

ORIGINAL ARTICLE

Comparison between capnodynamic and thermodilution method for cardiac output monitoring during major abdominal surgery

An observational study

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BACKGROUND Cardiac output (CO) monitoring is the basis of goal-directed treatment for major abdominal surgery. A capnodynamic method estimating cardiac output (CO_{EPBF}) by continuously calculating nonshunted pulmonary blood flow has previously shown good agreement and trending ability when evaluated in mechanically ventilated pigs.

OBJECTIVES To compare the performance of the capnodynamic method of CO monitoring with transpulmonary thermodilution (CO_{TPTD}) in patients undergoing major abdominal surgery.

DESIGN Prospective, observational, method comparison study. Simultaneous measurements of CO_{EPBF} and CO_{TPTD} were performed before incision at baseline and before and after increased (+10 cmH₂O) positive end-expiratory pressure (PEEP), activation of epidural anaesthesia and intra-operative events of hypovolemia and low CO. The first 25 patients were ventilated with PEEP 5 cmH₂O (PEEP₅), while in the last 10 patients, lung recruitment followed by individual PEEP adjustment (PEEP_{adj}) was performed before protocol start.

SETTING Karolinska University Hospital, Stockholm, Sweden.

PATIENTS In total, 35 patients (>18 years) scheduled for major abdominal surgery with advanced hemodynamic monitoring were included in the study.

MAIN OUTCOME MEASURES AND ANALYSIS Agreement and trending ability between CO_{EPBF} and CO_{TPTD} at different clinical moments were analysed with Bland–Altman and four quadrant plots.

RESULTS In total, 322 paired values, 227 in PEEP₅ and 95 in PEEP_{adj} were analysed. Respectively, the mean CO_{EPBF} and CO_{TPTD} were 4.5 ± 1.0 and 4.8 ± 1.1 in the PEEP₅ group and 4.9 ± 1.2 and 5.0 ± 1.0 l min⁻¹ in the PEEP_{adj} group. Mean bias (levels of agreement) and percentage error (PE) were -0.2 (-2.2 to 1.7) l min⁻¹ and 41% for the PEEP₅ group and -0.1 (-1.7 to 1.5) l min⁻¹ and 31% in the PEEP_{adj} group. Concordance rates during changes in CO_{EPBF} and CO_{TPTD} were 92% in the PEEP₅ group and 90% in the PEEP_{adj} group.

CONCLUSION CO_{EPBF} provides continuous noninvasive CO estimation with acceptable performance, which improved after lung recruitment and PEEP adjustment, although not interchangeable with CO_{TPTD} . This method may become a tool for continuous intra-operative CO monitoring during general anaesthesia in the future.

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Introduction

Goal-directed treatment based on cardiac output (CO) optimisation, the main determinant of organ oxygen

supply, has been shown to improve postoperative outcomes in high-risk abdominal surgery.^{1–4} In the operating

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theatre, rapid haemodynamic changes are to be expected and their detection depends on reliable continuous haemodynamic monitoring. Ideally, a *CO* monitor should detect changes immediately, independent of the operator, without extra complexity and costly disposables. Monitoring methods and interventions have changed drastically in the last decades, trending towards less invasive and more individualised treatment.

Carbon dioxide (CO_2) elimination can be used to estimate *CO* by calculating the nonshunted blood flow to the alveoli using the differential Fick principle as first described by Gedeon *et al.*⁵ in 1980. By including this principle in a capnodynamic equation, a continuous breath by breath estimation of *CO* (CO_{EPBF}) is accomplished by inducing small changes in the alveolar concentration of CO_2 from continuous variation in alveolar ventilation, automatically carried out by the ventilator. The so-called capnodynamic method has been extensively studied in large animal models, providing reliable, real-time, continuous monitoring under a wide range of both haemodynamic and respiratory conditions.^{6–9} However, as expected, CO_{EPBF} underestimated *CO* at high shunt fractions but in a recent severe lung injury model it unexpectedly overestimated *CO* after lung recruitment and PEEP adjustment.¹⁰ Despite reduced accuracy during these conditions, both precision and trending ability were within acceptable limits.¹⁰ In addition, CO_{EPBF} has been shown to provide stable *CO* monitoring in healthy infants undergoing cleft-lip surgery, and in piglets during hypoxic vasoconstriction.^{11,12}

In this clinical study in patients undergoing major abdominal surgery, our main objective was to compare the performance of the capnodynamic method for measurement of cardiac output with the transpulmonary thermodilution method during stable conditions as well as haemodynamic changes commonly encountered during surgery.

Methods

Ethics

The study was approved by the Stockholm regional ethics committee (Dnr. 2010/1296-31, chairperson A. Markus) on 8 September 2010 and registered with the US National Institutes of Health (clinicaltrials.gov; Identifier: NCT03444545). All included patients gave informed written consent.

Study design and settings

The prospective clinical *CO* comparison study was conducted at the Karolinska University Hospital, Stockholm, Sweden between October 2015 and September 2018.

Participants

The operating schedule was screened the week before planned surgery and eligible patients were contacted during the preoperative visit or by telephone. The long

duration of recruitment was because of lack of availability of investigators who were trained in using these methods. On the basis of historical data and current recommendations,^{13,14} 25 patients older than 18 years undergoing elective major abdominal surgery were included in the study. After primary data analysis, 10 patients were added to the study where a recruitment manoeuvre with PEEP adjustment was included before recording of haemodynamic variables. Exclusion criteria were symptomatic ischaemic heart disease and emphysema. See flow chart (Fig. 1) for details.

Study measurements

An epidural catheter was inserted during light sedation. Anaesthesia was induced and maintained with a target-controlled infusion (TCI) of propofol and complemented with opioid (remifentanyl) infusion at the discretion of the attending anaesthesiologist. Neuromuscular blockade was used to facilitate intubation. All patients received maintenance fluid, either buffered 2.5% glucose solution or Ringer's acetate 1 ml kg h^{-1} . Patients were mechanically ventilated in a volume-controlled mode (SERVO-i, Maquet Critical Care AB, Solna, Sweden), with tidal volumes (V_T) 6 to 8 ml per kg predicted body weight and the respiratory rate adjusted to achieve normocapnia. A mainstream infrared sensor (Capnostat-3, Respirationics Inc, Wallingford, Connecticut, USA) was connected to the endotracheal tube and used to measure the expired CO_2 concentration. Gas flow was measured by the flow sensor incorporated in the ventilator and data transmitted to a laptop computer performing continuous mathematical analysis with a dedicated software written in Matlab (The Mathworks Inc, Natick, Massachusetts, USA). The results were displayed on the laptop screen in real time (see video in the online version, for example, <http://links.lww.com/EJA/A592>).

A central venous catheter was inserted in the internal jugular vein and a thermistor tipped catheter (Pulsio-cath, PV2015L20F or PV2014L08A; Pulsion Medical Systems SE, Feldkirchen, Germany) in either the femoral or axillary artery, depending on the type of surgery and patient position. According to the hospital routines, the need for extra fluid was assessed by oesophageal Doppler monitoring (Cardio Q, ODM; Deltex Medical, Inc., Chichester, UK). The epidural anaesthesia was initiated with a bolus of local anaesthetics as a separate step in the experimental protocol (see details below) and proceeded with a continuous infusion (ropivacaine $20\text{--}25 \text{ mg h}^{-1}$) until the end of surgery. Core temperature was maintained at 36 to 37°C with a forced air warming system.

Calculations and measurements of cardiac output

The capnodynamic method estimates *CO* based on effective pulmonary blood flow calculated by the capnodynamic equation, describing the mole balance of CO_2

Fig. 1 Patient flow chart

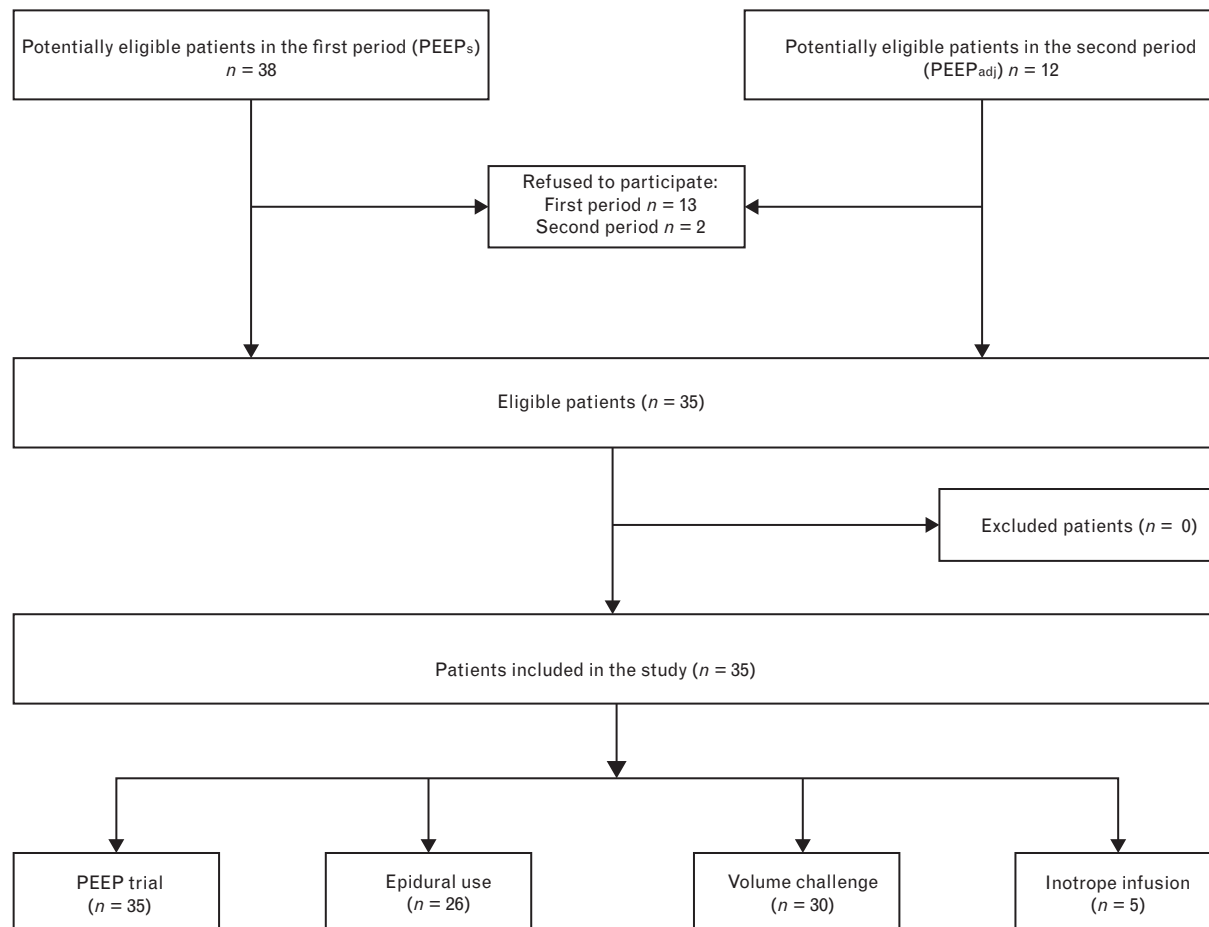


Diagram illustrating the flow of patients in the study.

transport in the lungs and the rate of change of the CO₂ content in the lungs achieved by a superimposed breathing pattern.

$$\begin{aligned} & ELV \times (F_A CO_2^n - F_A CO_2^{n-1}) \\ &= EPBF \times \Delta t^n \times (C_v CO_2 - C_c CO_2^n) - VT CO_2^n \end{aligned}$$

ELV, effective lung volume (l) containing CO₂ at the end of expiration; EPBF, effective pulmonary blood flow (l min⁻¹); *n*, current breath; *n*-1, previous breath; F_ACO₂, alveolar CO₂ fraction; C_vCO₂ mixed venous CO₂ content (l_{gas} l_{blood}⁻¹); C_cCO₂, lung capillary CO₂ content (calculated from F_ACO₂ and haemoglobin concentration); VT CO₂ⁿ, volume (l) of CO₂ eliminated by the current, *n*th, breath; and Δ*t*ⁿ, current breath cycle time (min).

Briefly, short automatic expiratory pauses (4–5 s) are introduced in three consecutive breaths out of every nine breaths, resulting in small differences (0.5–1 kPa) in

the alveolar concentration of CO₂ over a cycle of nine breaths. By least square-error optimisation of the fit between the left and right side of the equation, ELV and EPBF can be calculated from a set of nine equations. Each breath creates a new equation replacing the oldest equation, providing continuous calculations representing the average of the preceding nine breaths (link to video, <http://links.lww.com/EJA/A592>).

Transpulmonary thermodilution (TPTD) was used as a reference for CO (CO_{TPTD}) as a well validated clinical method.¹⁵ In this study, we used the PiCCO₂ monitor (Pulsion Medical Systems SE, Feldkirchen, Germany) where each CO_{TPTD} represents the average of triple thermodilutions with ice cold Ringer's Acetate. Measurements were considered accurate based on visual assessment of the thermodilution curve and if the difference between the three measurements was less than 15%. The CO_{EPBF} values immediately before and after the first and last thermodilution were averaged and compared with the CO_{TPTD} value.

Study protocol

The study protocol was constructed in a pragmatic way with haemodynamic variations commonly observed during surgery. In the first 25 patients (PEEP₅) CO_{EPBF} and CO_{TPTD} measurements were performed before the start of surgery; on three successive occasions at PEEP 5 cmH₂O (baseline, BL₁₋₃), 1 to 2 min after adding 10 cmH₂O to the baseline PEEP, 1–2 min after returning to baseline, before epidural activation (pre-EDA) and 10 to 15 min after epidural activation (EDA) at unchanged PEEP levels. Additional data sets were obtained whenever haemodynamic changes, such as decreases in cardiac output, hypotension or haemorrhage, occurred before and after the corrective measure, that is, fluid or dobutamine infusion were undertaken, as described below. In the second cohort (PEEP_{adj}), which included 10 patients, a recruitment manoeuvre with a stepwise rise and reduction in inspiratory pressure and PEEP was performed before starting the protocol. The level of PEEP resulting in maximum dynamic compliance at the desired V_T was considered the closing pressure. Adjusted individualised PEEP was set at 1–2 cmH₂O higher than the closing pressure and the ventilatory mode was changed back to volume control. The steps in the protocol were identical to those described above, the only difference being the baseline PEEP levels.

Epidural activation was performed at the discretion of the attending anaesthesiologist with a bolus of mepivacaine 20 mg ml⁻¹ (average 7 ml; range 5–8 ml), except two cases where bupivacaine 5 mg ml⁻¹ (5 ml) was used.

Throughout the surgery, the attending anaesthesiologist assigned to the patient routinely assessed if fluid optimisation was indicated based on the institutional algorithm for ODM. If suitable, measurements were performed before and after fluid infusion. In total, 41 fluid boluses were captured in 30 patients. Most commonly 300 ml (range 200–400 ml) of either Plasmadex ($n=17$), Ringer's Acetate ($n=5$), Albumin 5% ($n=4$), combination of Albumin 20% and Ringer's Acetate ($n=6$), erythrocyte concentrate ($n=1$) or plasma ($n=3$). Of those, five measurements were excluded as the second measurement could not be completed during stable conditions. In case of low cardiac output ($CI < 2.5 \text{ l min}^{-1} \text{ m}^2$) despite fluid optimisation, measurements were performed before and after dobutamine infusion ($n=5$), when haemodynamic stability was attained.

The attending anaesthesiologist could, at any time, change the order of the steps in the protocol: i.e. if fluid optimisation or dobutamine was indicated before changing the PEEP or epidural activation.

Data collection

All haemodynamic measurements (heart rate, mean arterial blood pressure, central venous pressure and systemic vascular resistance) were photographed directly from the

monitoring screen at the time of each measurement. Continuous data for CO_{EPBF} was automatically transferred to an excel file after each case. Baseline data collected included preoperative patient characteristics, BMI and ASA class. Other perioperative information recorded in the case report file included the total fluid balance, blood transfusion requirements and duration of surgery. Fluid balances were calculated by subtracting total output (urine output, blood loss, loss from drains and vomitus) from total input (all intravenous fluid administered and parental medications). Third space losses were not included, as they were considered negligible. Mortality at 30 days was recorded.

Statistical analyses

D'Agostino – Pearson omnibus K2 test was used to check for normal distribution. Proportional bias, that is, the spread of bias at different CO levels, was analysed with visual assessment and by a linear regression. Results are presented as mean \pm SD. An unpaired t test was used to analyse difference between the mean values of CO and bias for each group, with Mann–Whitney adjustments whenever normality was violated. Correlation between weight and bias was measured with the Pearson coefficient at the third baseline measurement. A P value of less than 0.05 was considered significant for all analyses. Statistical calculations were performed in Graph Pad Prism (version 6.0 for Windows, Graph Pad Software, La Jolla, California, USA). Calculations of all confidence intervals (CI) were performed in Excel (version 2007). Correction for repeated measurements was not applied as patients were allowed to stabilise during and between each haemodynamic intervention.^{14,16}

Precision

Inherent precision (defined as twice the coefficient of variation ($CV = SD_{\text{method}}/\text{mean } CO_{\text{method}}$)) of $CO_{EPBF\text{exp}}$ and CO_{TPTD} was calculated during the baseline conditions providing six CO_{EPBF} measurements and three triplicate measurements with CO_{TPTD} .¹⁷

Absolute values and percentage error

Bland–Altman methodology was used to measure the mean difference (bias) between the methods and the precision (levels of agreement – LoA) calculated as bias \pm 1.96 \times SD of the bias.^{18–20} Mean percentage error was used to estimate the precision and was calculated as $100\% \times 1.96 \times \text{SD of the bias between the methods, divided by the mean } CO \text{ of the reference method.}^{14,20}$ A priori, CO_{EPBF} was considered interchangeable to CO_{TDTT} if percentage error was less than 30%.²⁰

Trending ability

The agreement in the direction and magnitude of the change was assessed with a four-quadrant plot by dividing the number of data points within the two quadrants of agreement with the total number of data points.²¹ The

Table 1 Baseline characteristics and surgical-related parameters in the different groups

	PEEP ₅	PEEP _{adj}	P value
Age (years)	68 ± 9	63 ± 7	0.14
Women (%)	52	70	0.45
BMI (kg m ⁻²)	26 ± 4	27 ± 4	0.56
ASA	2.3 ± 0.4	2.2 ± 0.4	0.70 ^a
CO _{EPBF} (l min ⁻¹)	4.6 ± 1.0	4.9 ± 1.2	0.006 ^b
CO _{TPTD} (l min ⁻¹)	4.8 ± 1.1	5.0 ± 1.0	0.003 ^b
PEEP BL/intervention (cmH ₂ O)	5/15	8 ± 1.2/18 ± 1.2	0.001 ^b
Duration of surgery (min)	506 ± 188	424 ± 191	0.26
Blood loss (ml)	1816 ± 2261	1990 ± 2183	0.63 ^a
Fluid balance (ml)	2081 ± 1023	1998 ± 791	0.82 ^a
Fluid balance/surgical time (ml h ⁻¹)	72 ± 23	72 ± 54	0.80 ^a
Norepinephrine during protocol (µg kg ⁻¹ min ⁻¹)	0.03 ± 0.02	0.03 ± 0.02	0.53

BL, Baseline; BMI, body mass index; CO_{EPBF}, cardiac output estimated with the capnodynamic method; CO_{TPTD}, cardiac output measured with transpulmonary thermodilution; PEEP, positive-end expiratory pressure; PEEP₅, 25 patients with PEEP 5 cmH₂O at baseline; PEEP_{adj}, ten patients where lung recruitment and PEEP adjustment were performed before start. ^aMann-Whitney test. ^bSignificant difference between groups. Mean (SD).

least significant change (LSC) detected by the reference method, calculated as inherent precision $\times \sqrt{2}$ was used to set the exclusion zone at 15%.¹⁷ Concordance rates of greater than 90% calculated by the four-quadrant plot was considered good.²²

Results

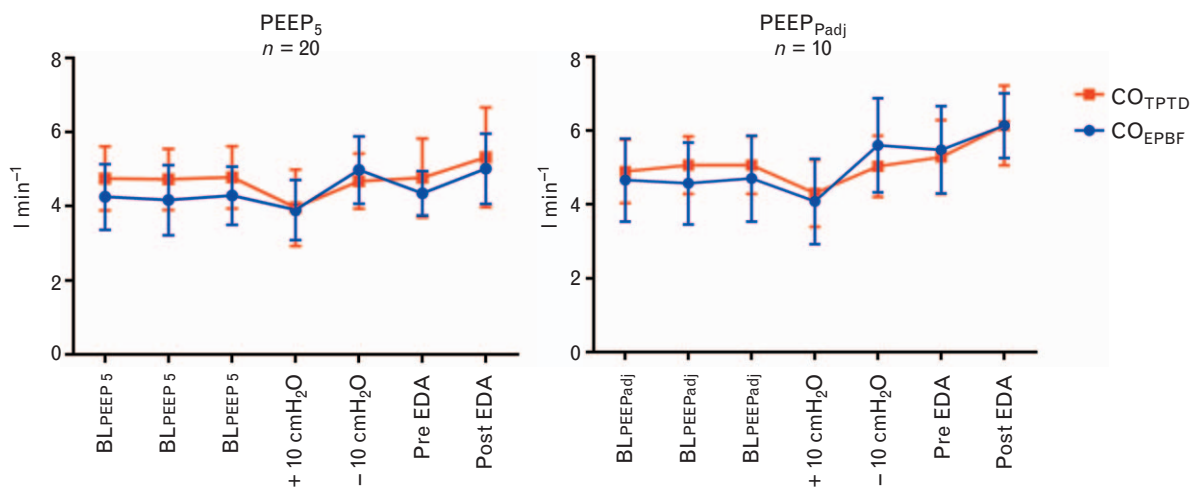
In total, 35 patients finished the protocol, creating 322 paired values, 227 in PEEP₅ and 95 in PEEP_{adj}. There were no differences in patient characteristics between the groups or in factors related to the surgery (Table 1). The calculated inherent precision during baseline conditions was 10 and 11% for CO_{EPBF} and 11 and 9% for CO_{TPTD} in PEEP₅ and PEEP_{adj}, respectively.

Mean CO was 4.5 ± 1.0 and 4.9 ± 1.2 l min⁻¹ for CO_{EPBF} and 4.8 ± 1.1 and 5.0 ± 1.0 l min⁻¹ for CO_{TPTD} in PEEP₅ and PEEP_{adj}, respectively, and changed in accordance

with the different events described (see event lines, Fig. 2). There were no significant differences between the means of CO_{EPBF} and CO_{TPTD} in PEEP₅ ($P=0.06$) and PEEP_{adj} ($P=0.5$), respectively.

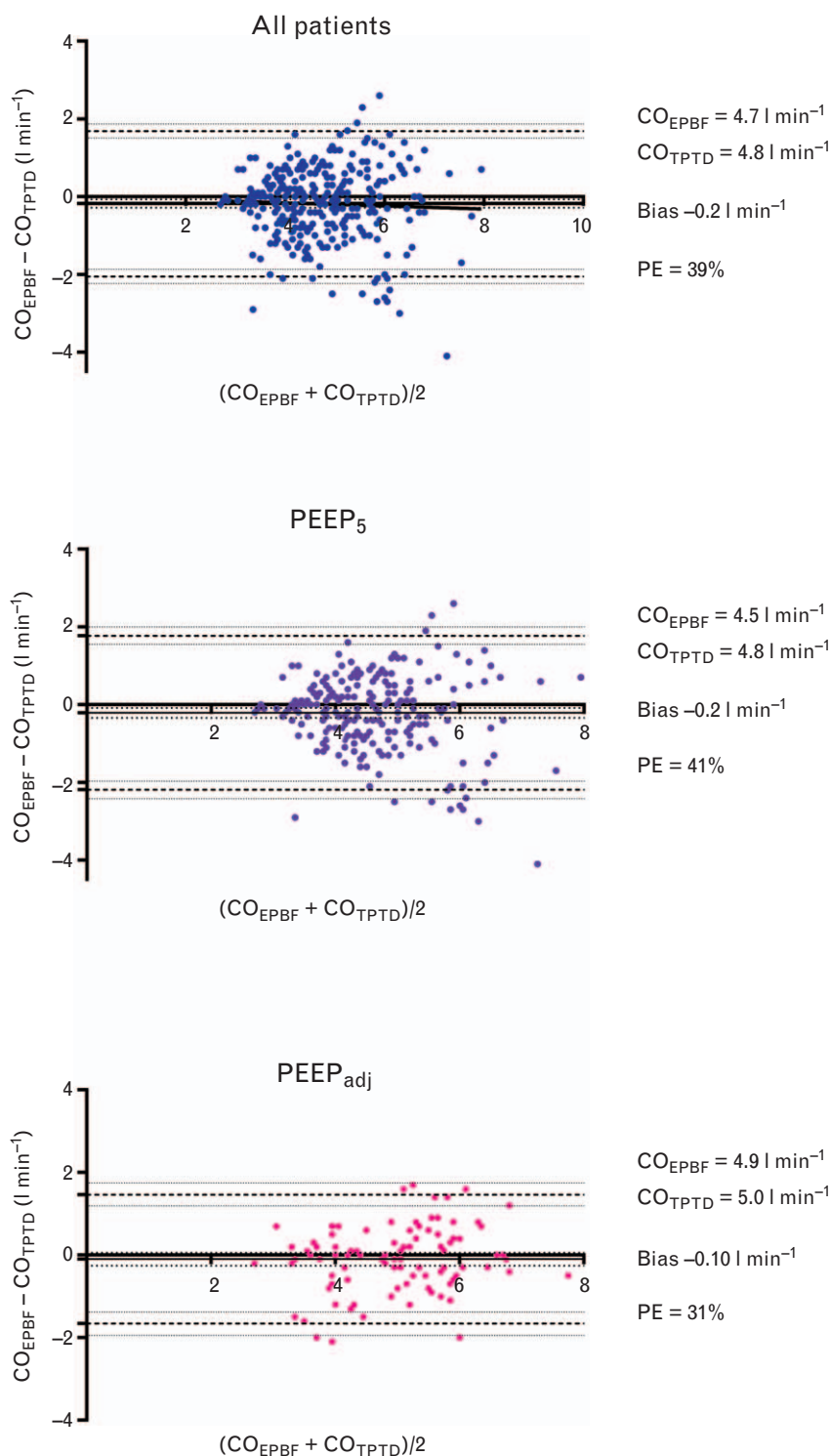
Bias, LoA and percentage error pooled for all patients was -0.21 min⁻¹, -2.1 to 1.7 l min⁻¹ and 39%,² for the PEEP₅ group -0.21 min⁻¹, -2.2 to 1.7 l min⁻¹ and 41%, and finally for the PEEP_{adj} group -0.11 min⁻¹, -1.7 to 1.5 l min⁻¹ and 31% (Fig. 3 and Table 2). Proportional bias between CO_{EPBF} and CO_{TPTD} was not visually observed, although linear regression showed a small but significant deviation from zero in both the PEEP₅ ($P=0.03$) and PEEP_{adj} ($P=0.04$) groups. This means there was a tendency towards a small underestimation of CO in the PEEP₅ group at higher CO and a small underestimation at lower CO and overestimation at higher CO in the PEEP_{adj} group.

Fig. 2 Event line displaying cardiac output measured with the capnodynamic (CO_{EPBF}) and transpulmonary thermodilution (CO_{TPTD}) methods in the PEEP₅ (left) and PEEP_{adj} (right) groups in patients who successfully completed all the steps in the protocol in the correct order.



BL, baseline measurements; PEEP ± 10 cmH₂O, 10 cm H₂O was added to the baseline PEEP; PEEP -10 cmH₂O, PEEP was lowered to the baseline level; pre-EDA, preepidural analgesia post-EDA, 10–15 min after activation of epidural analgesia post-EDA, 10–15 min after activation of epidural analgesia.

Fig. 3 Bland–Altman plots for 322 paired values from all included patients (top – blue dots), 227 paired values in PEEP₅ (middle – purple dots), and 95 paired values in PEEP_{adj} (bottom – pink dots) for CO_{EPBF} versus CO_{TPTD}.



Bias is represented with a solid line and upper and lower LoA with broken lines. CI for respective values are shown with dotted lines. The *x*-axis represents the average of the two methods and the *y*-axis the difference between the methods. CO_{EPBF}, cardiac output estimated with effective pulmonary blood flow; CO_{TPTD}, cardiac output measured with a triplicate of thermodilutions; PE, percentage error.

Table 2 Bland–Altman values for respective groups categorized by condition

Condition	PEEP ₅ (n = 25)			PEEP _{adj} (n = 10)		
	Bias (l min ⁻¹)	LoA (l min ⁻¹)	PE (%)	Bias (l min ⁻¹)	LoA (l min ⁻¹)	PE (%)
BL_1–3 (n = 75/30)	–0.4	–2.2 to 1.5	40	–0.2	–2.1 to 1.7	39
PEEP + 10cmH ₂ O (n = 25/10)	–0.1	–1.5 to 1.3	34	–0.2	–1.3 to 0.9	26
PEEP -10cmH ₂ O (n = 25/10)	0.3	–1.7 to 2.3	41	0.6	–0.8 to 1.9	27
Pre EDA (n = 17/9)	–0.4	–2.3 to 1.5	39	0.2	–1.3 to 1.7	28
EDA (n = 17/9)	–0.3	–2.2 to 1.7	36	0.0	–1.7 to 1.7	28
Event (n = 30/13)	–0.4	–2.3 to 1.6	42	–0.3	–1.4 to 0.9	24
Post event (n = 30/13)	–0.4	–2.5 to 1.8	41	–0.2	–1.3 to 0.8	20
All measurements ^a (n = 227/95)	–0.2	–2.2 to 1.7	41	–0.1	–1.7 to 1.5	31

BL, baseline; EDA, 10–15 min after activation of epidural analgesia; LoA, level of agreement; PE, percentage error; PEEP, positive end expiratory pressure; PEEP₅PEEP₅, the first 25 patients with PEEP 5 cmH₂O at baseline; PEEP_{adj}, 10 patients had lung recruitment and PEEP adjustment performed before start; PEEP +10 cmH₂O, 10 cm H₂O was added to the baseline PEEP; PEEP-10 cmH₂O, PEEP was lowered to the baseline level; pre-EDA, preepidural analgesia; event was defined as hypovolemia or low cardiac output and postevent was a measurement after personalized treatment. ^aIncludes separate simultaneous measurements (n=8 and n=1) not related to the protocol per se.

Concordance with a 15% exclusion zone (0.75 l min⁻¹) was 92 and 90% in PEEP₅ and PEEP_{adj}, respectively, when all induced changes in CO were included (Fig. 4). The concordance was 100% after volume infusion in both groups.

Episodes of haemorrhage and resuscitation were captured with continuous trace CO_{EPBF}, the calibrated pulse contour CO (PCCO) analysis and CO_{TPTD} measurements before and/or after treatment (Fig. 5 shows the trace from one patient).

Data analysis after the first 25 patients (PEEP₅) showed a clear negative proportional bias concerning weight and the Bland–Altman-calculated bias ($P < 0.01$), with a moderate negative correlation (Pearson $r = -0.63$; $P < 0.001$) when tested during the third baseline measurement. This observed underestimation of CO_{EPBF} compared with CO_{TPTD} was primarily caused by two patients with BMI 30 and 34 kg m⁻² and with predominantly an abdominal fat distribution, presumably exerting pressure on the diaphragm causing mismatch in ventilation and perfusion. Their mean bias was -2.1 ± 1.0 and -1.9 ± 0.7 l min⁻¹, with the smallest bias observed during the temporary PEEP increase step. On the basis of our department clinical routine suggesting recruitment manoeuvre with individualised PEEP in overweight patients and the fact that the capnodynamic method has no intrinsic shunt correction, 10 more patients where PEEP was individually adjusted after a recruitment manoeuvre were included in the study. In the PEEP_{adj} group, no proportional bias was detected and no significant correlation was established between weight and bias as opposed to the PEEP₅ group.

One patient developed a small dissection in the axillary artery after removal of the thermistor tipped catheter, causing acute arterial thrombosis partially occluding the peripheral flow. The patient had full recovery after conservative anticoagulation treatment. One patient died on the 12th postoperative day after a sudden cardiac arrest (30 day mortality 2.9%).

Discussion

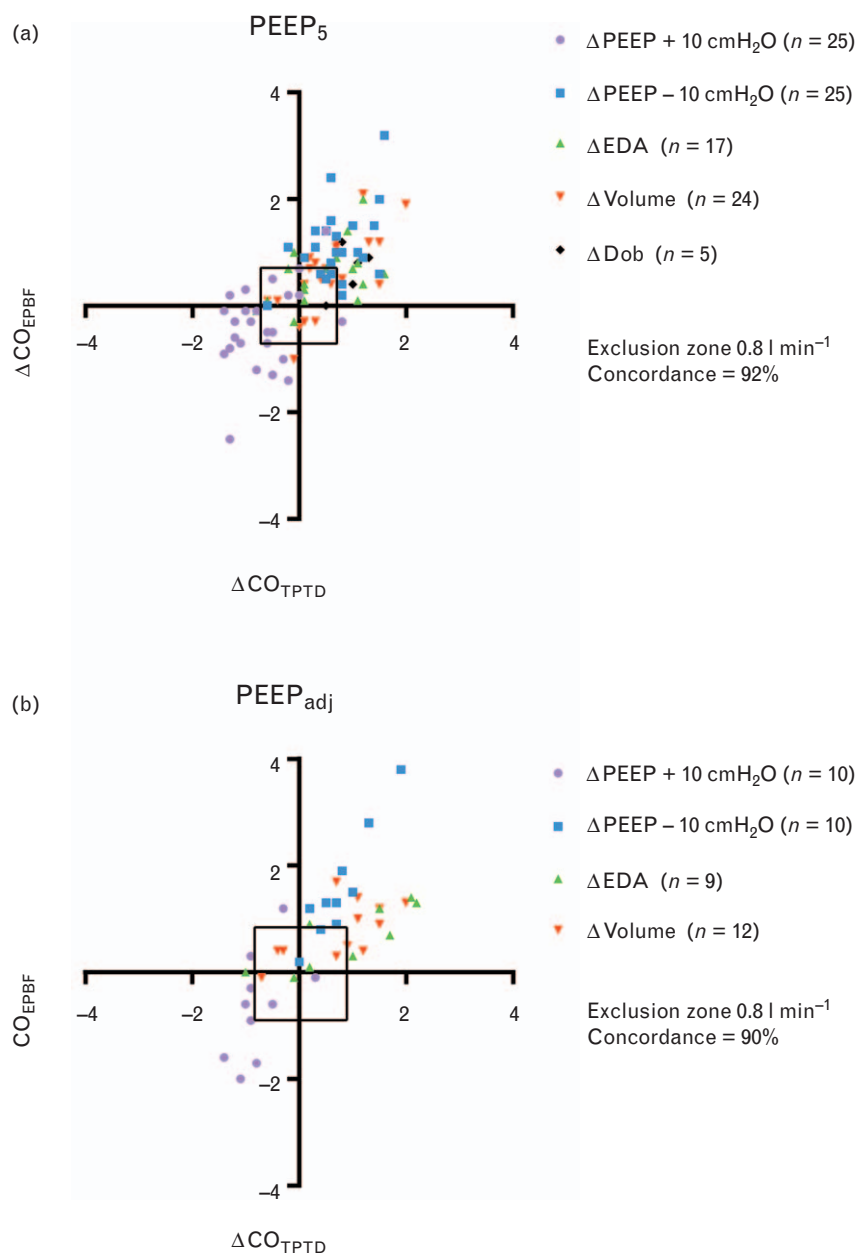
In this study, we have compared the capnodynamic method against transpulmonary thermodilution in cancer patients undergoing major abdominal surgery. Without any shunt correction algorithm included, we obtained a low bias and acceptable precision when tested in the operating theatre. The overall trending ability was good.

Cardiac output estimated with the capnodynamic method, shunt and individual positive end-expiratory pressure adjustment

CO_{EPBF} calculates the nonshunted blood flow to the alveoli, and is therefore, sensitive to pulmonary changes that increase shunt, such as anaesthesia and obesity.²³ The first 25 patients all had PEEP 5 cmH₂O from the start without any lung recruitment. The PEEP step in the protocol included a sudden increase (+10 cmH₂O) in the end expiratory pressure, followed by a swift decrease to baseline level. Without any lung recruitment, the PEEP₅ group had percentage error 41% and showed good concordance (92%) with 15% exclusion zone. During the +PEEP step, bias improved from baseline -0.4 to -0.11 l min⁻¹ and PE from 39 to 34%. A more in-depth analysis revealed a moderate correlation between weight and bias, mainly driven by two patients with the strongest influence on bias; both male with the highest weight (118 and 98 kg) and predominantly abdominal fat, presumably exerting pressure on the diaphragm in the supine position. Interestingly, they both had a rapid rise in CO_{EPBF} when PEEP was raised, implying that they had significant shunt that was reduced. As already suggested by Gedeon in 1985, a capnodynamic method calculating effective pulmonary blood flow could be useful for the clinician to optimise the PEEP for the individual patient with regards to pulmonary perfusion and its effect on venous return, and therefore the oxygen delivery.²⁴

In light of the results in the PEEP₅ group and current anaesthesia practice, we included recruitment and PEEP adjustment before the protocol start in 10 additional

Fig. 4 Four-quadrant plots for PEEP₅ (a) showing 96 paired delta values and PEEP_{adj} (b) showing 41 paired delta values displayed by the capnodynamic method (CO_{EPBF}) and transpulmonary thermodilution (CO_{TPTD}) from all interventions.



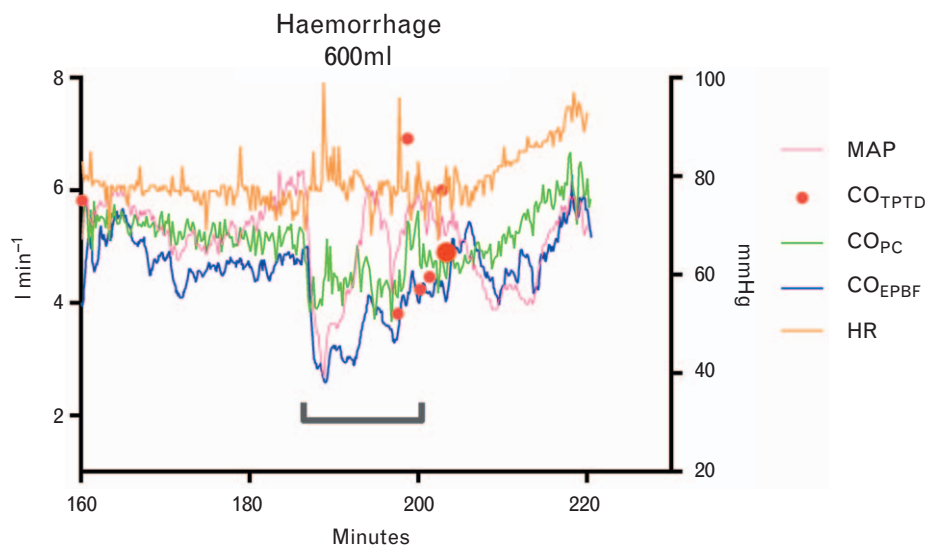
Δ Dob (*black rhomboid*), before and after dobutamine infusion; Δ EDA (green triangle up), before and after epidural activation with 10–15 min apart; Δ PEEP +10 (purple dots), increase in PEEP from 5 to 15 cmH₂O in the PEEP₅ group and +10 cm H₂O in the PEEP_{adj} group; Δ PEEP -10 (blue squares), decrease in PEEP from 15 to 5 cm H₂O in the PEEP₅ group and back to baseline in the PEEP_{adj} group; Δ Volume (orange triangle down), before and after volume bolus.

patients. As expected, the opening of the lungs with a quick compliance-based recruitment manoeuvre and PEEP adjustment improved the overall performance, with a slightly decreased bias of -0.2 to -0.1 l min⁻¹ and percentage error from 41 to 31%, although not statistically significant.

Performance of cardiac output estimated with the capnodynamic method versus other noninvasive cardiac output methods

The current capnodynamic method, had a similar bias and percentage error but higher concordance (92 versus 82.1%) with the same exclusion zone, when compared

Fig. 5 A continuous trace of various haemodynamic parameters from one patient with a sudden blood loss (600 ml) from a large pelvic artery and an ongoing resuscitation with fluids and increase in norepinephrine.



Mean arterial pressure (MAP, pink line) was measured in the femoral artery from the thermistor-tipped catheter. Red dots indicate single transpulmonary thermodilution measurements (CO_{TPTD}) and the largest red dot is the average of the five preceding measurements; CO_{EPBF} (blue line), CO estimated with the capnodynamic method; CO_{PC} (green line), CO derived from the PiCCO pulse contour analysis; HR (orange line), heart rate.

with the second-generation Capnotracking method, developed by Peyton, and recently validated during cardiac and liver surgery.²⁵

The precision of the capnodynamic method compared favourable with other noninvasive CO methods described in meta-analyses, which are notably restricted by large clinical heterogeneity and lack of studies in noncardiac surgery.^{26,27} None of these techniques seems to be close to the 30% cut-off in dynamic situations, as proposed by Critchley and Critchley.²⁰ It should be kept in mind that both the test and reference methods are measuring a moving target especially during haemodynamic changes. Even the performance of a pulmonary artery catheter has not been encouraging, when compared with an aortic flow probe in large animal models.²⁸ This has led researchers to propose more clinically reasonable percentage error limits.²⁹ Some have even suggested abandoning the use of thermodilution methods as a reference because of their lack of both inherent precision and resilience in dynamic situations, and replacing them with a multitude of other minimally or noninvasive methods with a focus on the trending capabilities.^{30,31} This is perhaps more in line with clinical reality where clinicians use CO monitoring more heuristically, reacting to haemodynamic changes as they appear, which requires a good trending ability and a short response time. The capnodynamic method reacted promptly to changes, as seen in the trace from a patient with a sudden haemorrhage. The interventions and observed events resulted in clinically relevant (>15%)

changes in CO in 75% of all measurements and the overall concordance rate between CO_{EPBF} and CO_{TPTD} was 92%. After volume boluses, with or without an increase in norepinephrine dosage, the concordance was 100%, although with variance in the magnitude of change.

Strength and limitations of the capnodynamic method

The capnodynamic method described in the current study has been extensively studied in large animal models. The method continuously computes the mass balance for CO_2 , thus requires no calibration and moreover adapts swiftly to changes in mixed venous CO_2 .^{6-9,11,32} Furthermore, the method also provides assessment of SvO_2 as VO_2 is easily calculated by the respiratory quotient and CvO_2 solved from the Fick equation as the only unknown.³³ A prerequisite for the capnodynamic method described here is a precise synchronisation between gas flow and CO_2 concentration conveyed with a mainstream sensor. The method provides reliable real-time monitoring a few minutes after ventilation is initiated, a valuable feature during emergency surgery and can be used in patients with all types of heart rhythm. Importantly, CO_{EPBF} adds no risk to patient care, as opposed to the invasive methods, as observed in this study.

The capnodynamic method is currently only available as a research module and has several limitations. It can only be used in mechanically ventilated patients with a mainstream volumetric capnometer, although a side-stream sensor has been used with a similar method and

comparable results.²⁵ The method has not yet been validated in obese or respiratory compromised patients. Theoretically, large changes in haemoglobin might affect the accuracy of the method, as it is needed for calculation of the CO₂ content in blood. However, new noninvasive techniques for haemoglobin measurements are emerging and most major surgical patients receive arterial and/or central venous catheters from which blood gases and haemoglobin values can be easily obtained.

Limitations of the study

In this study, we tested the capnodynamic method in the operating theatre in dynamic conditions commonly occurring during major abdominal cancer surgery. Despite good inherent precision and waiting for haemodynamic stability before initiating measurements, approximately 12% of each triplicate varied more than 15%, necessitating additional thermodilution, suggesting that the dynamicity was to some extent affecting the thermodilution measurements. Values for CO_{EPBF} are presented as an average of two time points immediately before and after the TPTD measurements and not over the whole thermodilution period, which would have been more accurate. The PEEP_{adj} group includes only 10 patients, which makes it difficult to draw firm conclusions. Even though lung recruitment had a positive and plausible physiological effect on the performance of the capnodynamic method, more data is needed to confirm these results.

As the studied method and reference method measure different entities and shunt correction was not included, some differences are to be expected.

Conclusion

In patients undergoing high-risk abdominal surgery with standard ventilator settings, the capnodynamic method provided continuous noninvasive CO monitoring with acceptable overall performance which further improved after lung recruitment and individualised PEEP adjustment when compared with transpulmonary thermodilution. Despite that the precision was not interchangeable with transpulmonary thermodilution, the trending ability was good in common clinical situations. The capnodynamic method may become a useful clinical tool for continuous CO monitoring in anaesthetised patients receiving controlled mechanical ventilation. However, larger studies are needed in order to be able to use this method in other clinical settings.

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