Comparison between an uncalibrated pulse contour method and thermodilution technique for cardiac output estimation in septic patients

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The optimization of oxygen delivery (DO2) represents the cornerstone of goal-directed therapy in septic patients.1 To this end, it is important to monitor and improve blood oxygenation, haemoglobin values, and cardiac output (CO).1 2

CO measurement using the thermodilution (ThD) method is regarded as the gold standard technique in haemodynamically stable subjects.3 However, pulmonary artery catheter (PAC) insertion is an invasive procedure with associated complication risks.4 5 As alternatives, several pulse contour methods (PCMs) have been developed. These are less invasive beat-by-beat monitoring techniques using specific algorithms to compute CO from analysis of arterial pressure waveforms.6 7 These monitoring systems can be divided into two main categories: (A) PCMs requiring an indicator dilution CO measurement and patient characteristics to calibrate the system for arterial impedance estimation; and (B) PCMs that can work without calibration or additional user-entered data.6 8

In septic patients, changes in vascular impedance and compliance often occur (e.g. after vasopressor therapy adjustment), thus a systematic recalibration of PCM CO monitors belonging to category A could be necessary to avoid incorrect measures of CO.7 8 Conflicting points of view are present in the literature about recalibration of PCMs after vasopressor therapy adjustment.9 10

The MostCare® system (Vytech Health, Laboratoires Pharmaceutiques Vygon, Ecouen, France) is the only currently available pulse contour monitor belonging to

Editor’s key points

- Different algorithms are available to estimate CO from the arterial pressure waveform.
- MostCare monitor uses pressure recording analysis and may not require external calibration.
- In septic patients MostCare overestimated CO by 0.26 litre min⁻¹ compared with thermodilution.
- Changing vascular tone did not have a clinically important effect on bias and limits of agreement.

Background. The purpose of this study was to evaluate the reliability of a new uncalibrated pulse contour method, the MostCare, in determining cardiac output (CO) in septic patients.

Methods. Thirty patients with septic shock admitted to an intensive care unit, receiving a norepinephrine infusion and requiring haemodynamic monitoring with a pulmonary artery catheter, were prospectively enrolled. Thermodilution measurements of CO (ThD-CO) were considered as the ‘gold standard’. MostCare was connected to the monitoring system of the radial arterial pressure waveform to obtain a continuous CO calculation (MostCare-CO). ThD-CO and MostCare-CO measurements were recorded at three different haemodynamic states: baseline (T1), after raising mean arterial pressure (MAP) to 90 mm Hg by increasing the norepinephrine infusion (T2), and after returning the MAP to baseline value by decreasing vasopressor therapy (T3). A Bland–Altman and linear regression analyses were performed.

Results. A total of 90 paired ThD-CO and MostCare-CO measures were obtained (range 4.1–13.9 litre min⁻¹ for ThD-CO and 4.5–13.5 litre min⁻¹ for MostCare-CO). A good correlation between ThD-CO and MostCare-CO was observed (R = 0.93). The mean bias between the two techniques was −0.26 litre min⁻¹ (SD 0.98 litre min⁻¹) and the 95% limits of agreement were −2.22 to 1.70 litre min⁻¹. The percentage of error was 25%. Pearson’s R was 0.94, 0.92, and 0.93 at T1, T2, and T3, respectively.

Conclusions. MostCare-CO and ThD-CO showed a good agreement at each time of the study. The reliability of the MostCare system was not affected by the vascular tone changes produced by a norepinephrine infusion.

Keywords: cardiac output; pulse contour methods; sepsis; thermodilution technique

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category B, because neither calibration nor adjustments based on user-entered data are required. This system is based on PRAM (pressure recording analytical method) which has been validated under different clinical conditions but never in septic patients. It remains unclear whether the MostCare monitor algorithm is accurate and reliable in septic patients in the event of changes in vascular compliance and impedance caused by vasopressor therapy.

The aim of our study is to investigate the level of agreement between CO values determined by ThD-CO and by the MostCare monitor (MostCare-CO) in septic patients during vasopressor therapy adjustment.

**Methods**

**Patients**

Thirty patients (18 males, 12 females) with septic shock admitted to the intensive care unit (ICU) and requiring haemodynamic monitoring with a PAC were enrolled. Approval from the Institutional Review Board was obtained along with written informed consent from all patients. Exclusion criteria were: (i) age under 18; (ii) the presence of arrhythmias with haemodynamic instability; (iii) aortic regurgitation or stenosis; (iv) tricuspid valve insufficiency; or (v) ascending aorta pathologies. Patients were mechanically ventilated and managed following sepsis international guidelines.

**ThD data acquisition**

A ThD PAC (7 F Baxter-Edwards, Irvine, CA, USA) was introduced through the right internal jugular vein. Five consecutive injections of 10 ml of 5% glucose cold solution were made randomly during the respiratory cycle over a 5 min period for each CO estimation. The lowest and the highest CO values were discarded and ThD-CO was calculated as the mean of the three remaining measurements. In the absence of haemodynamic stability (discrepancy in the CO measurements >10%), the series of CO measurements were discarded and repeated until satisfactory measurements were obtained. All the injections were performed by the same operator.

**MostCare system data acquisition**

The MostCare system is a PCM which provides a beat-to-beat estimation of stroke volume (SV) and CO derived from the arterial pressure waveform. This device does not need external calibrating factors and uses the PRAM algorithm. As the MostCare device does not require a dedicated catheter-transducer system, it was connected via a simple cable connection to the main monitoring system for the continuous recording of the radial arterial pressure waveform. Arterial pressure was measured in all patients using an 18 G arterial catheter (radial artery) connected to pressure tubing and a pressure transducer (Edwards Lifesciences, Irvine, CA, USA). For each determination of ThD-CO, a corresponding value from the MostCare monitor was obtained by averaging the individual beats over the approximate time needed for each ThD-CO measurement. Finally, the average of three MostCare-CO measurements was used for data analysis.

**Study intervals and experimental procedure**

For each patient, CO determinations were performed at three different times: at baseline (T1), after raising mean arterial pressure (MAP) to 90 mm Hg by increasing the norepinephrine infusion (T2, intervention), and after returning the MAP to baseline value by decreasing vasopressor infusion (T3, control). CO determinations were performed after 5 min of stable MAP under haemodynamic steady-state conditions. The duration of the study period (from T1 to end of T3) was about 50 min.

During the measurements, the patients were sedated and ventilated in a pressure-controlled mode, and no changes to ventilator variables, sedation, or fluids infusions were made.

After zeroing the pressure-transducer system and before each CO measurement, the ‘fast-flush’ test was used to determine the dynamic response of the catheter-transducer system. This test allows clinicians to determine in vivo the natural frequency and damping coefficient of an invasive arterial pressure monitoring system. It consists of a brief opening of the catheter-transducer system to the high-pressure flush bag, to obtain a transient square wave in the arterial signal. The catheters were flushed and aspirated easily and the waveform was optimized if necessary by manipulating the catheter and extending the wrist.

**Statistical analysis**

Statistical analysis was performed using StatsDirect version 2.5.8 (Cheshire, UK), GraphPad PRISM version 4.0 (San Diego, CA, USA) and R version 2.11.1 (2010-05-31 R Foundation for Statistical Computing, Vienna, Austria). The comparison of the data collected at three different haemodynamic states was made using analysis of variance for repeated measures and by the Student–Newman–Keuls method. Correlation coefficient, bias (mean difference between measurements), and limits of agreement were calculated for the entire data set. The Bland–Altman method for repeated measures was used to assess the agreement between ThD-CO and MostCare-CO. The percentage error was calculated as the limits of agreement (2 SD of the bias divided by the mean CO from the two methods, as proposed by Critchley: 100(2 SD of Bias)/[(ThD-CO+MostCare-CO)/2]. The estimate of SD was adjusted for repeated measures as described below. The data for the three time points studied were also analysed separately. Changes (Δ) in CO were calculated by subtracting the first from the second measurement (T2–T1) and the second from the third (T3–T2). Bias and 95% limits of agreement as a percentage of the mean value of ThD-CO measurements were also calculated (bias % = 100 × bias/ThD-CO; 95% limits of agreement % = 100 × lower limit/ThD-CO – 100 × upper limit/ThD-CO).
The methods suggested by Myles and Cui were used to adjust for the effects of repeated measurements in the Bland–Altman analysis. A random effects model for repeated-measures data was analysed using the R’s package MethComp (R package version 1.2-1). To check the essential postulation of the Bland–Altman method (i.e. the variance of the repeated measurements for each subject by each method is independent of the mean of the repeated measures), a plot of within-subject SD against the mean of each subject by each method was used. This was valid for both ThD-CO and MostCare-CO.

The ability of the MostCare to follow changes or trends in CO with reliability was assessed according to the statistical method used by Biancofiore and colleagues. Following the methods used in other studies, after excluding all the pairs of CO where at least one value was zero, we analysed the direction of change between ThD-CO and MostCare-CO to assess the percentage of concordance between the records both including and excluding a △ThD-CO of <0.5 litre min⁻¹. A P-value of <0.05 was considered statistically significant.

Results

Patients’ characteristics are reported in Table 1. Ninety comparisons of paired CO measurements were made. CO values from all time points are reported in Table 2. During the three different haemodynamic states, there were no statistically significant variations of haemodynamic variables apart from MAP and systemic vascular resistance (SVR) (Table 2).

ThD-CO values ranged from 4.1 to 13.9 litre min⁻¹ and MostCare-CO values ranged from 4.5 to 13.5 litre min⁻¹. Overall, a good correlation between ThD-CO and MostCare-CO was observed (R = 0.93, P < 0.01). The Bland–Altman plots for each time point of the study are shown in Figure 1. The mean bias of all 90 CO measurements corrected for repeated measures using random effects modelling was −0.26 litre min⁻¹ with an SD of 0.98 litre min⁻¹ and a percentage error of 25% (Table 3). Although MostCare-CO tended to overestimate ThD-CO over the study period, good agreements and low percentages of error were found between the two methods at each time point of the study. The mean difference between ThD-CO and MostCare-CO, 95% limits of agreement, and mean percentage error at different times are reported in Table 3. Linear correlations between ThD-CO and MostCare-CO demonstrated R values of 0.94, 0.92, and 0.93 at T1, T2, and T3, respectively. The change in CO with changes in norepinephrine infusion (ΔCO) was calculated separately for ThD-CO and MostCare-CO. Comparison of the changes measured by the two methods demonstrated a correlation of 0.89 (P < 0.01) (Fig. 2) and a mean bias of −0.007 litre min⁻¹ (2 SD of 1.7 litre min⁻¹).

Four ΔCO pairs were excluded from the analysis of the direction of changes as at least one ΔCO value was zero. The concordance of ΔCO was 89% (50 of 56 pairs of ΔCO agreed) and it improved to 100% (39/39) when 17 ThD-CO < 0.5 litre min⁻¹ were excluded from the analysis. There was no correlation between changes in peripheral resistance and bias in CO measurement (R = −0.18, P = 0.09) (Fig. 3).

Discussion

In this study, we compared CO values determined by ThD and MostCare in patients with septic shock during changes in of MAP produced by manipulating vasopressor therapy. Over the study period, CO measurements obtained from the MostCare monitor tended to overestimate CO relative to the reference values obtained from ThD-CO (approximately of 0.3 litre min⁻¹); however, a significant difference between MostCare and the established reference technique was not identified.
This agreement persisted, despite vasopressor therapy and changes in MAP (Table 2). In our opinion, in septic patients with high CO values (the mean CO value in our study was 7.66 litre min$^{-1}$), an absolute error in CO of 0.3 litre min$^{-1}$ is less likely to influence the decision-making about therapy than CO variations during vasopressor therapy adjustment. Secondly, the percentage errors were within the clinically acceptable limits proposed by Critchley and Critchley$^{18}$ for a new method at each setting of norepinephrine infusion (Table 3). Finally, a good agreement in detecting changes ($D$) in CO between the two different techniques is also supported by our results (Fig. 2).

Recently, in a similar study, Sakka and colleagues$^{25}$ assessed the reliability of Vigileo monitor (Edwards Lifesciences), a device that belongs to category A of PCMs as it requires patient gender, age, height, and weight for CO determination. The authors found that pulse contour analysis-derived CO underestimated CO obtained by transpulmonary ThD technique in septic patients (mean bias between techniques was 0.5 litre min$^{-1}$, SD of 2.3 litre min$^{-1}$). Thus, Sakka and colleagues$^{25}$ did not consider the Vigileo as reliable as transpulmonary ThD in septic patients.

We repeated the study described by Sakka and colleagues$^{25}$ who assessed the Vigileo monitor reliability in...
patients with septic shock during norepinephrine dosage adjustments. Similarly, we compared the ThD technique with MostCare as this system was never studied in septic patients. Unlike the study by Sakka and colleagues, our findings showed a better agreement between the two monitoring techniques compared. There are two main reasons that could explain these findings. First, in our study, the MostCare system was compared with the intermittent pulmonary ThD, while Sakka and colleagues compared the Vigileo against the transpulmonary ThD. Secondly, more importantly, although Vigileo and MostCare systems might seem similar (they do not need external calibration), they use different algorithms and belong to different categories of PCMs (A and B, Vigileo and MostCare, respectively).11–14 25 26

The most used PCM approach (e.g. used by Vigileo monitor) relies on the aortic pressure–cross-sectional area relationship that is modelled from unrelated in vitro measurements on segments of human thoracic aorta.23 27 To obtain absolute values of CO from the majority of pulse contour monitors (e.g. PICCO, Pulsion Medical System), it is necessary to determine at least once for each patient a calibration factor by comparing PCM result with an absolute CO estimate in order to compensate for the inter-individual differences in arterial compliance. This may greatly limit the usefulness of PCMs, since the calibration techniques are invasive and must be applied each time there are changes in experimental procedures or clinical practice which may alter the physical properties of the arteries either iatrogenically (e.g. vasopressor therapy) or spontaneously (e.g. sepsis-related changes in SVR).1 7 The Vigileo monitor is a clinically attractive device because it does not require injection of thermal solution. This monitor calculates the SV using a constant K derived from the patient’s specific vascular impedance and compliance based on patient characteristic and physical characteristics (sex, age, height, and weight), according to the method described by Langewouters and colleagues.27 The software recalculates the K value at a fixed interval of time on the basis of the arterial pressure curve modifications that reflect the changes in arterial impedance and compliance.25 26 The MostCare system uses the PRAM which has been validated in different clinical settings.11–14 The PRAM algorithm is the practical application of a model developed completely a priori (the model did not require adjustments based on experimental data for SV determination) and is based on the physics theory of perturbations by which each physical system under the effects of a perturbing factor tends to react to reacquire its own condition of stability (i.e. the situation of minimal energy required).11 With PRAM (MostCare), the systemic impedance is not theoretical (e.g. age-, sex-, weight-, height-related), but it is determined by the actual physical characteristics of the circulatory system of the subject under study from the morphological analysis of the pressure waveform sampled at a frequency

![Fig 2 Relationship between changes (Δ) in CO estimated by intermittent ThD (ΔThD-CO) and by MostCare (ΔMostCare-CO). Four-quadrant trend plot (a) and modified Bland–Altman trend plot (b). Correlation coefficient (R) was equal to 0.89 [bias of -0.007 litre min⁻¹ (2 SD = 1.7 litre min⁻¹)]. (a) Solid line, line of regression. (b) Solid line, mean difference (bias); dotted lines, limits of agreement [bias (2 SD)]. Δ in CO was calculated by subtracting the first from the second measurement (T2 – T1), and the second from the third (T3 – T2).](https://academic.oup.com/bja/article-abstract/107/2/202/297990)

![Fig 3 Bias between ThD-CO (CO obtained with intermittent ThD) and MostCare-CO (CO obtained with MostCare) plotted against SVR. The graph shows that SVR changes and bias between CO measurements are not related. Data from all three time points used (n = 90).](https://academic.oup.com/bja/article-abstract/107/2/202/297990)
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of 1000 Hz. These different algorithms may explain the differences between our results and those obtained by Sakka and colleagues who compared the Vigileo monitor with the transpulmonary ThD.

Recently, Monnet and colleagues used PICCO and Vigileo devices to monitor cardiac index in 80 patients with septic circulatory failure treated with either volume expansion (40 patients) or norepinephrine (40 patients). The authors confirmed Sakka’s findings and demonstrated that the more the SVR changed, the less accurately the Vigileo’s algorithm measured cardiac index changes.

Biais and colleagues conducted a study with the Vigileo in a population of cirrhotic patients who underwent liver transplantation. They did not find good agreement between CO values obtained with Vigileo and those obtained with pulmonary ThD. The authors attributed their poor findings to the lack of an external calibration of Vigileo. Similar results were obtained by Biancofiore and colleagues in a similar group of cirrhotic patients. Although they used a new software version of the device (version 01.10), a poor agreement between Vigileo and ThD CO measurements was found (mean bias 1.3 litre min⁻¹ m⁻², 95% limits of agreement −1.5 to 4.1 litre min⁻¹ m⁻², percentage error 54%). The authors stated that the typical haemodynamic status of such patients, which is characterized by increased CO, decreased SVR, and extremely variable mechanical arterial properties, may have played a pivotal role in determining the disagreement between the two techniques. In fact, they found that the lower the SVR, the greater the bias in CO measurements between the two methods. Thus, the authors concluded that the Vigileo system may not provide reliable CO values when changes in the compliance and peripheral resistance of the circulation occur.

In our study, SVR and bias between the two techniques were not correlated (Fig. 3), suggesting that the MostCare algorithm was not impaired by changes in arterial tone. We found a good relationship between ΔMostCare-CO and ΔThD-CO as demonstrated by the four-quadrant trend plot (R=0.89). Moreover, MostCare agreed with ThD regarding the direction of change in CO as we found a concordance of 89% without excluding any records and a concordance of 100% when ΔThD-CO <0.5 litre min⁻¹ were excluded from the analysis.

Several factors could affect the accuracy of CO measurements based on the analysis of arterial waveforms with MostCare, such as stenosis of the arterial tree and arterial pathology in the proximal segments. These need to be further investigated. Either over- or under-damped arterial pressure waveforms may influence the precision of the pressure wave analysis by PCMs. Finally, data regarding the wedge pressure and mixed oxygen venous saturation represent important information that allows accurate interpretation and treatment of low CO states. The absence of these measures may be a disadvantage of PCMs, but it is the penalty for being less invasive. On the other hand, MostCare can provide information on pulse pressure and SV variations (PPV, SVV), thus it can be useful in predicting fluid responsiveness. It also gives a new promising index of cardiac cycle efficiency which has been recently investigated in cardiac surgery patients. This new variable, together with the dynamic indexes of fluid responsiveness (PPV, SVV), may help clinicians in the haemodynamic assessment and management of critically ill patients.

The present study has some limitations: (i) we have compared an intermittent ThD technique with a continuous CO monitor. Although the injections of the cold solution were performed by the same operator, we cannot exclude that some variability in the ThD method could have affected our results. We did not evaluate a third reference CO monitoring device. It would have been interesting to study a continuous calibrated pulse wave analysis-based CO monitoring system. (ii) We compared MostCare and ThD only during haemodynamic changes related to vasoconstrictor infusion and did not assess the value of this PCM in different haemodynamic scenarios related to different therapies of sepsis (e.g. fluid challenge or inotropics). (iii) Data were obtained during stable haemodynamic conditions. Further studies are required to assess the reliability of MostCare in the setting of haemodynamic instability.

In conclusion, MostCare system tracks CO changes evaluated by conventional ThD, despite modifications in arterial impedance caused by norepinephrine therapy in septic patients. This device seems a practical alternative to the traditional ThD method when the indwelling of a PAC is harmful or not recommended and not essential for clinical management. To our knowledge, this is the first study that investigated the accuracy of MostCare in septic patients.

Conflict of interest

S.M.R. discloses his participation in the development of the mathematical algorithm of PRAM and is the owner of the PRAM patent.

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