Comparison of esCCO and transthoracic echocardiography for non-invasive measurement of cardiac output intensive care

B. Bataille1*, M. Bertuit1,2, M. Mora1, M. Mazerolles3, P. Cocquet1, B. Masson1, P. E. Mousset1, J. Ginot1, S. Silva3 and J. Larché1

1 Department of Intensive Care, Service de Réanimation Polyvalente, Centre Hospitalier de Narbonne, Bd Dr Lacroix, F-11100 Narbonne, France
2 Poˆle d’Anesthésie-Réanimation, Centre Hospitalier Universitaire, F-34090 Montpellier, France
3 Poˆle d’Anesthésie-Réanimation, Centre Hospitalier Universitaire, CHU Purpan, Place du Dr Baylac, F-31059 Toulouse Cedex 9, France
* Corresponding author. E-mail: b_bataille2@yahoo.fr

Editor’s key points
- This study compared a new non-invasive monitor of cardiac output (CO), the esCCO, with transthoracic echocardiography in critically ill patients.
- There was a reasonable correlation between CO values but wide limits of agreement between the devices.
- The percentage error was 49% and the concordance for trend values was 73%.
- Further data are required.

Background. The esCCO monitor (ECG–SpO2 estimated Continuous Cardiac Output, Nihon Kohden®) is a new non-invasive tool for estimating cardiac output (CO). It derives CO from the pulse wave transit time (PWTT) estimated by the ECG and the plethysmographic wave. An initial calibration is needed to refine the relation linking pulse pressure (measured by arterial pressure cuff) to PWTT. To assess the accuracy and reliability of the esCCO system, we performed an analysis of agreement of CO values obtained by transthoracic echocardiography (TTE).

Methods. Thirty-eight intensive care unit patients were prospectively included. CO was determined simultaneously using esCCO (COesCCO) and TTE (COTTE) as our reference method.

Results. A total of 103 paired readings from 38 patients were collected. The correlation coefficient between COesCCO and COTTE was 0.61 (P<0.001). The Bland and Altman analysis corrected for repeated measures showed a bias of −1.6 litre min⁻¹ and limits of agreement from −4.7 to +1.5 litre min⁻¹, with a percentage error (2 SD/mean CO) of 49%. The correlation for CO changes was significant (R=0.63, P<0.001), but the concordance rate was poor (73%). Polar plot analysis showed an angular bias of −9° with radial limits of agreement from −54° to +36°. The bias appeared to correlate with systemic vascular resistance (R=−0.45, P<0.001).

Conclusions. In critically ill patients, the performance of the esCCO monitor was not clinically acceptable, and this monitor cannot be recommended in this setting. Moreover, the esCCO failed to trend CO data reliably.

Keywords: cardiac output; Doppler echocardiography; heart; intensive care; physiological monitoring

Accepted for publication: 16 April 2012

Cardiac output (CO) is monitored routinely in critically ill patients in order to titrate therapy to maintain adequate tissue perfusion. Thermodilution measurement of CO using a pulmonary arterial catheter (PAC) is considered as a gold standard, but the value of the PAC has been questioned in recent years and its impact on outcome is controversial.1 2 To avoid the risks associated with PAC, alternative techniques3 have been developed for routine CO monitoring.4 These techniques include transthoracic bioimpedance, oesophageal Doppler, arterial pulse wave analysis (Vigileo®), transthoracic echocardiography (TTE), and more recently ECG–SpO2 estimated Continuous Cardiac Output system (esCCO).

The esCCO measurement system (Nihon Kohden®, Tokyo, Japan) is a truly non-invasive system. It estimates CO with an ECG and a percutaneous oxygen saturation waveform.5 The arterial compliance is evaluated with pulse wave transit time (PWTT), pulse pressure (PP) measured by arterial pressure cuffs, and patient characteristics (height, weight, age, and sex).

The validity of esCCO monitoring has not been evaluated for critically ill patients in intensive care. Therefore, we performed an observational blinded study to evaluate the agreement between CO measurement obtained using TTE (COTTE) and the esCCO system (COesCCO). Non-invasive CO measurement with TTE has been validated in other studies.6–10 McLean and colleagues9 achieved excellent correlation between TTE and PAC in patients with a broad range of diagnoses, including sepsis (R=0.93, P<0.0001). The bias was 0.2 litre min⁻¹ and limits of agreement of −1.5 to +1.9 litre min⁻¹. The TTE repeatability was good with an inter-observer coefficient of variation varying between 5%11.
and 7%.\textsuperscript{7} Bergenzaun and colleagues\textsuperscript{11} have showed that TTE was feasible for 95% of patients admitted to the intensive care unit (ICU). We choose to use TTE as our reference technique for CO measurement, because this was the technique used routinely in our centre for initial flow evaluation.\textsuperscript{12} TTE has the advantage of being non-invasive, painless, and immediately feasible in patients with spontaneous or mechanical ventilation. The primary aim of this study was to evaluate the agreement between CO\textsubscript{TTE} and CO\textsubscript{esCCO}. On the basis of the work of Critchley and Critchley,\textsuperscript{13} we prospectively decided that the new technique (esCCO) would be considered suitable to replace TTE for CO estimation if limits of agreement represented <30% of the mean CO value. A secondary aim was to evaluate the ability of esCCO measurements to detect CO change, and a concordance rate of 80% was considered the upper limit of acceptance for reliable trending.\textsuperscript{14}

**Methods**

This single-centre observational study was conducted in the ICU of Narbonne Hospital, France. After institutional approval, 38 patients admitted to ICU were included. No additional invasive procedure or blood samples were necessary for this study; therefore, the need for informed consent was waived.\textsuperscript{15} Patients from all diagnostic categories were included. Patients were excluded if they were <18 yr old, or if they had severe aortic stenosis.

**Measured variables**

Patient characteristics (age, sex, height, and weight), SAPS2, use of vasoactive agents, and haemodynamic data, that is, heart rate (HR), systemic pressure (systolic, diastolic, and mean), and PWTT, were collected. In addition, we measured CO using both esCCO and TTE. A calibration of esCCO system, with standard monitoring, was made before each measurement. The investigators were blinded to the results of each other. This process was repeated each time a patient required a CO reading during a period when an investigator was available. Consequently, a variable number of CO readings were obtained per patient.

**esCCO measurements**

Initial standard monitoring at the admission included continuous ECG, non-invasive arterial pressure, pulse oximetry, and CO measurement using esCCO monitor (CO\textsubscript{esCCO}). The algorithm calculates esCCO stroke volume (SV) continuously with the negative correlation between SV and PWTT.\textsuperscript{5} PWTT is the measure of the interval between the ECG R wave and the pulse plethysmograph upstroke.\textsuperscript{16} Both the ECG and the plethysmograph wave were obtained from standard monitoring equipment. SV can be expressed according to the equation:

\[ CO = HR \times SV \]

\[ SV = K \times PP \]

where the constant K quantifies arterial compliance and vascular resistance. PP, corresponding to PWTT, is expressed by the equation:

\[ PP = \alpha \times PWTT + \beta \]

\( \alpha \) is a value obtained experimentally from previous studies.\textsuperscript{5} \( \beta \) is determined by the following equation:

\[ \beta = \frac{(SV - K \times \alpha \times PWTT)}{K} \]

Multivariate analysis based on age, sex, height, weight, and arterial pressure and also the patient’s HR and PWTT at the initial point of calibration is performed to obtain the CO value used.

**TTE measurements**

The TTE measurements were taken by an investigator blinded to the measurements determined by esCCO. All TTE measurements were performed using a ‘Sonosite® MicroMaxx’ with a probe of 2–4 MHz. The Doppler estimated CO (CO\textsubscript{TTE}) was derived from the Doppler estimated SV using the velocity–time integral (VTI) of flow through the left ventricular outflow tract (LVOT), the diameter of the LVOT, and HR recorded during the imaging study, using the following formula:

\[ CO_{TTE} = \left( VTILVOT \times \text{diameter of LVOT}^2 \times \frac{\pi}{4} \right) \times HR \]

Aortic VTI was recorded by pulsed-wave Doppler from an apical long-axis view by placing a 5 mm Doppler sample volume in the LVOT at the level of the aortic valve. The VTI value was average over five consecutive measurements. The diameter for LVOT is measured at the aortic annulus from the inner edge to inner edge in a parasternal long-axis view. As the estimate of central venous pressure by the central venous catheter was not always available, a semi-quantitative approach was used by the assessment of the inferior vena cava (IVC) diameter and respiratory response: 5 mm Hg if IVP was not dilated and with a caval index of >50%, 10 mm Hg if the IVC was dilated, but with an index of >50%, and 15 mm Hg if the IVC was dilated and with an index of <50% (<12% during mechanical ventilation).\textsuperscript{17, 18}

Systemic vascular resistance (SVR) was estimated using the equation:

\[ SVR \, (\text{dyn s cm}^{-5}) = (MAP - CVP) \times \frac{80}{CO_{TTE}} \]

where CO\textsubscript{TTE} was our best estimate of CO.

**Statistical analysis**

The normality of the quantitative data was verified using a Kolmogorov–Smirnov test, and expressed as means standard deviation (SD). The sample size (at least 84 measurements) was calculated for an equivalence trial\textsuperscript{19} with a range of equivalence of \pm 0.5 litre min\textsuperscript{-1} and acceptable
Comparison of esCCO and echo-Doppler

limits of agreement (i.e. 2 SD) of ± 2 litre min⁻¹ (i.e. 30% of a mean CO equal to 6 litre min⁻¹), with a two-sided significance of 0.05 and a power of 80%. The relationship between CO TTE and CO esCCO was analysed using a linear mixed effect model. The agreement between CO estimated using esCCO and TTE was shown using scatter plots and Bland and Altman plots. The bias (mean difference between CO esCCO and CO TTE) represents the systematic error between the two methods. The precision (SD of the bias) represents the random error or variability between the different techniques. The limits of agreement, calculated as bias ± 1.96 SD, define the range in which 95% of the differences between the methods are expected to lie. The percentage error was calculated as the ratio of 1.96 SD of the bias to the mean CO; this value was considered clinically acceptable if below 30%, as suggested by Critchley and Critchley. Bias and limits of agreement were in the presence of repeated measurements in each subject, we used the method described by Myles and Cui to take account of repeated measures. The method described by Myles and Cui uses a random effects model to estimate the within-subject variance. For studying the ability of esCCO to follow changes or trends in CO, a four quadrant plot was performed, and the concordance of the direction of change between consecutive readings from the esCCO and TTE was scored as a percentage of data point that agreed. We measured the concordance rate with no data exclusion. The magnitude of CO changes and degree of agreement were represented using a polar plot, in conformity with the methodology described previously by Critchley and colleagues. The distance from the centre of the plot represents the mean change in CO and the angle with the horizontal axis represents agreement. The more the CO changes are in agreement, the more the data pairs are distributed closely along the horizontal radial axis. Data with good trending will lie within ± 30° limits. However, data with poor trending will be scattered throughout the plot and lie outside the limits of good trending ability. Moreover, the limits of agreement proposed by Critchley and colleagues for good trending ability were an angular bias less than ±5° and radial limits of agreement of less than ± 30° when a central zone with radial limits of ± 0.5 litre min⁻¹ (i.e. dominated by a large random error) was excluded from the analysis. The effect of HR difference (ΔHR), PP difference (ΔPP), MAP difference (ΔMAP), and PWTT difference (ΔPWTT) between each measurement point on ΔCO esCCO and ΔCO TTE was evaluated by the linear mixed effect model. All results were corrected for repeated measurements. The statistical analysis was performed using R software, SigmaPlot 11 (Systat Software, Inc., San Jose, CA, USA), and Tanagra 1.4.35 (Rakotomalala, Lyon University, France).

Results

Thirty-eight patients were included in this study (Table 1). Six patients were excluded from the study: four for a calibration problem in the context of arrhythmia, one because the plethysmograph wave was absent in the context of septic shock with disseminated intravascular coagulation, and one because a good quality of the transthoracic echo-Doppler was impossible in the context of left pneumothorax. A total of 103 pairs of CO TTE and CO esCCO data were analysed. The overall mean CO esCCO was 7.1 (1.9) litre min⁻¹, which was significantly higher than the overall mean CO TTE, which was 5.6 (1.4) litre min⁻¹ (P<0.0001).

Table 1 Age expressed as median (range). Values are expressed as mean (SD) or number (%)

<table>
<thead>
<tr>
<th>Patient characteristics (n=38)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Age (yr) (range)</td>
<td>65 (20–85)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>75 (17)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168 (10)</td>
</tr>
<tr>
<td>Female/male [n (%)]</td>
<td>13 (34)/25 (66)</td>
</tr>
<tr>
<td>SAPS2 score</td>
<td>37 (14)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Cardiogenic pulmonary edema</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Severe sepsis or septic shock</td>
<td>26 (68)</td>
</tr>
<tr>
<td>Neurological</td>
<td>5 (13)</td>
</tr>
<tr>
<td>Intoxication</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Mechanical ventilation [n (%)]</td>
<td>18 (47)</td>
</tr>
<tr>
<td>Use of catecholamines [n (%)]</td>
<td>14 (37)</td>
</tr>
<tr>
<td>HR (beats min⁻¹)</td>
<td>91 (18)</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>95 (20)</td>
</tr>
<tr>
<td>PP (mm Hg)</td>
<td>66 (21)</td>
</tr>
<tr>
<td>PWTT (ms)</td>
<td>224 (40)</td>
</tr>
<tr>
<td>CO TTE (litre min⁻¹)</td>
<td>5.6 (1.4)</td>
</tr>
<tr>
<td>CO esCCO (litre min⁻¹)</td>
<td>7 (1.9)</td>
</tr>
</tbody>
</table>

Bland and Altman analysis

Analysis of the overall relationship between CO TTE and CO esCCO (Fig. 1) showed a significant correlation between CO TTE and CO esCCO (R=0.61, P<0.0001). The bias and limits of agreement were −1.6 litre min⁻¹ (−4.7; +1.5 litre min⁻¹) (Fig. 2). The percentage error for CO measurement was 49%.

Trending ability

The changes in CO between two consecutives measurements, as measured with TTE and esCCO, were also compared. The linear mixed effect model showed a significant correlation between ΔCO TTE and ΔCO esCCO (R=0.63, P<0.0001). Twenty-seven per cent of variations in CO yielded opposite changes, that is, negative variation with one technique and positive with the other. These data points are located in the upper left and lower right corners of Figure 3. The polar plot represents the trending ability and is shown in Figure 4. Sixty-three per cent of the data points lie within the ± 30° lines. After exclusion of values with ΔCO mean < 0.5 litre min⁻¹, 82% of the data points lie within the ± 30° lines, with an angular bias (so) of −9° (23°), and radial limits of agreement from −54° to +36°, which was superior to the limits of agreement.
proposed by Critchley and colleagues for good trending ability (i.e. angular bias less than ±5° and radial limits of agreement of less than ±30°). Also, there was a significant correlation between ΔCOesCCO and ΔHR, ΔPP, ΔMAP, and ΔPWTT. ΔCO_TTE appeared correlated only with ΔHR and ΔPWTT (Table 2).
Effect of SVR on the bias

There was a significant log-linear relationship between the bias and the estimation of SVR ($R^2 = 0.45, P < 0.0001$; Fig. 5).

Discussion

To our knowledge, this is the first study conducted in critically ill patients to assess the agreement between CO measurements using a new non-invasive technique (esCCO), derived from PWTT, with reference values obtained using the TTE. TTE is accepted as a reliable method for CO measurement in clinical practice and has been validated in comparison with thermodilution by several studies.\(^6\)\(^-\)\(^10\) McLean and colleagues\(^9\) reported a TTE bias of 0.2 litre min\(^{-1}\) and limits of agreement of ±1.5 to ±1.9 litre min\(^{-1}\). The inter-rater variability was good and varied between 5%\(^11\) and 7%.\(^7\) In our centre, this technique has been routinely used as a non-invasive alternative to thermodilution. Because this technique has the advantage of being fully non-invasive, it can be used in the early phase of sepsis\(^12\) in patients with spontaneous ventilation and those with mechanical ventilation. Thus, we decided to use TTE as our reference method for CO measurement.

The CO\(_{\text{esCCO}}\) percentage error of 49% was above the range considered clinically acceptable. Apart from our study, the esCCO system has never been tested in ICU, but the principle of calculation is analogous to pulse contour-derived CO (Vigileo\(^6\)) with transoesophageal echocardiography,\(^{24}\)\(^\text{25}\) thermodilution,\(^{26}\)\(^\text{27}\) or TTE.\(^{28}\) Furthermore, esCCO failed to reliably trend CO data, with a concordance compared with a TTE of 73%, which was below an acceptable level of 80%.\(^{14}\) The initial calibration of esCCO depends on patient characteristics (age, weight, height, gender) and the measures of PP and PWTT. Its exact algorithm remains undisclosed by the manufacturer, but relies on the assumption that SV is proportional to PP and to a factor reflecting arterial compliance, such as patient characteristics and PWTT.\(^{16}\)\(^\text{29}\) However, arterial pressure may change so quickly that intermittent non-invasive measurements may be too slow and inaccurate to allow early detection and prompt treatment. Therefore, PWTT offers beat-to-beat cardiovascular information. The esCCO algorithm assumed a linear relationship between PWTT and arterial pressure. This relationship was directly proportional in healthy volunteers, but was altered in patients with heart failure.\(^{30}\) Otherwise, a previous study indicated that oscillometric measurements of arterial pressure underestimated direct intra-arterial readings, and although this was observed for all levels of arterial pressure, the negative bias was larger for systolic arterial pressure measurements.\(^{31}\) There was a log-linear relationship between SVR and an increase in the bias. The estimation of SV by the equation $SV = K \times (\alpha \times \text{PWTT} + \beta)$ was a linear approximation.\(^5\) PWTT was divided into three intervals: (i) the
pre-ejection period, (ii) the PWTT through the elastic artery, and (iii) the PWTT through peripheral arteries. The PWTT through the elastic and peripheral arteries was dependent on the blood vessel resistance. According to the Bramwell–Hill relationship, derived from Newton’s second law of motion, the elastic arterial pulse wave velocity is expressed as follows:

\[
\text{Velocity} = \sqrt{\left(\frac{\Delta P}{\Delta V}\right) \times \left(\frac{V}{\rho}\right)}
\]

where \(\Delta P/\Delta V\) is the arterial elasticity, \(V\) the baseline volume in steady-state conditions, and \(\rho\) the blood density. Consequently, the COesCCO does not provide reliable measurements when changes in arterial compliance and peripheral resistance occur. This problem is similar to another non-invasive technique such as Vigileo: the study of Biancofiore and colleagues, comparing the CO measured by Vigileo and thermodilution, showed clearly a significant relationship between bias and SVR. In addition, COesCCO was affected by changes in PP, signifying that COesCCO was vulnerable to changes in vascular tone at the initial point of calibration. These facts may

![Polar plot used to show trending ability. The distance from the centre of the plot represents the mean change in CO, the angle with the horizontal axis represents disagreement. Sixty-three per cent of the data lie inside the limits of good trending ability (i.e. ± 30° represented by dotted lines).](image)

**Table 2** Results of linear mixed effect model between physiological variables and changes in CO. The bold values are significant \((P < 0.05)\)

<table>
<thead>
<tr>
<th>Regression coefficient</th>
<th>Variables</th>
<th>Coef. (\beta) (SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\Delta CO_{esCCO})</td>
<td>(\Delta HR)</td>
<td>0.045 (0.006)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>(\Delta MAP)</td>
<td>0.013 (0.005)</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>(\Delta PP)</td>
<td>0.028 (0.006)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>(\Delta PWTT)</td>
<td>-0.015 (0.003)</td>
<td>0.001</td>
</tr>
<tr>
<td>(\Delta CO_{TTE})</td>
<td>(\Delta HR)</td>
<td>0.049 (0.007)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>(\Delta MAP)</td>
<td>0.008 (0.006)</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>(\Delta PP)</td>
<td>-0.009 (0.007)</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>(\Delta PWTT)</td>
<td>-0.008 (0.003)</td>
<td>0.02</td>
</tr>
</tbody>
</table>
explain the inaccuracy of the measures of esCCO. Based on this finding, the esCCO does not measure or track changes in CO with sufficient clinically acceptable reliability, at least in critically ill patients.

Our study had some limitations. The most significant was the use of an imprecise reference method. Several studies concluded that the limits of agreement for TTE, by comparison with PAC, were acceptable and Jardin and colleagues conclude that PAC data may be less reliable than TTE, in the context of sepsis, for the estimation of myocardial contractility. Gola and colleagues compared TTE and thermodilution methods with the Fick oxygen method in patients with advanced congesting heart failure: they reported a TTE bias of -0.2 litre min^-1 (2 SD=1 litre min^-1) and a thermodilution bias of 0 litre min^-1 (2 SD=1.4 litre min^-1). The authors concluded that in this population, the agreement of Doppler echocardiography with Fick measurements of CO was closer than that obtained by thermodilution and independent from the presence of low CO, tricuspid regurgitation, or both. Therefore, these data indicated that the Doppler echocardiography method for measuring CO represented a valid alternative to invasive methods. Ideally, the highly reliable reference standard to make comparisons of CO is an aortic flow probe applied directly to the aorta, but this technique is not possible in clinical practice. TTE is a non-invasive method for the estimation of CO by measuring the VTI directly through the LVOT. However, it does not allow continuous monitoring of CO, hence the search for alternative techniques such as esCCO. For assessing trending ability, despite no current consensus, we have used: (i) four quadrant plot of serial change in CO with concordance analysis, which is the method most frequently used with the advantage of showing the relationship between paired measurement and permit to compare results from different study and (ii) the polar plot as described recently by Critchley and colleagues. The angular bias was greater than ±5°, indicating that the calibration of the esCCO system significantly differed from our reference method, and the radial limits of agreements were greater than ±30°, indicating a poor trending ability.

In conclusion, we found a significant correlation between the two methods of measuring CO in ICU patients, but the percentage error of 49% is still clinically unacceptable. The concordance rate of 73% during CO changes is insufficient. Therefore, the esCCO monitor cannot be recommended for critically ill patients. An improved calibration algorithm seems necessary for increasing the accuracy of esCCO in the future.

Acknowledgement

The authors wish to thank all the paramedical team of Narbonne Hospital for their help during the implementation of the study.

Declaration of interest

None declared.

Funding

Nihon Kohden loaned us esCCO monitors. No other funding supported this work.
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