Novel continuous capnodynamic method for cardiac output assessment during mechanical ventilation

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Background. It is important to be able to accurately monitor cardiac output (CO) during high-risk surgery and in critically ill patients. The invasiveness of the pulmonary artery catheter (PAC) limits its use, and therefore, new minimally invasive methods for CO monitoring are needed. A potential method is estimation of CO from endogenous carbon dioxide measurements, using a differentiated Fick’s principle to determine effective pulmonary blood flow (EPBF). In this study, we aimed to validate a novel capnodynamic method (COEPBF) in a wide range of clinically relevant haemodynamic conditions.

Methods. COEPBF was studied in 10 pigs during changes in preload, afterload, CO increase, and bleeding. An ultrasonic flow probe around the pulmonary artery was used as reference method of CO determination. CO was also measured using a PAC thermodilution technique (COPAC). CO and other haemodynamic data were recorded before and during each intervention. Accuracy and precision and also the ability to track changes in CO were determined using Bland–Altman, four-quadrant plot and polar plot analysis.

Results. COEPBF and COPAC showed equally good agreement, with a tendency to overestimate CO (bias 0.2 and 0.3 litre min⁻¹, respectively). The overall percentage error was 47% for COEPBF and 49% for COPAC. The concordance for tracking CO changes was 97 and 95% for COEPBF and COPAC, respectively, with an exclusion zone of 15% and radial limits of ±30°.

Conclusions. COEPBF showed reliable trending abilities, equivalent to COPAC. COEPBF and COPAC also showed low bias but high percentage errors. Further studies in animal models of lung injury and in high-risk surgery patients are warranted.

Keywords: carbon dioxide, measurement; heart, cardiac output; measurement techniques, carbon dioxide; measurement techniques, cardiac output; measurement techniques, thermodilution

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Methods

The Animal Research Ethics Committee of Uppsala University approved the study which was performed at the Hedenstierna Laboratory in Uppsala.

Anaesthesia and surgical preparation

Ten pigs, mean weight 28 kg and range 24–29 kg, were sedated with 0.04 mg kg⁻¹ atropine (NM Pharma AB, Sweden), 6 mg kg⁻¹ tiletamine-zolazepam (Zoletil, Vibrac Laboratories, France), and 2.2 mg kg⁻¹ xylazine chloride (Rompun, Bayer AG, Germany) administered intramuscularly. Infusion of 5 μg kg⁻¹ fentanyl (Fentanyl Braun, Germany), ketamine 30 mg kg⁻¹ h⁻¹, midazolam 0.1 mg kg⁻¹ h⁻¹ and fentanyl 4 μg kg⁻¹ h⁻¹ was used for maintenance of anaesthesia and rocuronium 2 mg kg⁻¹ h⁻¹ for muscle relaxation. Ringer’s acetate 10 ml kg⁻¹ h⁻¹ was administered throughout the experiments. After tracheal intubation normoventilation was achieved in a volume-controlled mode (Servo I, Maquet, Solna, Sweden): tidal volume 10 ml kg⁻¹, FIO₂ 0.4 and positive end expiratory pressure (PEEP) 5 cm H₂O. A balloon-tipped 7.5 Fr PAC was inserted via the right jugular vein into the pulmonary artery. CO was determined by the mean of three 5 ml bolus injections of ice cold saline (CO PAC). The jugular vein and femoral artery were cannulated for administration of vasoactive drugs and arterial pressure recordings. A 13.5 Fr catheter was placed in an artery for controlled bleeding. An 8 F Fogarty occlusion catheter was inserted into the femoral vein for later vena caval occlusion. A urinary catheter was introduced into the urinary bladder. By a left side thoracotomy a 16-mm ultrasonic flow probe (T 401; Transonic System, Inc., Ithaca, NY, USA) was placed around the pulmonary trunk for continuous measurement of CO (CO₃). The chest was closed and the pigs positioned in a semi-lateral position. The body temperature was maintained at 38–39°C. Pressure readings and signals from the ultrasonic flow probe were sampled into a data acquisition system (version 3.2.7, Acknowledge, BioPac Systems, Santa Barbara, CA, USA).

Measurement of EPBF by COₑPB₅F

EPBF was calculated in accordance with the new capnodynamic method. The additional software in the ventilator creates recurrent periods of hyperventilation and hyperventilation by varying the inspiratory pause.¹⁴ This breathing pattern (Supplementary Fig. S1) cyclically varies the i'CO₂ by ~0.5–1.0 kPa. Expired CO₂ was measured by the ordinary main stream CO₂-transducer and gas flow was analysed by the flow sensor in the ventilator. The CO₂ and flow data were exported to a computer and then analysed using a specially designed software application written in Matlab™ (Mathworks, Natick, MA, USA). The algorithm is based on the assumptions that EPBF, the effective lung volume (ELV), and the carbon dioxide content in venous blood (CcCO₂) are constant during the 10 most recent breaths and the carbon dioxide content in the lungs (CvCO₂) are constant during the 10 most recent breaths and the carbon dioxide content in the lungs (CvCO₂) are constant during the 10 most recent breaths and the carbon dioxide content in the lungs (CvCO₂) are constant during the 10 most recent breaths. By optimizing the fit between the lung model and measured data, the equation system can be solved. Thus, it is possible to determine EPBF, which is the blood flow through the lungs participating in gas exchange.

The equation below describes a mole balance of CO₂ in the lung and contains three unknown variables: ELV, the lung volume containing CO₂; EPBF, effective pulmonary blood flow participating in gas exchange; and CᵥCO₂. The left side reflects the difference in CO₂ content in the lung between two breaths and the first term on the right side describes the circulatory supply of CO₂ in the alveolar compartment between two breaths. The CO₂ content in the lung capillary blood, CᵥCO₂, is calculated from the alveolar CO₂ fraction and the dissociation curve described by Copek and Roy in 1988. The second term is the amount of CO₂ eliminated from the lungs by the nth tidal volume.

\[
ELV \cdot (F_A CO_{2} - F_A CO_{2}^{-1}) = EPBF \cdot \Delta t \cdot (C_v CO_{2} - C_v CO_{2}^{-1}) - VTCO_{2}^{-1}
\]

ELV, effective lung volume (litre) containing CO₂ at the end of expiration; EPBF, effective pulmonary blood flow (litre min⁻¹); n, current breath; n – 1, previous breath; F_A CO₂, alveolar CO₂ fraction; CᵥCO₂, lung capillary CO₂ content (calculated from F_A CO₂); VTCO₂⁻¹, volume (litre) of CO₂ eliminated by the current, nth, breath; \( \Delta t \), current breath cycle time (min).

The test cycle consists of 10 breaths. Each breath creates a new equation. Thus, 10 breaths create 10 equations with 3 unknown variables. By optimizing the fit between the lung model and measured data, the equation system can be solved. Thus, it is possible to determine EPBF, which is the blood flow through the lungs participating in gas exchange.

Experimental protocol

After 30 min of stabilization, baseline measurements were recorded. Then, the haemodynamics were altered by: (i) caval occlusion reducing CO₂ by ~50%. (ii) Infusion of phenylephrine (0.11–0.21 μg kg⁻¹ min⁻¹) increasing mean arterial pressure (MAP) to ~150% of baseline. (iii) Infusion of nitroprusside (1.4–2.1 μg kg⁻¹ min⁻¹) decreasing MAP to 60% of baseline. (iv) Infusion of dobutamine (60–100 μg kg⁻¹ min⁻¹) increasing CO₃ to ~200% of baseline. (v) A volume challenge of 500 ml colloid (Hesra, Baxter, Chicago, IL, USA). (vi) Reduction of MAP to 35 mm Hg by controlled bleeding. Each haemodynamic intervention was followed by a stabilization period. One baseline reading between every haemodynamic event and three readings during every haemodynamic manipulation were obtained during the experiment. All paired CO data were recorded under haemodynamic steady-state conditions as judged by the ultrasonic flow probe. After the experiment, the animals were killed.

Statistics

The distributions of the differences between CO data obtained from the three methods were tested for normality using the Kalmogorov–Smirnov test. Data are presented as mean (SD). Precision [defined as twice the coefficient of variation, CV (SD/mean)] for each monitor device was calculated from the initial three consecutive baseline measurements during haemodynamic steady state. The inherent PAC precision was calculated as twice the coefficient of error (CE) (CV/sqrt(3)), of the three
averaged thermodilution curves of a baseline measurement. For absolute CO values, the overall agreement between COEPBF and COTS, and COEPBF and COPAC was calculated according to the method described by Bland and Altman, and adjusted for multiple measurements within subjects. The bias between methods was calculated as the mean difference, and the precision of the estimates as the limits of agreement ([bias (1.96 SD)]. The percentage error was calculated as 1.96 SD of the difference divided by the mean CO. In addition, a separate Bland–Altman analysis was performed for each intervention. To investigate the capacity of COEPBF to track changes in CO (ΔCO), we calculated the Pearson correlation coefficient (r) for paired ΔCO values for all interventions. The trending ability was assessed by calculating the concordance (the percentage of the total number of paired ΔCO values having the same directional change) for COEPBF and COTS, and COEPBF and COPAC, respectively, using four-quadrant plots. Since central data points correspond to small changes in CO and reflect random measurement errors rather than trending ability, concordance rates were calculated using a 15% exclusion zone. To assess the agreement not only for the directions of change, but also for the magnitudes of change in CO, we have in addition used polar plot methodology, as recently described by Critchley and colleagues. In a polar plot, the mean of the pairwise ΔCO values of the reference method and the test method represent the radial length of the vector. The polar angle represents the agreement of the magnitudes of change in CO between methods, and the mean polar angle (angular bias) indicates how well the test method is calibrated compared with the reference method. Good calibration can be considered to exist when the angular bias is ±5° or less. A concordance of >95% of polar data points within radial limits of agreement of ±30° indicates good trending ability. Sigma Plot (version 12.0 for Windows, Systat software, Inc., GmbH, Germany) was used to construct polar plots. GraphPad Prism (version 6.0 for Windows, GraphPad Software, San Diego, CA, USA) was used for all other statistical calculations.

**Results**

All the animals survived throughout the experimental protocol. The PACO₂ – ECO₂ gradient at baseline was low, indicating a small pulmonary shunt and alveolar dead space ventilation (data not shown).

**Response to hemodynamic alterations**

All the interventions resulted in marked haemodynamic alterations with a COTS ranging from 1.2 to 4.9 (mean 2.6) litre min⁻¹. Dobutamine infusion was aborted in four animals because of arrhythmias. The changes in HR, MAP, and systemic vascular resistance (SVR) in relation to COTS are displayed in Figure 1.

**CO measurements**

The calculated precision for the CO methods was ±1% for COTS, ±2.5% for COEPBF, and ±4.3% for COPAC at baseline. The inherent precision of COPAC was ±7%.

**COEPBF vs COTS**

COEPBF showed an overall consistency in relation to COTS in response to haemodynamic interventions (Fig. 2). There was a tendency to overestimate CO at basal conditions but negligible

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**Fig 1** Haemodynamic data for all protocolled interventions. Left y-axis represents cardiac output (litre min⁻¹), as measured by the ultrasonic reference method, COTS. Right y-axis represents MAP (mm Hg), HR (beats min⁻¹), and SVR (mm Hg litre min⁻¹). Each haemodynamic challenge was followed by a baseline stabilization period. Data are presented as mean (SEM), n=6–10.
Bias was seen for interventions yielding an increase in CO. For all interventions together, bias (limits of agreement) was 0.2 (2.0–1.0) litre min\(^{-1}\) (i.e. 95% of COEPBF will be expected to be between 32% below and 48% above COTS). The percentage error (PE) for COEPBF was 47%. For bias (limits of agreement) at each intervention see Table 1. Paired data from all interventions are plotted in Figure 3.

The trending ability of COEPBF was assessed by calculating delta values from CO readings before and during each intervention. The correlation between ΔCOEPBF and ΔCOTS was high (r=0.96, P<0.0001). The concordance was 97% assessed by the four-quadrant plot (Fig. 4), and 97% (+30° radial limits) using polar plot methodology (Fig. 5), with 15% exclusion zones applied. Polar plot analysis also showed that the magnitudes of changes agreed for COEPBF and COTS. The angular bias was −5.6 (CI −28–16)% as demonstrated by the data points being closely centred to the horizontal line (Fig. 5).

**CO\(_{\text{PAC}}\) vs CO\(_{\text{TS}}\)**

CO\(_{\text{PAC}}\) also showed an overall consistency with CO\(_{\text{TS}}\), with a tendency to overestimate at all interventions, except during nitroprusside infusion. Bias (limits of agreement) was 0.3 (−1.0–1.6) litre min\(^{-1}\), so that 95% of COEPBF will be expected to be between 38% below and 62% above CO\(_{\text{TS}}\). PE for CO\(_{\text{PAC}}\) was 49%. For detailed data at each intervention, see Table 1. As expected, the trending ability of CO\(_{\text{PAC}}\) was good with a correlation of r=0.95 (P<0.0001) and concordance rates from 95 to 100% as assessed by the four-quadrant plot (Fig. 4) and polar plot (Fig. 6), respectively. Good trending ability was also
COEPBF vs COPAC

When comparing COEPBF with COPAC, the Bland–Altman analysis showed good agreement for all interventions apart from dobutamine infusion, with a bias (limits of agreement) of 0.6 (−1.3 to −1.1) litre min⁻¹ (Table 2), PE 40%. As expected when using a less precise reference method, the trending analysis showed less accuracy seen as a correlation of $r=0.91$ ($P<0.0001$) and concordance rates ranging from 82 to 91%, as assessed by four-quadrant plot and polar plot, respectively.

Discussion

We have investigated a new, continuous capnodynamic method for assessment of CO during mechanical ventilation. The evaluation included a wide range of haemodynamic alterations. COEPBF showed reliable trending abilities and excellent concordance rates when compared with the reference method COTS. In addition, in comparison with both COTS and COPAC, the COEPBF method showed an acceptable mean bias in a variety of haemodynamic states.

For CO monitoring, the PAC has been the gold standard method in high-risk surgery and critically ill patients, but because of its invasiveness and associated complications, its use has declined. Furthermore, the continuous CO PAC methodology has limited capability to detect rapid changes in CO. Less invasive methods, such as arterial waveform analysis, may perform poorly during severe bleeding and significant changes in vasomotor tone. The oesophageal Doppler is well documented for intra-operative haemodynamic management but has limitations such as user dependency, interference from electric cautery, and distribution of blood flow between the upper and lower part of the body. Consequently, there is a need for reliable, rapidly responding, minimally invasive and feasible method for CO monitoring.

The Fick’s principle is a well-proven gold standard for CO assessment but is not applicable in a clinical setting. However, modifications of Fick’s principle based on CO₂ measurements have been used clinically. These methods measure EPBF which is equal to non-shunt CO and consequently affected by pulmonary shunts. The NICO system (NICO, Novametrix Medical Systems, Wallingford, CT, USA) based on CO₂ rebreathing has been shown to accurately measure and track changes in CO. However, it is semicontinuous, and needs additional devices mounted at the Y-piece. This adds external dead space to the breathing system necessary for the CO₂ alternation. In a recent study, Peyton presented a method based on expiratory holds requiring a 45-s calibration procedure where non-shunt pulmonary capillary blood flow was calculated. After shunt correction CO estimation was possible by continuously following the breath-by-breath change in CO₂ elimination. Peyton showed good accuracy, precision, and concordance when compared with thermodilution. This method needs either a new calibration or a calculation of alveolar ventilation based on an estimation of anatomical dead space following any change in minute ventilation. The calibration step of the Peyton method and the COEPBF method used in the current study, is based on a concept originally described by Gedeon and colleagues. Like the original concept, the COEPBF uses an inspiratory instead of an expiratory pause. This might entail lung recruitment and subsequent reduction of intra-pulmonary shunt fraction. The algorithm for COEPBF calculates EPBF and venous partial pressure of CO₂. This is done by determining the optimal fit of a lung model of CO₂ exchange to the measured COTS.

![Fig 3](https://academic.oup.com/bja/article-abstract/112/5/824/272703)

![Fig 4](https://academic.oup.com/bja/article-abstract/112/5/824/272703)

**Fig 3** Bland–Altman plot for 112 paired CO values obtained using the new capnodynamic method (COEPBF) and the ultrasonic flow probe (CO₂TS) as the reference method during haemodynamic interventions in a porcine model ($n=6–10$). Black dotted lines represent mean difference (bias) and limits of agreement [bias (1.96) SD].

**Fig 4** Four-quadrant plot showing the trending abilities for the capnodynamic method (COEPBF) and thermodilution (COPAC), using the ultrasonic flow probe (COTS) as reference method. Fifty-six paired delta CO values (litre min⁻¹) were generated from measurements before and during each haemodynamic intervention. The correlation coefficients for both test methods are shown in the figure. Data points plotted in one of the two quadrants of agreement were considered concordant. A 15% (0.4 litre min⁻¹) exclusion zone of central data is displayed.
data of flow and expired CO₂, averaged over the 10 most recent breaths. This enables presentation of breath-by-breath values of CO₂PBF without any calibration. During highly unstable conditions with rapid haemodynamic changes, an optimal fit may not be obtained. However, it usually only requires one cycle of 10 breaths to create a new measurement after haemodynamic stabilization.

In the current study, we challenged this method in a wide range of clinically relevant haemodynamic conditions. These interventions included changes in preload, afterload, adrenergic receptor stimulation and hypovolaemic shock and resulted in notable alterations in CO, arterial pressure, and vascular resistance. We used CO₇₅ as the reference method because of its high reliability, rapid response time, and extensive use in experimental CO assessment studies. Owing to its status as a clinical reference method, we also chose to include the PAC for comparisons with both CO₇₅ and CO₂PBF.

The overall consistency for the CO₂PBF with CO₇₅ was high and the bias did not increase in response to haemodynamic alterations when compared with baseline conditions. In fact, the bias was insignificant when CO was increased. When comparing methods to assess CO in humans, a percentage error of 30–45% is considered acceptable with thermodilution as reference method. We applied this concept in an animal model with much lower absolute CO levels, the denominator in the PE equation. As expected, high calculated errors were noted for both CO₂PBF and CO PAC. The importance of the magnitude of the CO value for the calculated PE is reflected by the fact that dobutamine, yielding a two-fold increase in CO, had percentage errors of only 24 and 19%, respectively. Perhaps, more important than preciseness in absolute figures is the capacity to track changes in CO. In the current study, trending was studied by means of significant changes in CO induced by relevant interventions also inducing alterations in vascular resistance. The correlation between CO₂PBF and the reference method was high (r=0.96). Concordance rates, as evaluated by four-quadrant plots and polar plots were high, and mean angular bias gave proof of a reliable trending ability equivalent to the performance of the PAC. In fact, in comparison with several other methods currently accepted as tools for assessment of CO in the clinical setting, these results indicate excellent trending capacity for the CO₂PBF method.

Our study has certain limitations. The CO₂PBF method is based on the pulmonary blood flow participating in gas exchange and might under specific circumstances differ from CO (i.e. pulmonary trunk blood flow). A significant intra-
The breathing pattern, essential for the method, could in theory affect CO by inducing changes in intra-thoracic pressure. However, the pattern is based on 10 variable breaths in cycles that were repeated continuously. In order to minimize potential confounding effects by respiratory-induced circulatory changes, all CO\textsubscript{TS} measurements were averaged over at least one manoeuvre cycle.

In summary, this novel continuous capnodynamic method for CO estimation provides a feasible technology that can be integrated in a ventilator system. The method was evaluated in a wide range of clinically relevant haemodynamic challenges and showed an acceptable mean bias and good trendinig abilities when compared with the reference methods CO\textsubscript{TS} and CO\textsubscript{PAC}. This method may prove to be useful for CO assessment in both perioperative and intensive care settings but needs to be further evaluated in models of pulmonary dysfunction, and most importantly, in clinical studies.

Table 2 Bland–Altman analysis for CO\textsubscript{EPBF} with CO\textsubscript{PAC} as the reference method. CO (litre min\textsuperscript{-1}) according to the clinical reference method pulmonary artery catheter thermodilution (CO\textsubscript{PAC}, and results from Bland–Altman analysis assessing the agreement (bias (LOA); litre min\textsuperscript{-1}) for the capnodynamic method (CO\textsubscript{EPBF}) at baseline and during each haemodynamic intervention. LOA, limits of agreement, n=6–10

<table>
<thead>
<tr>
<th>Event</th>
<th>CO\textsubscript{PAC}, mean (SD)</th>
<th>CO\textsubscript{EPBF}, bias (LOA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>2.5 ± 0.7</td>
<td>0.3 (−0.8–1.4)</td>
</tr>
<tr>
<td>Cavae occlusion</td>
<td>1.5 ± 0.4</td>
<td>0.0 (−0.7–0.7)</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>2.5 ± 0.6</td>
<td>0.2 (−1.0–1.3)</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>2.9 ± 0.9</td>
<td>−0.1 (−1.3–1.0)</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>5.4 ± 0.8</td>
<td>−0.6 (−2.5–1.3)</td>
</tr>
<tr>
<td>Volume load</td>
<td>3.3 ± 0.9</td>
<td>−0.4 (−1.2–0.4)</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>1.9 ± 0.6</td>
<td>−0.2 (−1.0–0.6)</td>
</tr>
</tbody>
</table>

pulmonary shunt induces such a difference. Since all animals had healthy lungs and were normoventilated at a PEEP level of 5 cm H\textsubscript{2}O, it is unlikely that this explains the differences seen in mean bias during the haemodynamic challenges.32

Supplementary material

Supplementary material is available at British Journal of Anaesthesia online.
Authors’ contributions
C.H.S., A.O., and H.B.: study design, data collection and analysis, and drafting of manuscript. M.H. and M.W.: study design, data collection and analysis, and critical revision of manuscript. P.E.: data collection and analysis.

Declaration of interest
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