes in pulmonary artery temperature after cardiopulmonary bypass results in errors.\textsuperscript{198}

Summary

Errors related to technical limitations in thermal signal acquisition and processing are inevitably included in any TD CO measurement. Operator errors are avoided by fully automating the measurements as in the current study, but such systems are not commercially available and neither clinically applied on a regular basis. Procedures to do multiple measurements under hemodynamically steady circumstances to obtain stable baselines may be controlled in research settings but are challenging in routine clinical practice. TD CO measurements under conditions of hemodynamic variability c.q. arrhythmia should be discarded altogether. These requirements are regularly not met, explaining the large spread of errors between different clinical studies with TD CO as reference.

The precision error ranges for the three main error sources for triplicate bolus TD CO are listed in Table 3.S1. Since the three precision errors are independent, the combined error can be determined as square root of the summed squares. The smallest (almost theoretical) precision error is close to 20%, as suggested by Critchley and Critchley for TD CO as reference method.\textsuperscript{199} The largest precision error is close to the reported combined TD CO – pulse contour percent error of 41.3%.\textsuperscript{134} In contrast, in Table 3.S1 the errors apply to the TD
CO method itself, not the combined errors of two methods. Thus, TD CO method has several inherent errors; some are related to the system (choice of catheter and monitor). Other errors are related to the execution of the measurements (operational errors). Optimizing measuring conditions and avoiding hemodynamic variability seem the most effective way to reduce the TD CO error.

**Table 3.S1** Error sources in thermodilution measurements

<table>
<thead>
<tr>
<th></th>
<th>Min - Max</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technical limitations</td>
<td>13.0% - 28.1%</td>
<td>194</td>
</tr>
<tr>
<td>Operator errors</td>
<td>0.0% - 13.3%</td>
<td>195, 196</td>
</tr>
<tr>
<td>Physiological variability</td>
<td>14.4% - 27.8%</td>
<td>177</td>
</tr>
<tr>
<td>Total</td>
<td>19.4% - 41.7%</td>
<td></td>
</tr>
</tbody>
</table>

Percent error ranges in thermodilution cardiac output measurements taken from the literature.

Factors affecting noninvasive pulse contour cardiac output measurement

In the steps along the way from noninvasive pressure measurement to CO determination, errors related to technical aspects, to the operator and to model assumptions accumulate and these are discussed here.

Technical limitations in pressure signal acquisition

Finger arterial blood pressure measurement technology as implemented in the Nexfin is based on the volume clamp method and relies on Physiocal to calibrate the pressure measurement. The volume clamp method requires that the artery enclosed by the cuff is unloaded, having a diameter at which the vessel wall has no influence on the pressure balance between intra- and extravascular (cuff) pressure during the measurement. Physiocal searches for this unloaded diameter; however, in case of large changes in finger arterial tone more frequent recalibrations are needed, resulting in shortening of the interval at which Physiocal activated (< 30 beats).

The cut-off value for pulse pressure as an exclusion criterion for NAP was determined based upon an earlier study that compared NAP against IAP, with NAP pulse pressure not lower than 20 mm Hg. If an invasive measurement would deliver such a pulse pressure, likely the anesthesiologist would check the catheter-manometer system. When a patient is on cardiopulmonary bypass, low pulsatility can be expected and can be correctly measured with Nexfin, so the 20 mm Hg cut-off value for pulse pressure is not a contraindication for such measurements.
Two earlier studies in an intensive care setting demonstrated that CO from invasive vs. noninvasive pressure is comparable.\textsuperscript{10,191} Recent studies in the medical or surgical intensive care reported accuracy and precision of Nexfin CO-trek CO without including invasive arterial pressure in the comparison. With respect to vasoconstriction due to vasopressors and body temperature Monnet\textit{ et al.}\textsuperscript{185} reported large percent errors that persisted when excluding patients with atrial fibrillation and/or norepinephrine from analysis, indicating other sources of errors. These sources were not disclosed since data on execution or performance of TD CO measurements are lacking (e.g. whether they were simultaneous with the noninvasive measurements, how many injections were averaged, what the injection volume was, how outliers were handled, if hemodynamic variability was present). Hofhuizen\textit{ et al.},\textsuperscript{191} found no influence of core temperature and vasoactive drugs on bias; it should be noted that core temperature was not below 35.4°C and norepinephrine dosage did not exceed 0.1 µg/kg per minute.\textsuperscript{191} Ameloot\textit{ et al.}\textsuperscript{200} divided noninvasive CO versus transpulmonary TD CO in groups with low and high systemic vascular resistance and found larger percent errors for high resistance states. This indicates that the noninvasive method may have more difficulty in measuring in such circumstances. However it should be noted that percent error is inversely proportional to CO, implying that percent error is proportional to systemic vascular resistance.\textsuperscript{200}

\textit{Operator errors in performing finger cuff technology measurements}

Some sources of error in continuous noninvasive hemodynamic monitoring using finger cuff technology are attributable to the operator or related to incorrect set up of the measurements. The heart reference system (HRS) corrects finger cuff derived BP levels for the vertical distance between finger and heart. Correct placement of the heart reference sensor is challenged by moving the patient in a different plane, e.g. from supine to a lateral or to (anti-)Trendelenburg. In an offline analysis on the data of one of the patients in the current study (male of 62 years old, 170 cm tall and weighing 95 kg, well representing the “average patient”), the HRS correction value was changed and the effect on CO was calculated.\textsuperscript{9} The correct CO was 5.0 litres min\textsuperscript{-1}, with the HRS value changed from -15 to +15 mm Hg, CO changed from 5.6 to 4.4 litres min\textsuperscript{-1} (Figure 3.51).

Also errors may ensue from the way the finger cuffs are applied. Depending on the tightness and skewness of the application and on how well the cuff is centred between the knuckles of the phalanx, the measured BP can vary and therefore the resulting CO may also show variation. In an internal study in 17 subjects, a cuff was re-applied ten times and the measured CO values were compared to simultaneously determined CO values from a cuff on an adjacent finger left in place during the experiment. Variation in CO, expressed as the SD of differences of each subject was 0.19 ± 0.17 litres min\textsuperscript{-1} ranging from 0.06 – 0.78 litres min\textsuperscript{-1}. 
Incorrect parameter assumptions for the hemodynamic models

The measured finger arterial pressure is reconstructed to brachial artery pressure used as input to the CO-trek algorithm. This reconstruction involves waveform filtering and level correction. Both elements were established on large databases of simultaneous invasive and noninvasive blood pressure measurements. Although it was shown to be difficult to improve on the generalized approaches by individualization, improvement was shown to be possible during physiological stress, as was reported by Stok et al. for exercising patients. In extreme situations such as sepsis the generalized models may be no longer valid.

The Windkessel model used to calculate CO from pressure is personalized by a limited set of patient data (gender, age, height and weight). These data are used in the algorithm to approximate the patient’s aortic properties, including aortic cross-sectional area, the aortic pressure-area relation and the effective length, which in turn determine Windkessel compliance and characteristic impedance. Obviously, aortic properties in a certain patient may differ from population-based predictions and particularly the aortic cross-sectional area is variable. An incorrect assumption for the cross-sectional area will give rise to a multiplicative error, comparable to using a wrong outflow tract cross-sectional area when calculating flow from an echo-Doppler derived velocity profile. This explains why bias in PC CO methods is best eliminated by a multiplication factor.

We assessed the effect of using wrong patient data on CO by modifying the characteristics in an example patient of the current study (same patient as in the HRS analysis in the “Operator errors” section: male of 62 years, 170 cm and 95 kg). The original CO was 5.0 litres min⁻¹; when the gender was changed from “male” to “female”, CO became 4.7 litres min⁻¹. The results for changes in the other patient data are summarized in Figure 3.51 B-D. Aging causes major changes in the aortic pressure-area relationship and the largest errors arise from incorrect patient age. Mutatis mutandis, the errors occurring in CO when a patient’s vascular system differs from the model assumptions may be inferred from this analysis.

**Figure 3.51** The effect of incorrect values of the Heart Reference System (HRS) and the effect of incorrect model assumptions on cardiac output (CO). Correct CO (indicated by dots) was 5.0 litres min⁻¹ for this patient (male of 62 years, 170 cm and 95 kg). The HRS value was changed (in steps of 5 mm Hg) from −15 to +15 mm Hg which corresponds with a height difference −20.4 to +20.4 cm (A). Age (steps of 5 years, B), height (steps of 5 cm, C) and weight (steps of 5 kg, D) were also varied and resulting model based CO was calculated.
Summary

Instrument limitations include variable physiological conditions as indicated by short intervals between Physiocals, the automatic calibrations of the noninvasive pressure measurements. The arterial volume under the cuff must remain clamped at the diameter where the arterial wall is unloaded and this diameter is subject to physiological influences. In the present study, data with the interval between Physiocals less than 30 beats accounted for part of the variance in the invasive-noninvasive pressure based CO comparison with TD CO. One patient was excluded due to inadequate finger perfusion.

Operator errors in finger cuff application are relatively small and controllable by making sure that the basic requirements concerning cuff positioning are met. Incorrect placement of the HRS of 20 cm resulted in an error of approximately 0.5 litres min⁻¹. It is therefore worthwhile to maintain correct positioning of the HRS.

The reconstruction of brachial arterial pressure from finger arterial pressure employs a generalized model, which is sufficient except in extreme states like circulatory shock. The Windkessel parameters in the CO model are optimised with patient characteristics; incorrect age gives the largest error. Wrong patient data contribute to bias but not to within-subject variability.

Considerations on comparison of cardiac output methods

When evaluating a particular monitoring system it is important to keep in mind for which purpose it will be used: invasive versus noninvasive, continuous versus intermittent, absolute values versus tracking. Assessment of absolute values and tracking is the main subject of discussion here, together with some remarks about timing are made and issues specifically related to simultaneous NAP CO and IAP CO.

Comparison of absolute values

In comparison studies usually accuracy (also called bias) and precision values are calculated; currently the focus is mainly on precision, while cut off values for bias are hardly a point of interest. For more background on this subject we refer to an excellent review by Cecconi et al.

Critchley and Critchley proposed to express precision as percent error, and further suggested a maximal percent error of 30% of the tested method against pulmonary artery TD CO to be acceptable. This criterion was generated by a Pythagorean approach with the accuracy of both, the tested method and the TD reference method, set at ±20%, based on an evaluation of the latter method during stable hemodynamics. In most patients with a clinical indication for CO monitoring, including those in the present study, absence of hemodynamic variability is unlikely. In patients undergoing coronary artery bypass surgery, a comparison of TD CO vs. ultrasonic transit time flow probe derived CO positioned on the ascending aorta resulted in percent errors of 42% and 46% pre- and post-cardiopulmonary bypass, respectively. In a porcine model with pharmacologically induced hemodynamic instability, TD had an overall percent error of 49% against transit time flow.
authors also evaluated several less invasive methods for CO monitoring and did not identify TD as superior to these methods. A study comparing pulse contour CO and transthoracic Doppler echocardiography showed an improvement from 49.3% to 29.5% error when patients with irregular heart rhythm or aortic stenosis were excluded. These findings indicate that hemodynamic variability has a major impact on method-comparisons. In a meta-analysis of accuracy and precision of pulse contour, oesophageal Doppler, partial CO$_2$ rebreathing and transthoracic bioimpedance methods, percent errors were all above 40%. In the current study, no percent errors higher than 40% were found.

It is often forgotten the example by Critchley and Critchley, leading to the 30% percent error limit, was based on an average CO of 5 litres min$^{-1}$. Obviously, when CO values are higher, the percent error will become lower for a similar spread in the data. It could be argued that a wider spread is acceptable for higher CO values, while a better precision is required for low CO values. Such different precisions could be captured by using an error grid that widens for higher values, like the Clark error grid for comparing glucose measurement methods. Importantly Cecconi et al. recommend quantifying the inherent error in the reference technique instead of assuming a 20% inherent error. Often the standard method in use in a certain clinical setting is conveniently considered the gold standard, with limited or at least acceptable errors of its own. The methodology proposed Cecconi et al. uses variability in the reference measurements to quantify the precision. A caveat is that this approach tacitly assumes CO remains constant during the measurements with any variation in the values attributable to measurement technique errors. This may not be the case, as the current study illustrates. Nonetheless, the description of the measurements in comparison studies should at least detail how hemodynamic variability was assessed and addressed, outliers were handled, with specific attention to injectate volume and temperature, number of shots, checking of the TD curve.

**Comparison of tracking**

Tracking or trending quantifies the ability of a method to follow changes, with disregard of the absolute value. In the current study, the absolute value of the test method (AP CO) was set equal to the reference method (TD CO). Both test and reference method should then be set at this average level to assess tracking. Another way to assess the agreement of two methods in following changes is concordance analysis. With this method, the information is reduced to direction while magnitude is disregarded. To solve this shortcoming, the polar plot was introduced, however, the analysis as performed in the present study allows a direct comparison of tracking vs. absolute values. Additionally, polar plots may exclude opposite responses of methods from analysis. Recently, clinical concordance method was introduced which assesses trending with an error grid. Tracking- and concordance analysis further differ in that the former uses calibration with a multiplication factor while the latter uses subtraction of the averaged value. With pulse contour CO methods, bias is best described by a multiplication factor (see section “Factors affecting noninvasive pulse contour cardiac output measurement”). The within-subject precision analysis further illustrates that the percent error of an individual patient is smaller than the group error by a factor 2 to 3. Thus, the individual biases result in relatively large precision error of the group, while the random errors around the biases of the subject-averaged data remain small. This can also be ascertained from the plots with averaged CO values, where individual vertical error bars are
smaller than the 95% confidence intervals. Interestingly, since the tracking seems to be less sensitive, it appears that variability may introduce a bias in individuals, which is removed in the tracking analysis.

**Effect of timing**

The effect of timing is also important when evaluating two methods. Ideally comparisons should be made simultaneously; slow and fast variations may be present, and CO methods may have different response times, affecting the spread in the comparison. For instance, when data is obtained from different phases in the ventilatory cycle, stroke volumes can be 20% different, and (assuming that HR remains similar) also the CO can be 20% different. Thus, if values are simply (sequentially) read from two monitors, a large spread can be introduced in the comparison in a matter of seconds. Since hemodynamic monitors usually average their values over some period, these errors are mitigated to a certain extent, although the averaging periods may be different. When assessing tracking, although changes may be slower, also correct timing is important.

**Comparing simultaneous IAP and NAP CO**

When comparing two continuous pulse contour methods with beat-to-beat information available for both timing is no longer an issue. A question specific to the comparison of simultaneous NAP CO and IAP CO is whether measurements should be obtained from the same or from opposite arms. With ipsilateral measurements, the catheter in the radial artery will partly block the vessel and this may introduce a pressure drop. The pressure in the finger will be affected depending on the amount of obstruction and the supply by the ulnar artery. Additionally, the catheter may introduce a site for pressure wave reflection, increasing the pulse pressure. On the other hand, contralateral measurements have the drawback of introducing an unknown left-to-right difference. We prefer to use ipsilateral measurements, and also according to Dr Imminck (Academic Medical Center, Amsterdam, the Netherlands) an ipsilateral NAP versus IAP comparison has less spread than a contralateral comparison (unpublished data).

Some simple calculations can give insight in the effect of both under- and over dampened measurements and the effect of frequency independent (resistive) changes. A pressure recording of a male of 62 years, 170 cm and 95 kg with a CO was 5.0 litres min$^{-1}$ was reanalysed (the same patient as in section “Factors affecting noninvasive pulse contour cardiac output measurement”). To simulate under- or over dampened measurements, pulse pressure (“oscillatory pressure”) was increased respectively decreased while mean arterial (“steady”) pressure was kept constant. For the assessment of resistive changes, pulse pressure and mean arterial pressure where changed concordantly. The analysis showed CO changed almost linearly with oscillatory pressure when steady pressure remained the same Figure 3.52). A dampening of a factor 0.5 resulted in a CO of 3.3 litres min$^{-1}$; with an under-dampening of 1.5 CO became 6.4 litres min$^{-1}$. When both oscillatory pressure and steady pressure were decreased simultaneously (resistive dampening) CO decreased in a highly nonlinear fashion; factor 0.5 resulted in a CO of 3.8 litres min$^{-1}$, factor 0.3 resulted in a CO of 2.6 litres min$^{-1}$. Increasing both oscillatory pressure and constant pressure gave a somewhat lower CO; please note that it is physically impossible for the steady pressure to increase in
the arteries or in a catheter-manometer system. The result of hydrostatic errors (affecting only steady pressure) can be inferred from the analysis on the HRS (see section “Factors affecting noninvasive pulse contour cardiac output measurement”).

**Summary**

Bias, the average error over a group, is not a major concern nowadays. More focus is placed on precision, which can be seen a measure of performance in an individual. Critchley and Critchley proposed that the precision expressed as a percent error should be below 30%. This is achievable only in well controlled studies. However, precision does not give information on tracking for which several analysis methods are available.

Correct timing of CO samples in a comparison is important since e.g. ventilation induced changes can be substantial. Some particular attention is needed when using both NAP as well IAP measurements as basis for CO calculation. The catheter may affect the pressure transfer to the finger in ipsilateral measurements; contralateral measurements may be influenced by left-to-right differences.

Validation studies are not simple to perform: errors which will affect the comparison are easily introduced and differences are then usually attributed to the device under test. It should be remembered that there is no “gold standard” method for clinical CO measurement.

**After pump period analyses**

In the combined before and after pump data (tables 3.S2, 3.S3 and figure 3.S3), biases were not different between classes and not different from before pump; variance was larger than before pump but not different between classes. Within-group comparisons of NAP CO and IAP CO revealed different biases but variance was equal in each case. Variances for tracking were smaller than the variances of the absolute values. The within-subject variance (table 3.S2) increased compared to the before pump period.

NAP and IAP show similar percent errors after pump; consequently, in clinical practice, NAP CO measurements after extracorporeal circulation would seem acceptable. This has to be investigated in more detail in future studies.
<table>
<thead>
<tr>
<th>Grade</th>
<th>(N = 18, n = 47)</th>
<th>TD CO [l. min(^{-1})]</th>
<th>AP CO [l. min(^{-1})]</th>
<th>AP CO – TD CO [l. min(^{-1})]</th>
<th>Percent error [%]</th>
<th>Concord. [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute</td>
<td>4.96 ± 1.47 (2.48, 8.84)</td>
<td>NAP CO</td>
<td>5.33 ± 1.45 (2.68, 9.26)</td>
<td>0.37 ± 0.87 (–1.04, 2.39)</td>
<td>33</td>
<td>92</td>
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<tr>
<td>IAP CO</td>
<td>4.79 ± 1.41 (2.50, 9.33)</td>
<td>–0.17 ± 0.81 (–1.52, 1.52)</td>
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<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tracking</td>
<td>NAP CO</td>
<td>4.96 ± 1.43 (2.48, 8.87)</td>
<td>(0) ± 0.41 (–1.29, 0.75)</td>
<td>16</td>
<td></td>
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<tr>
<td>IAP CO</td>
<td>4.96 ± 1.48 (2.48, 9.78)</td>
<td>(0) ± 0.46 (–1.03, 1.70)</td>
<td>18</td>
<td></td>
<td></td>
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</tbody>
</table>

- **Grade B (N = 23, n = 93)**
- **Grade C (N = 25, n = 70)**
- **Grade D (N = 27, n = 157)**

Cardiac output (CO) values for thermodilution (TD CO) arterial pressure (AP) based pulse contour CO, from noninvasive (NAP CO) and invasive (IAP CO) AP and their differences: AP CO – TD CO, expressed as average ± SD (minimum, maximum). N = number of patients, n = number of data points. Grade A data: data pairs not included in case of >5% variability in heart rate, >5% variability in mean arterial pressure, arrhythmia or a Physiocal interval <30 beats during the TD CO. Effect of variability, grade B data: data pairs with variability in heart rate / mean arterial pressure >5% or arrhythmia included; grade C data: data pairs with Physiocal interval <30 beats included; grade D, all data. For percent error and concordance (Concord.) see Methods.
Table 3.S3 Within-subject cardiac output variability and precision (before and after pump)

<table>
<thead>
<tr>
<th></th>
<th>Within-subject variability [l. min⁻¹]</th>
<th>Within-subject precision [l. min⁻¹]</th>
<th>Within-subject percent error [%]</th>
<th>Group (subject-averaged) percent error [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade A (N = 18, n = 47)</td>
<td></td>
<td></td>
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<tr>
<td>TD CO &amp; NAP CO</td>
<td>0.71 ± 0.51</td>
<td>0.43 ± 0.23</td>
<td>17</td>
<td>27</td>
</tr>
<tr>
<td>TD CO &amp; IAP CO</td>
<td>0.71 ± 0.52</td>
<td>0.44 ± 0.25</td>
<td>18</td>
<td>28</td>
</tr>
<tr>
<td>Grade B (N = 23, n = 93)</td>
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<td></td>
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<tr>
<td>TD CO &amp; NAP CO</td>
<td>0.80 ± 0.43</td>
<td>0.38 ± 0.19</td>
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<td>33</td>
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<td>TD CO &amp; IAP CO</td>
<td>0.78 ± 0.42</td>
<td>0.38 ± 0.24</td>
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<tr>
<td>Grade C (N = 25, n = 70)</td>
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<td></td>
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<tr>
<td>TD CO &amp; NAP CO</td>
<td>0.87 ± 0.76</td>
<td>0.38 ± 0.21</td>
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<tr>
<td>TD CO &amp; IAP CO</td>
<td>0.84 ± 0.75</td>
<td>0.38 ± 0.23</td>
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<td>32</td>
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<tr>
<td>Grade D (N = 27, n = 157)</td>
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<td></td>
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<tr>
<td>TD CO &amp; NAP CO</td>
<td>0.84 ± 0.53</td>
<td>0.45 ± 0.18</td>
<td>18</td>
<td>37</td>
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<td>TD CO &amp; IAP CO</td>
<td>0.82 ± 0.52</td>
<td>0.40 ± 0.20</td>
<td>17</td>
<td>38</td>
</tr>
</tbody>
</table>

Within-subject variability describes the range of CO in an individual; the within-subject precision is a measure of precision in an individual. The within-subject percent error is calculated from the within-subject precision. Group (subject-averaged) percent error assesses the precision of the comparison over the group, after averaging the individual values for each subject. Grade A data: data pairs not included in case of >5% variability in heart rate, >5% variability in mean arterial pressure, arrhythmia or a Physiological interval <30 beats during the TD CO. Effect of variability, grade B data: data pairs with variability in heart rate, mean arterial pressure >5% or arrhythmia included; grade C data: data pairs with Physiological interval <30 beats included; grade D, all data. For the calculations see Methods.
Figure 3. Cardiac output (CO) comparisons of thermodilution (TD CO) and invasive (red) and non-invasive (green) arterial pressure based CO (AP CO) of periods both before and after pump. Grade A data (A1-A6): data pairs not included in case of >5% variability in heart rate, >5% variability in mean arterial pressure, arrhythmia or a Physiocal interval <30 beats during TD CO. Effect of variability: grade B data including of data pairs with variability in heart rate / mean arterial pressure >5% or arrhythmia (B1-B6); grade C data including data pairs with Physiocal interval <30 beats (C1-C6); grade D, all data (D1-D6). Scatter plot for absolute values (A1-D1), scatter plots for tracking (A2-D2; data only shown when more than one comparison was available) and the concordance plots (A3-D3) with an exclusion zone of ± 0.5 l·min⁻¹. Bland-Altman plots of the absolute values (A4-D4), for tracking (A5-D5) and of the subject-averaged values (A6-D6), with error bars indicating within-subject variability (horizontal) and within-subject precision (vertical). Dashed lines: 95% confidence intervals.
SECTION III

BLOOD VOLUME AND ITS DISPLACEMENT DURING ORTHOSTATIC STRESS