M. Biais1,2,3,*, R. Berthezène4, L. Petit4, V. Cottenceau4 and F. Sztark2,3,4

1Department of Anaesthesiology and Critical Care III, Bordeaux University Hospital, F-33000 Bordeaux, France, 2INSERM, Adaptation Cardiovasculaire à L’ischémie, U1034, F-33600 Pessac, France, 3Univ. Bordeaux, Adaptation Cardiovasculaire à L’ischémie, U1034, F-33600 Pessac, France, and 4Department of Anaesthesiology and Critical Care I, Bordeaux University Hospital, F-33000 Bordeaux, France

*Corresponding author. E-mail: matthieu.biais@chu-bordeaux.fr

Abstract

Background: We investigated whether cardiac output measured with pulse wave transit time (esCCO, Nihon Kohden, Tokyo, Japan) is able to track changes in cardiac output induced by an increase in preload (volume expansion/passive leg-raising) or by changes in vasomotor tone (variation in norepinephrine dosage) in critically ill patients.

Methods: Eighty patients for whom the decision to give fluid (500 mL of saline over 15 min) (n=20), to perform passive leg-raising (n=20), and to increase (n=20) or to decrease (n=20) norepinephrine were included by the physician. Cardiac output was measured with pulse wave transit time (CO-esCCO) and transthoracic echocardiography (CO-TTE) before and after therapeutic intervention.

Results: Comparison between CO-TTE and CO-esCCO showed a bias of −0.7 l min⁻¹ and limits of agreement of −4.4 to 2.9 l min⁻¹, before therapeutic intervention and a bias of −0.5 l min⁻¹ and limits of agreement of −4.2 to 3.2 l min⁻¹ after therapeutic intervention. Bias was correlated with systemic vascular resistance (r²=0.60, P<0.0001). Percentage error was 61% before and 59% after therapeutic intervention. Considering the overall data (n=80), the concordance rate was 84%, polar plot analysis revealed an angular bias (sd) of −11°(35°) and radial limits of agreement of (50°). With regard to passive leg-raising and volume expansion groups (n=40), the concordance rate was 83%, the angular bias (sd) was −20°(36°) and radial limits of agreement (50°). Considering variations in norepinephrine dosage groups (n=40), the concordance rate was 86%, the angular bias (sd) was −1.8° (33°) and radial limits of agreement (40°).

Conclusions: esCCO was not able to track changes in cardiac output, induced by an increase in preload or by variations in vasomotor tone. Therefore, esCCO cannot guide haemodynamic interventions in critically ill patients.

Key words: cardiac output; echocardiography; hemodynamics; monitoring

Cardiac output monitoring is necessary in many patients in the intensive care unit and operating room. For many years, cardiac output was usually calculated using pulmonary arterial thermodilution. However, the pulmonary artery thermodilution technique is not now used routinely because it is time-consuming and has potentially harmful complications.1–3 Currently, cardiac output and stroke volume can be assessed by using less invasive methods. The esCCO measurements system (Nihon Kohden®, Tokyo, Japan) is a totally non-invasive system, requiring no additional connection other than the ECG and the plethysmographic wave.4 This technology is based on the relationship between pulse wave transit time (PWTT) and stroke volume. PWTT is the

† Bordeaux University Hospital, Department of Anaesthesiology and Critical Care, F-33000 Bordeaux, France.

Accepted: March 30, 2015

© The Author 2015. Published by Oxford University Press on behalf of the British Journal of Anaesthesia. All rights reserved.

For Permissions, please email: journals.permissions@oup.com
sum of the pre-ejection period and pulse wave arrival time from the ascending aorta to the peripheral pulse oximetry (SpO₂) probe site. PWTT is calculated from the interval R wave of ECG and peripheral (SpO₂) pulse wave arrival when ECG and (SpO₂) are simultaneously recorded. Early studies evaluating this technology showed it had good accuracy but that the device required thermodilution calibration, thereby limiting its clinical applications for routine circulatory monitoring. Since then, the software has been updated and calibration has been replaced by adjustment to morphometric parameters. Unfortunately, validation studies failed to show any significant correlation compared with thermodilution or echocardiography. Although absolute cardiac output values are of importance, changes in cardiac output induced by therapeutic intervention are probably at least as important. Indeed, changes in arterial pressure are not able to identify variations in cardiac output after a volume expansion or changes in vasopressor.

Therefore, the aim of the present study was to evaluate the ability of esCCO to track changes in cardiac output induced by an increase in preload (volume expansion or passive leg-raising) and variations in vasomotor tone (increase or decrease in noradrenaline infusion rates) in critically ill patients.

Methods

Patients

This single-centre study was approved by the local ethics committee (Comité de Protection des Personnes Sud-Ouest et Outre Mer III, Bordeaux, France N°DC2011/46). Eighty ICU patients were included (after informed consent from next of kin) if passive leg-raising (n=20), volume expansion (n=20), and an increase (n=20) or decrease (n=20) in the norepinephrine dose was planned by the physician. Patients younger than 18 yr old, with arrhythmia, severe aortic stenosis and unsatisfactory cardiac echocardiographic characteristics were not included.

Measured variables

Measurements were performed before and after therapeutic intervention: these were cardiac output (obtained using esCCO and TTE), heart rate, mean arterial pressure, tidal volume, plateau pressure, respiratory rate and norepinephrine dosage.

esCCO measurements

ECG, pulse oximetry wave, non-invasive arterial blood pressure and pulse wave transit time were obtained with a BSM-6000 bedside monitor (Nihon Kohden, Tokyo, Japan). The algorithm calculating CO-esCCO continuously has been previously described. Briefly, CO-esCCO is calculated according to the following equation:

\[
CO - \text{esCCO} = k \times (\alpha \times \text{PWTT} + \beta) \times HR
\]

where \(\alpha\) is a value obtained experimentally from previous studies. \(k\) and \(\beta\) are calculated by using patients’ data (age, sex, height and weight) and data obtained by calibration (PWTT, heart rate and arterial pressure).

Transthoracic echocardiography measurements

All TTE measurements were performed with a Vivid SS™ (GE Healthcare; Wauwatosa, WI, USA). SV=stroke volume; VTIAo=area under the envelope of the pulsed-wave Doppler; AoVA=aortic valve area; LVEF=Left ventricular ejection fraction; SVR=systemic vascular resistance.

\(\text{CO-TTE=SV} \times \text{heart rate}\)

\(\text{Stroke volume was calculated as follow: SV=VTIAo×AoVA.}\)

\(\text{AoVA=}\text{diameter}^2/4\) (the diameter of the aortic cusp was measured using parasternal long axis view in systolic time).

VTIAo was measured at the level of the aortic annulus (apical five-chamber view) and was averaged over five consecutive measurements.

\(\text{LVEF=}\text{Simpson’s biplane method was used to calculate LVEF.}\)

\(\text{SVR=}\text{(mean arterial pressure}×80)/\text{CO-TTE.}\)

Echocardiography were performed by two operators (RB and LP) who were unaware of CO-esCCO measurements (esCCO monitor was wrapped and was not visible) and clinical context. Another operator recorded data from esCCO monitor.

Inter and Intra-observer reproducibility of VTIAo measurements was tested before the beginning of the study. VTIAo were measured twice in 10 patients by the same observer (intra-observer reproducibility; RB) and a second observer (inter-observer reproducibility; LP). The mean difference was calculated and divided by the mean of the two values.

Study design

The first measurement was obtained immediately before the therapeutic intervention. The second measurement was obtained according to the assigned group:

- Fluid challenge group: volume expansion was performed with 500 ml saline 0.9% over 15 min. Second measurements were performed 5 min later.
- Passive leg-raising group: a passive leg-raising test using the semi-recumbent method was performed and second measurements were taken when CO-TTE reached its highest value.
- Norepinephrine dosage changes: the second measurement was obtained 5 min after stabilization of mean arterial pressure (attested by changes less than 10%)

Statistical analysis

Results were expressed as median [25–75% interquartile range] or mean (±SD) as appropriate. Data recorded during the first and second set of measurement were compared using the Wilcoxon test. CO-TTE and CO-esCCO obtained at baseline and after therapeutic intervention were compared with the Bland and Altman method and their relationship was tested with the Spearman Rank test. Percentage error (2SD of the bias/mean CO-TTE) was
calculated. Two cardiac output measurements are considered as interchangeable if percentage error is less than 30%. Variation in cardiac output (ΔCO) obtained by esCCO and TTE was compared using Bland and Altman method and four-quadrant plot. Concordance rate was calculated for overall data and for ΔCO-TTE≥10%. A concordance rate >90–95% is expected. Polar plot was used as previously described. Critchley and colleagues proposed that a cardiac output monitor is able to track changes in cardiac output when the angular bias is less than <5° and radial limits of agreement <30°. P<0.05 was considered as significant. Statistical analysis was performed by using NCSS 8 software 8.0.13 (NCSS, LLC, Kaysville, Utah, USA).

Results
Patient’s characteristics are shown in Table 1. Four patients were not included because of unsatisfactory cardiac echogenicity and CO-esCCO was obtained for all patients. Haemodynamic variables before and after therapeutic intervention are shown in Table 2. The mean [sd] interval between first and second set of measurements was 23 [2] min (fluid challenge group), 25[6] min (increase in norepinephrine dosage), 24 [6] min (decrease in norepinephrine dosage) and 75[10] sec (passive leg-raising group) after therapeutic intervention.

Comparison between CO-TTE and CO-esCCO
Before intervention, mean [sd] CO-esCCO (6.5 [1.2] l min<sup>−1</sup>) was higher than mean CO-TTE (5.7 [1.9] l min<sup>−1</sup>), (P<0.001). After therapeutic intervention, mean CO-esCCO (6.6 [1.2] l min<sup>−1</sup>) was higher than mean CO-TTE (6.1 [1.9] l min<sup>−1</sup>), (P<0.05). Comparison between CO-TTE and CO-esCCO showed a bias of –0.7 l min<sup>−1</sup> and limit of agreement of –4.4 to 2.9 l min<sup>−1</sup> before therapeutic intervention and a bias of –0.5 l min<sup>−1</sup> and limit of agreement of –4.2 to 3.2 l min<sup>−1</sup> after it (Fig. 1). Percentage error was 61% before and 59% after therapeutic intervention.

Ability of CO-esCCO to track changes in CO-TTE
Overall data
DCO-esCCO and DCO-TTE were poorly correlated (r²=0.23; P<0.0001). The bias between DCO-TTE and DCO-esCCO was 0.23 l min<sup>−1</sup> and limits of agreements were –1.06 l min<sup>−1</sup> to 1.52 l min<sup>−1</sup>. The concordance rate between ΔCO-TTE and ΔCO-esCCO (80 data sets) was 74%. 51% of the data points lie within the (30°), with an angular bias (sd) of –11° (35°) and radial limits of agreement of (50°). When excluding data with ΔCO less than 10%, the concordance rate was 84%. When excluding data with ΔCO less than 0.5 l min<sup>−1</sup>, 70% of the data points lie within the (30°), with an angular bias (sd) of –11° (24°) and radial limits of agreement of (50°).

Passive leg-raising and volume expansion
The bias between ΔCO-TTE and ΔCO-esCCO was 0.23 l min<sup>−1</sup> and limits of agreements were –1.06 l min<sup>−1</sup> to 1.52 l min<sup>−1</sup>. The direction of change in cardiac output of the 40 data sets agreed in 28 pairs with a concordance rate of 70% (Fig. 2). 35% of the data

Table 1 Main characteristics of patients at baseline. Values are mean [sd], number (n) or median [interquartile range 25–75%] as appropriate. SAPS II: Simplified Acute Physiologic Score. P<0.05 (After us Before intervention). PLR, Passive Leg-Raising; NE+, increase norepinephrine dosage; NE−, decrease norepinephrine dosage; HR, Heart Rate; MAP, Mean Arterial Pressure; CO-TTE, Cardiac Output obtained using Transthoracic Echocardiography; CO-esCCO, Cardiac Output obtained using esCCO; SVR, Systemic Vascular Resistance

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49 (18–82)</td>
</tr>
<tr>
<td>Sex, M/F (n)</td>
<td>54/26</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170 (10)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>77 (15)</td>
</tr>
<tr>
<td>SAPS II</td>
<td>42 (14)</td>
</tr>
<tr>
<td>Tidal volume (ml kg&lt;sup&gt;−1&lt;/sup&gt; of predicted body weight)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Respiratory rate (breath min&lt;sup&gt;−1&lt;/sup&gt;)</td>
<td>18 (4)</td>
</tr>
<tr>
<td>P&lt;sub&gt;Ao&lt;/sub&gt;/P&lt;sub&gt;O&lt;sub&gt;2&lt;/sub&gt;&lt;/sub&gt;, ratio of the arterial oxygen tension over the inspired oxygen fraction</td>
<td>342 (139)</td>
</tr>
<tr>
<td>Aetiology of ICU admission</td>
<td>Polytrauma (n) 62</td>
</tr>
<tr>
<td></td>
<td>Postoperative (n) 10</td>
</tr>
<tr>
<td></td>
<td>Septic Shock (n) 8</td>
</tr>
<tr>
<td>Vasopressors</td>
<td>Norepinephrine (n (%)) 26 (32)</td>
</tr>
<tr>
<td></td>
<td>Dosage of norepinephrine (µg kg&lt;sup&gt;−1&lt;/sup&gt; min&lt;sup&gt;−1&lt;/sup&gt;) 0.14 [0–0.35]</td>
</tr>
</tbody>
</table>

Table 2 Haemodynamic variables before and after therapeutic intervention in the 4 groups. Values are median [interquartile range 25–75%]. *P<0.05 (After us Before intervention). PLR, Passive Leg-Raising; NE+, increase norepinephrine dosage; NE−, decrease norepinephrine dosage; HR, Heart Rate; MAP, Mean Arterial Pressure; CO-TTE, Cardiac Output obtained using Transthoracic Echocardiography; CO-esCCO, Cardiac Output obtained using esCCO; SVR, Systemic Vascular Resistance

<table>
<thead>
<tr>
<th></th>
<th>Volume Expansion</th>
<th>PLR (n=20)</th>
<th>NE+ (n=20)</th>
<th>NE− (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>MAP</td>
<td>83</td>
<td>191</td>
<td>83</td>
<td>192</td>
</tr>
<tr>
<td>Dose of NE</td>
<td>[73–92]</td>
<td>0.00</td>
<td>[80–100]</td>
<td>0.00</td>
</tr>
<tr>
<td>CO-TTE</td>
<td>[0.00–0.21]</td>
<td>0.00</td>
<td>[0.00–0.21]</td>
<td>0.00</td>
</tr>
</tbody>
</table>
points lie within the (30°), with an angular bias (±) of −20° (36°) and radial limits of agreement of (50°). When excluding data with ΔCO less than 10%, the concordance rate was 83%. When excluding data with ΔCO less than 0.5 l min\(^{-1}\), 50% of the data points lay within the (30°), with an angular bias (±) of −19° (25°) and radial limits of agreement of (50°).
Fig 2 Variations in cardiac output (DeltaCO) induced by passive leg-raising (PLR). (a) Bland-Altman plots between changes in cardiac output (obtained using transthoracic echocardiography and esCCO). The continuous lines show the mean difference (bias) and the dotted lines show the 95% limits of agreement (±2SD). (b) Four-quadrant trend plots with central exclusion zone (10%) for assessing the ability of the esCCO to trend cardiac output data. (c) Polar plots used to show trending ability. The distance from the centre of the plot represents the mean change in cardiac output, the angle with the horizontal axis represents disagreement.
Fig 3 Variations in cardiac output (DeltaCO) induced by an increase (NE+) or a decrease (NE−) in norepinephrine dosage. (a) Bland-Altman plots between changes in cardiac output obtained using transthoracic echocardiography and esCCO. The continuous lines show the mean difference (bias) and the dotted lines show the 95% limits of agreement (two standard deviations). (b) Four-quadrant trend plots with central exclusion zone (10%) for assessing the ability of the esCCO to trend cardiac output data. (c) Polar plots used to show trending ability. The distance from the centre of the plot represents the mean change in cardiac output, the angle with the horizontal axis represents disagreement.
(33°) and radial limits of agreement of (50°). When excluding data with ΔCO less than 10%, the concordance rate was 86%. When excluding data with ΔCO less than 0.5 l min⁻¹, 95% of the data points lay within the (30°), with an angular bias (st) of −1.4° (19°) and radial limits of agreement of (40°).

**Factor impacting the accuracy of CO-esCCO**

There was a close relationship between bias (between CO-TTE and CO-esCCO) and SVR ($r^2=0.60$, $P<0.0001$) (Fig. 4). Bias between CO-TTE and CO-esCCO was not correlated with norepinephrine dosage, heart rate, mean arterial pressure, age or body mass index. Changes in systemic vascular was not correlated with bias between changes in esCCO and changes in CO-TTE.

**Inter- and intra-observer reproducibility**

For VTIAo measurements, the intra-observer reproducibility was 3.7% and the inter-observer reproducibility was 5.2%.

**Discussion**

The present study suggests that (i) cardiac output measured with esCCO is not interchangeable with cardiac output measured using transthoracic echocardiography, (ii) esCCO is not accurate for tracking variations in cardiac output induced by an increase in preload (volume expansion or passive leg-raising) or by variations in vasomotor tone (variation in norepinephrine dosage), and (iii) the bias between cardiac output measured with esCCO and with transthoracic echocardiography is highly affected by systemic vascular resistance.

Monitoring cardiac output in unstable critically ill patients is of major importance and is clearly recommended in patients with persisting shock, despite adequate fluid resuscitation. Continuous invasive arterial pressure monitoring is currently used in ICU patients. However, absolute values of arterial pressure (systolic, diastolic, pulse pressure) are not able to predict the effect of volume expansion, and changes in arterial pressure are poorly or not correlated with variations in cardiac output induced by fluid or changes in vasopressor dose. Therefore, cardiac output monitoring is essential in order to know the patient’s ventricle position on the Frank Starling curve or to identify the impact of variations in norepinephrine dosage.

Several cardiac output monitoring devices, from the very invasive to the totally non-invasive, have been available for several years. The esCCO technology is totally non-invasive, requiring no additional connection other than the ECG and the plethysmographic wave. Here, we found a percentage error of 61% and 59% when esCCO was compared with CO-TTE, exceeding the 30% limits proposed by Critchley and colleagues. Our results are comparable with previous published studies (percentage error between 51% and 80% in medical and surgical ICU). We also found a close relationship between bias and systemic vascular resistance. The esCCO technology is based on PWTT analysis and the negative relation between PWTT and stroke volume. esCCO is calculated with an equation including PWTT, variables derived from the patient’s data (such as sex, age, weight and height) and data obtained by calibration (PWTT, heart rate and arterial pressure). PWTT consists of a pre-ejection period, the pulse transit time through an elasticity artery, and the pulse transit time through peripheral resistance arteries, that are dependent on blood vessel resistance. We hypothesized that this would mainly explain the relationship between bias and systemic vascular resistance. The high percentage error between esCCO and CO-TTE may also be explained by the mathematical assumption used to determine α, β and k. Yamada and colleagues demonstrated that the accuracy of esCCO is not affected by time calibration. In our study, calibration was performed before the beginning of the protocol.

In our hands, esCCO was not accurate for tracking cardiac output variations induced by an increase in preload or by variation in norepinephrine dose. The angular bias was >5°, indicating that the calibration method of the esCCO is not adequate and that the radial limit of agreement was greater than (30°), indicating that its trending ability is poor. Interestingly, systemic vascular resistance significantly varied in the norepinephrine variation dosage group but not in the volume expansion or passive leg-raising group, suggesting that dramatic changes in systemic vascular resistance cannot explain our results. This was confirmed by the lack of correlation between changes in systemic vascular resistance and the bias between changes in esCCO and changes in CO-TTE. esCCO was not able to track rapid changes in cardiac output.

Our study has several limitations. First, we compared esCCO to cardiac output measured with transthoracic echocardiography, which was considered as the reference. Echocardiography has been validated as a reliable method for cardiac output measurements in clinical practice. Furthermore, only two operators performed the echocardiographic procedures and we verified the acceptability of their inter- and intra-observer variability (for VTIAO measurements) before the beginning of the study. As most of this study focused on cardiac output trends, we did not assess inter- and intra-observer variability for diameter of the aortic cusp and cardiac output measurements. As all methods evaluating cardiac output, transthoracic echocardiography may present some (few) errors. Consequently, discrepancy observed between esCCO and CO-TTE may not be only as a result of a measurement error of esCCO. However, we assume that this point does not impact the interpretation of the study results, because the observed discrepancies are huge. Second, we did not perform a priori sample size calculation. Third, the population of this study is not homogenous (trauma and postoperative patients). Fourth, changes in SpO2 probe site may occur during routine patient care and/or during passive leg-raising. We carefully ensured that all esCCO measurements were interpretable during
the study. Finally, we included 80 mechanically ventilated surgically critically ill patients. These findings cannot be extrapolated to other populations.

**Conclusion**

In our hands, cardiac output obtained with esCCO was not interchangeable with CO-TTE and could not track changes in cardiac output induced by changes in preload or vasomotor tone. Therefore, esCCO cannot guide haemodynamic interventions in critically ill patients.

**Authors’ contributions**

Study design/planning: M.B., F.S.
Study conduct: R.B., L.P., V.C.
Data analysis: M.B., R.B.
Writing paper: M.B.
Revising paper: All authors.

**Acknowledgements**

The authors thank Ray Cooke, Ph.D. (Assistant Professor and Director, Département Langues et Cultures, University of Bordeaux, Bordeaux, France) for reviewing this manuscript.

**Declaration of interest**

M.B received honoraria from Edwards Lifesciences and Pulsion Medical System as a lecturer.

**Funding**

Support was provided solely from institutional and/or departmental sources. Nihon Kohden, Tokyo, Japan kindly provided the esCCO device.

**References**

17. Le Manach Y, Hofer CK, Lehot JJ, et al. Can changes in arterial pressure be used to detect changes in cardiac output during volume expansion in the perioperative period? Anesthesiology 2012; 117: 1165–74

Handling editor: J. P. Thompson