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Utility of changes in end-tidal carbon dioxide after volume expansion to assess fluid responsiveness in the operating room: a prospective observational study

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Abstract

Background: From a physiological viewpoint, changes in end-tidal carbon dioxide ($EtCO_2$) could be a simple, noninvasive, and inexpensive way to monitor changes in cardiac index. This study aimed to assess the utility of changes in $EtCO_2$ as a marker of fluid responsiveness after volume expansion in the operating room.
Methods: A prospective observational study was conducted in a tertiary university teaching hospital, from August 2018 to February 2019. A total of 109 non-consecutive, mechanically ventilated adults undergoing neurosurgery in the supine position with cardiac output monitors were included. Patients with major respiratory disease, arrhythmia, or heart failure were excluded. Volume expansion with 250 ml of saline 0.9% was performed over 10 min to maximise cardiac output during surgery, according to current guidelines. A positive fluid challenge was defined as an increase in stroke volume index of more than 10% from baseline. Changes in stroke volume index (monitored using pulse contour analysis) and $EtCO_2$ were recorded before and after infusion.
Results: A total of 242 fluid challenges in 114 patients were performed, of which 26.9% were positive. Changes in $EtCO_2$ > 1.1% induced by infusions had utility for identifying fluid responsiveness, with a sensitivity of 62.9% (95% confidence interval [CI], 62.5–63.3%) and a specificity of 77.8% (95% CI, 77.6–78.1%). The area under the receiver operating characteristic curve for changes in $EtCO_2$ after volume expansion was 0.683 (95% CI, 0.680–0.686).
Conclusions: Changes in $EtCO_2$ induced by rapid infusion of 250 ml saline 0.9% lacked accuracy for identifying fluid responsiveness in mechanically ventilated patients in the operating room.
Clinical trial registration: NCT03635307.

Keywords: cardiac output; end-tidal carbon dioxide; fluid responsiveness; haemodynamic; stroke volume

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Editor's key points

- It is unclear if variation in $EtCO_2$ can be used a marker of fluid responsiveness during intraoperative volume expansion.
- Available studies of $EtCO_2$ mostly focus on intensive care patients or use large volume loading infusions.
- This study focused on the ability of $EtCO_2$ to assess fluid responsiveness after a 250 ml crystalloid volume expansion in the operating room.
- The sensitivity and specificity of $EtCO_2$ to assess fluid responsiveness was low.
- Based on these findings, $EtCO_2$ cannot replace cardiac output measurements to assess haemodynamic responses to a small volume loading dose.

Perioperative haemodynamic optimisation, based on stroke volume (SV) maximisation through rational fluid administration, might contribute to reduced morbidity.[1–3] Hypovolaemia can lead to organ failure through hypoperfusion, whereas hypervolaemia may induce peripheral oedema and cardiac overload.[4–6] Volume expansion only induces an increase in SV in case of cardiac preload dependence, corresponding to the ascending portion of the Frank–Starling curve. Conversely, in cases of preload independence (i.e. the flat portion of the curve) SV no longer increases, but the risk of deleterious effects does.

In the operating room, two strategies can be used to achieve haemodynamic optimisation. A widely used method[7–9] is prediction of volume expansion responsiveness through dynamic indices based on heart–lung interactions, such as pulse pressure variation (PPV) and stroke volume variation (SVV). However, use of these parameters is limited because of the generalisation of protective ventilation with low tidal volume.[10–12] The second strategy consists of titrating volume expansion while monitoring its effects on cardiac output, which has been shown to be reliable and cost-effective.[13,14]

The French Society of Anaesthesiologists (SFAR)[15] and the National Institute for Clinical Excellence[16] recommend haemodynamic optimisation through the monitoring and titration of volume expansion. One such approach relies on an algorithm in which an infusion of 250 ml over 10 min is repeated only if this bolus leads to an increase of more than 10% in SV. Volume expansion is reinstated during surgery if the SV decreases. However, this strategy seems difficult to apply widely because it relies on costly and invasive equipment. Indeed, cardiac output monitoring is still underperformed.[17] Over the past several decades, efforts have been made to develop noninvasive monitors and alternatives to assess cardiac output.

Minimal monitoring of mechanical ventilation under general anaesthesia includes the measurement of end-tidal carbon dioxide ($EtCO_2$). Physiologically, $EtCO_2$ depends on three variables: tissue CO_2 production, pulmonary blood flow (i.e. cardiac output), and alveolar ventilation.[18] Thus, $EtCO_2$ may accurately reflect cardiac output when ventilator parameters and CO_2 production are constant. This correlation has been tested in experimental[19] and clinical[20] studies. Therefore, it is theoretically possible to assess changes in SV after volume expansion according to variation in $EtCO_2$ if there is no major change in heart rate.

Several studies focused on $EtCO_2$ as a metric to evaluate the response to volume expansion, but their results are inconsistent, and most were performed in ICUs[21–24] or based on small surgical patient groups.[25,26] Fluid responsiveness was tested either by passive leg raising or infusion of large volumes of fluids (500 ml colloids or crystalloids). At present, it is not clear if variation in $EtCO_2$ can be considered a marker of fluid responsiveness during volume expansion in the operating room. Thus, the aim of the present study was to determine if changes in $EtCO_2$ index the SV effects of volume expansion with 250 ml saline 0.9% in the operating room.

Methods

Ethics approval

Ethical approval for this study (Ethical Committee No. ID-RCB 2018-A01197-48) was granted by the Comité de Protection des Personnes du Sud-Est IV, France, on May 28, 2018 (Dr D. Perol). Following French law, all patients were provided with written information about the study, and their consent to participate was obtained.[27] This study was registered on Clinicaltrials.gov with the following identifier: NCT03635307.

Patients

Patients undergoing neurosurgery in Bordeaux University Hospital from August 2018 to February 2019 were eligible for inclusion. The follow-up was restricted to the duration of the intervention. Inclusion criteria were as follows: older than 18 yr, scheduled for neurosurgery in the supine position, and equipped with a radial arterial catheter and cardiac output monitor. Exclusion criteria included the presence of chronic obstructive pulmonary disease with a modified Medical Research Council dyspnoea scale $\geq$3, arrhythmia, right or left heart failure (systolic, diastolic, or both), and refusal to participate.

Perioperative management

Standard monitoring included continuous ECG, noninvasive blood pressure, and oxygen saturation measured by pulse oximetry and $EtCO_2$. Total intravenous anaesthesia was achieved by target-controlled infusion of remifentanil and propofol. In cases of arterial hypotension, vasoconstrictors (ephedrine, phenylephrine, or norepinephrine) were permitted. Patients were mechanically ventilated in volume-control mode with a tidal volume of 6–8 ml kg^{-1} of ideal body weight. The ventilatory frequency was adjusted to maintain normocapnia, the inspired oxygen fraction was adjusted to maintain pulse oximetry above 96%, and positive expiratory pressure was set between 6 and 8 cm H_2O.

Haemodynamic monitoring

A radial arterial catheter was connected to a Pulsioflex® monitor (Maquet, Rastatt, Germany) via a specific transducer (ProAQT®; Maquet) for stroke volume index (SVI) monitoring. Cardiac output was determined by pulse contour analysis after initial autocalibration. Haemodynamic measurements included heart rate, systolic, diastolic, mean and pulse arterial pressure, SVI, PPV, and SVV, which were continuously displayed.

Ventilatory monitoring

$EtCO_2$ was monitored by a sensor linked to the intubation tube and connected to the ventilator, which allowed for analysis of expired gas samples and instantaneously displayed $EtCO_2$ in mm Hg. Other ventilatory measurements included tidal volume, ventilatory frequency, inspired oxygen fraction, and positive expiratory pressure. Minute ventilation was obtained by multiplying the tidal volume by the ventilatory frequency.

Study design

Volume expansion was achieved by infusion of 250 ml saline 0.9% over 10 min and was performed at the discretion of the attending physician according to current recommendations. Haemodynamic and ventilatory parameters were collected by the operator before volume expansion and 1 min after the infusion of 250 ml given over 10 min. For the same patient, volume expansion could be repeated if SVI previously increased by more than 10%, or at the discretion of the physician. This observational prospective diagnostic study follows as possible the requirements of the STARD statement (Supplementary Table S1).[28]

Statistical analysis

In total, 104 patients were required to achieve 90% sensitivity and specificity, considering a 70% threshold as relevant, with a power of 80% and an alpha value of 0.05.[29] We had planned to include an additional 10% of patients to be able to deal with data loss or incomplete records. Positive response of volume expansion was defined as an increase of more than 10% in SVI from baseline after infusion of 250 ml of crystalloids.[15,16,30]

Results are expressed as mean (standard deviation, SD) or median [inter-quartile range, IQR, 25–75%] according to the data distribution. Haemodynamic parameters at baseline were compared between positive and negative fluid challenges using the Mann–Whitney *U*-test or Student's *t*-test, as appropriate. Categorical variables were compared using χ^2 or Fisher's tests, as appropriate. Haemodynamic parameters before and after volume expansion were compared using Student's paired *t*-test and Wilcoxon signed-rank test for paired samples. The relationships between changes in SVI and $EtCO_2$ and between changes in CO and $EtCO_2$ were tested using repeated measurement correlation analysis.[31] Receiver operating characteristic (ROC) curves (95% confidence interval [CI]) were drawn for changes in $EtCO_2$, PPV, and SVV according to a variable discrimination threshold, and area under the ROC curve (AUCROC) values were calculated. An AUCROC greater than 0.75 was considered to have good diagnostic value.[29] The cut-off value maximising the Youden index (sensitivity+specificity−1) was chosen. The CIs for the AUCROC and all other diagnostic accuracy parameters were estimated using a bootstrap method. Because multiple fluid challenges could be performed in a single individual, random sampling was performed with replacement of individuals instead of measurements, to preserve the intra-individual correlation structure of the data. Thus, the IC were determined from 1000 estimated parameters for each sample.[32] Comparison between AUCROCs also took into account repeated measurements by using a 2000 bootstrap sample with replacement of individuals to estimate the SD of the difference between AUCROCs.[33] A *P*-value less than 0.05 was considered statistically significant. Statistical analysis was performed using R software.[34]

Table 1 Main characteristics of all patients at baseline (*n*=114) and patients included in analysis (*n*=109). Values are mean and standard deviation or number (%) as appropriate.

Characteristics	All patients	Patients included in analysis
	(*n*=114)	(*n*=109)
Age, yr	56 (13)	56 (14)
Sex, male, *n* (%)	48 (42)	46 (42)
ASA physical status, *n* (%)		
1	23 (20)	22 (20)
2	76 (66)	71 (65)
3	16 (14)	16 (15)
BMI, kg m^{-2}	25 (5)	25 (5)
Weight, kg	73 (16)	73 (16)
Ideal body weight, kg	62 (10)	62 (10)
Comorbidities, *n* (%)		
Stable respiratory disease	14 (12)	13 (12)
Chronic hypertension	35 (31)	35 (32)
Tobacco	24 (21)	22 (20)
Coronary artery disease	4 (4)	4 (4)
Surgery		
Cerebral tumour	77 (68)	74 (68)
Metastasis	10 (8)	9 (8)
Aneurysm clipping	11 (10)	11 (10)
Others	16 (14)	15 (14)

Results

Patient characteristics

A total of 262 volume expansions were performed in 114 non-consecutive patients scheduled for neurosurgery, mainly for brain tumour resection. Among those subjects, five received ephedrine, phenylephrine, or norepinephrine during all

Table 2 Main characteristics before fluid challenge (*n*=242) and number of fluid challenge per patient. Values are mean and standard deviation or median (percentile, 25–75) or number (*n*) as appropriate. Minute ventilation was obtained by multiplying tidal volume and ventilatory frequency.

Characteristics	
Tidal volume (ml)	417 (60)
Tidal volume of ideal body weight (ml kg^{-1})	6.7 (0.7)
Ventilatory frequency (cycles min^{-1})	13 [12–15]
Minute ventilation (L min^{-1})	5.6 (1.3)
PEEP (cm H_2O)	6 [6–6]
Driving pressure (cm H_2O)	7 [3–10]
FiO_2 (%)	40 [40–50]
Remifentanil concentration (ng ml^{-1})	4.0 [3.0–5.0]
Propofol concentration (μg ml^{-1})	4.0 [3.5–5.0]
No. patients receiving	
1 fluid challenge only (*n*)	23 (21)
2 fluid challenges (*n*)	50 (46)
3 fluid challenges (*n*)	28 (26)
4 fluid challenges (*n*)	5 (5)
5 fluid challenges (*n*)	3 (3)

Table 3 Haemodynamic and respiratory variables before and after volume expansion in positive fluid challenges (n=65) and negative fluid challenge (n=177). Values are median (25th to 75th percentile). Positive fluid challenges were defined as an increase in stroke volume index higher than 10% after 250 ml volume expansion. PPV, pulse pressure variation; SVV, stroke volume variation.

	Before volume expansion	After volume expansion	P-value
Heart rate (beats min^{-1})			
Positive fluid challenge	67 [56–76]	62 [56–73]	< 0.001
Negative fluid challenge	66 [60–75]	66 [59–73]	0.080
Mean arterial pressure (mm Hg)			
Positive fluid challenge	66 [59–78]	68 [61–77]	0.113
Negative fluid challenge	69 [63–78]	69 [63–76]	0.390
Stroke volume index (ml m^{-2})			
Positive fluid challenge	35 [30–38]	40 [35–45]	< 0.001
Negative fluid challenge	41 [36–45]	42 [37–46]	< 0.001
$EtCO_2$ (mm Hg)			
Positive fluid challenge	32 [30–35]	33 [31–36]	< 0.001
Negative fluid challenge	33 [31–35]	33 [31–35]	0.059
PPV (%)			
Positive fluid challenge	13 [10–16]	8 [5–12]	< 0.001
Negative fluid challenge	10 [7–15]	9 [6–12]	< 0.001
SVV (%)			
Positive fluid challenge	16 [12–20]	10 [7–14]	< 0.001
Negative fluid challenge	12 [8–17]	10 [7–15]	< 0.001
Minute ventilation (L min^{-1})			
Positive fluid challenge	5.2 [4.5–5.9]	5.2 [4.5–5.9]	1
Negative fluid challenge	5.4 [4.8–6.4]	5.4 [4.8–6.4]	1

volume expansions and were then excluded from analysis. A total of 242 volume expansions including 65 positive fluid challenges (26.9%) and 177 negative fluid challenges (73.1%) were so analysed (Supplementary Fig. S1). The main baseline characteristics of the patients are reported in Table 1, and patients included in analysis did not differ from all patients included. Ventilatory and anaesthetic characteristics before volume expansion are summarised in Table 2. There was no change in the ventilatory settings and in therapeutics (sedation, vasopressors) during the whole study period (Table 3 and Supplementary Table S2).

Changes during volume expansion

Haemodynamic and ventilatory variables, with positive and negative fluid challenges after 250 ml of volume expansion,

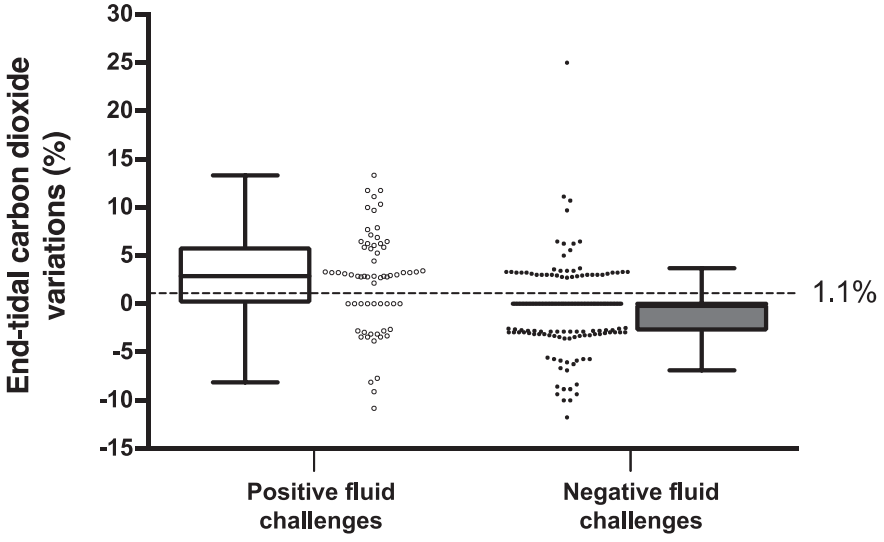

Fig 1. End-tidal carbon dioxide ($EtCO_2$) variations in negative and positive fluid challenge. Individual values with median and inter-quartile of percentage changes in $ETCO_2$ induced by volume expansion. Positive fluid challenges were defined as an increase in stroke volume index by 10% or higher after 250 ml volume expansion given in 10 min and negative fluid challenge if not.

Table 4 Diagnostic performance of PPV, SVV, and change in $EtCO_2$ and cardiac output. AUC, area under the curve; $\Delta EtCO_2$, change in end-tidal carbon dioxide LR+, positive Likelihood ratio; LR−, negative Likelihood ratio; PPV, pulse pressure variation; SVV, stroke volume variation.

	AUC	Best threshold (%)	Best threshold (kPa)	Specificity	Sensitivity	PV+	PV−	LR+	LR−	Youden index	P-value
Diagnostic performance for detecting fluid responsiveness defined by an increase in SV more than 10%											
$\Delta EtCO_2$	0.683 [0.680 −0.686]	1.087	0.066	0.778 [0.776 −0.781]	0.629 [0.625 −0.633]	0.513 [0.510 −0.517]	0.851 [0.849 −0.852]	2.978 [2.907 −3.048]	0.477 [0.472 −0.482]	0.405	ref
PPV	0.637 [0.635 −0.639]	9.500	–	0.507 [0.501 −0.513]	0.786 [0.781 −0.792]	0.372 [0.369 −0.375]	0.871 [0.869 −0.873]	1.629 [1.615 −1.642]	0.410 [0.403 −0.418]	0.279	0.377
SVV	0.649 [0.647 −0.652]	12.500	–	0.537 [0.528 −0.546]	0.731 [0.722 −0.739]	0.374 [0.370 −0.378]	0.856 [0.853 −0.858]	1.705 [1.673 −1.737]	0.75 [0.466 −0.483]	0.246	0.513
Diagnostic performance for detecting fluid responsiveness defined by an increase in CO equal to or more than 10%											
$\Delta EtCO_2$	0.738 [0.735 −0.740]	3.078	0.066	0.845 [0.842 −0.848]	0.587 [0.583 −0.592]	0.569 [0.564 −0.574]	0.859 [0.858 −0.861]	4.160 [4.081 −4.240]	0.487 [0.482 −0.492]	0.419	ref
PPV	0.532 [0.529 −0.535]	21.000	–	0.529 [0.505 −0.553]	0.525 [0.502 −0.549]	0.334 [0.329 −0.338]	0.808 [0.805 −0.811]	1.528 [1.471 −1.585]	0.765 [0.748 −0.781]	0.021	< 0.001
SVV	0.549 [0.546 −0.552]	13.500	–	0.517 [0.494 −0.540]	0.546 [0.523 −0.569]	0.305 [0.302 −0.308]	0.837 [0.835 −0.840]	1.928 [1.798 −2.058]	0.717 [0.699 −0.735]	0.161	0.003

are shown in Table 3. The increase in SVI was higher for positive *vs* negative fluid challenges (14.29% [IQR, 12.19–18.75%] *vs* 3.03% [IQR, 0–6.82%], $P<0.001$). Volume expansion induced a significant decrease in PPV and SVV with positive and negative fluid challenges. The extent of change in $EtCO_2$ differed significantly between positive and negative fluid challenges (2.39% [5.14%] *vs* −0.47% [4.12%], $P<0.001$) (Fig. 1).

No significant differences were found in minute ventilation, or propofol or remifentanil regimen, between negative and positive fluid challenges, before or after volume expansion. There was no difference in the usage of vasoconstrictors between positive and negative fluid challenges, before or after fluid challenge, except that ephedrine was administered more frequently before volume expansion in the positive fluid challenge group (Supplementary Tables S2 and S3).

Changes in $EtCO_2$ and SVI were weakly statistically correlated ($r=0.260$, $P=0.002$). Changes in $EtCO_2$ and cardiac index were better but also weakly statistically correlated ($r=0.454$, $P<0.001$).

Ability of changes in $EtCO_2$ to assess fluid responsiveness

The diagnostic performance of changes in $EtCO_2$ is shown in Table 4. When fluid responsiveness is defined as an increase in SVI by 10% or more, the AUCROC of ΔCO_2 was 0.683 (95% CI, 0.680–0.686) (Fig. 2) and the best threshold was a 1.09%, corresponding to a sensitivity of 62.9% and a specificity of 77.8%. When fluid responsiveness is defined as an increase in cardiac index by 10% or more, the AUCROC of ΔCO_2 was 0.738 (95% CI, 0.735–0.740) (Fig. 2) and the best threshold was a 3.08%, corresponding to a sensitivity of 58.7% and a specificity of 84.5%. AUCROCs were not different regardless of the definition of fluid responsiveness.

Performance of PPV and SVV in predicting fluid responsiveness

The utility of PPV and SVV for indexing fluid responsiveness is described in Table 4. Neither parameter can be considered an accurate diagnostic test.

Discussion

This study suggests that in mechanically ventilated patients in the neurosurgical operating room, variation in $EtCO_2$ is not able to identify accurately the SVI or cardiac index response to volume expansion. Several studies performed in a prehospital setting,[35] operating room, and intensive care have evaluated variations in $EtCO_2$ as a surrogate for changes cardiac output during volume expansion, passive leg raising or increase in PEEP level.[21–24] In intensive care, a strong correlation between changes in cardiac output and changes in $EtCO_2$ after volume expansion has been identified. In 2016, a study demonstrated that a positive response to volume expansion was associated with an increase of at least 2 mm Hg of $EtCO_2$ after passive leg raising in patients undergoing cardiac surgery. The negative predictive value of 86% was encouraging, but the positive predictive value of 54% was low.[25] Another study conducted on 40 patients anaesthetised for major noncardiac procedures, of whom 30% were in a septic state, showed that an increase of more than 2 mm Hg of $EtCO_2$ (i.e. an increase of >5.8%) accurately predicted a

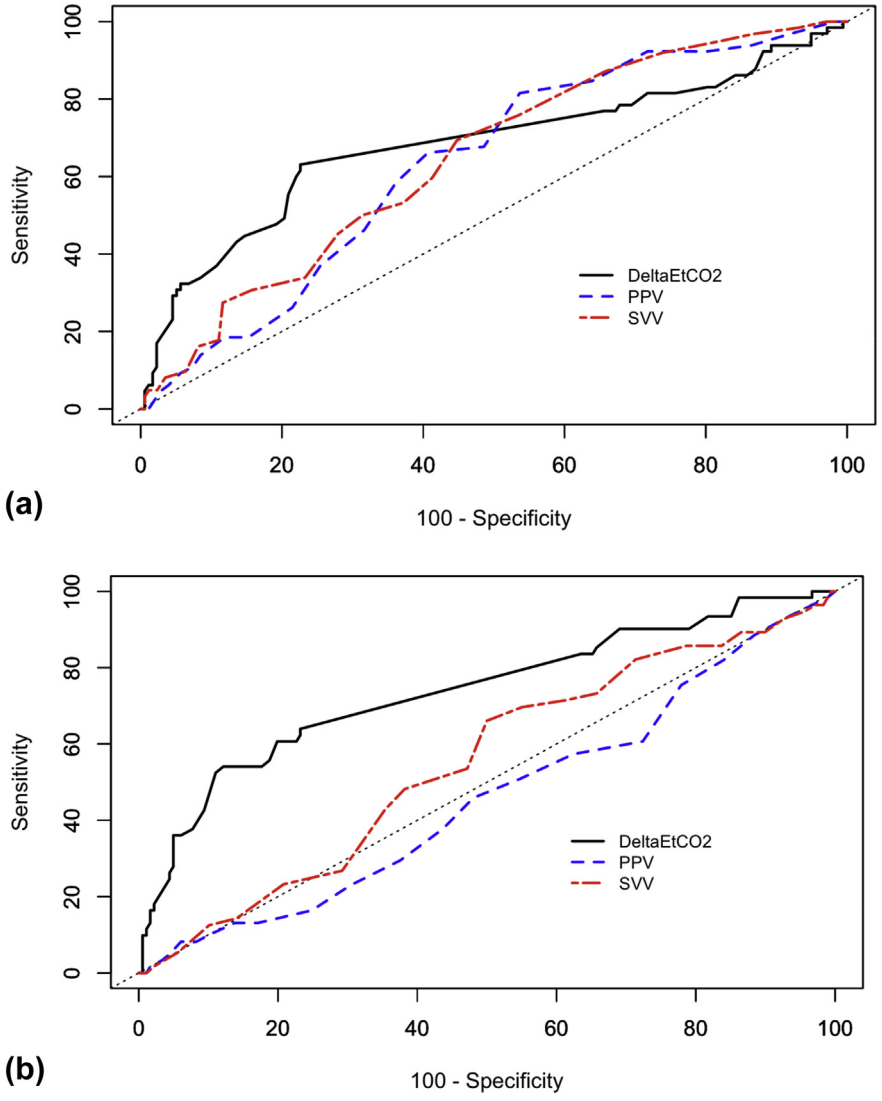

Fig 2. Receiver operating curves generated for changes in end-tidal carbon dioxide ($DeltaEtCO_2$) induced by a 250 ml volume expansion given in 10 min, pulse pressure variation (PPV) and stroke volume variation (SVV) before volume expansion. (a) Fluid responsiveness defined by an increase of more than 10% of stroke volume. (b) Fluid responsiveness defined by an increase equal to or more than 10% of cardiac output.

positive response to a 500 ml colloid volume expansion (AUC=0.80; 95% CI, 0.65–0.96).[26] However, a variation in $EtCO_2$ of less than 5.8% was not useful for distinguishing between responders and non-responders. It should be noted that the responders were probably highly hypovolaemic, having an increase in cardiac output of 32% (IQR, 20–42%). Our study differs in many ways from these previous studies. Most of them were performed in ICU and/or included patients suffering from acute circulatory failure, receiving vasopressors, or both. This is of major importance because the pathophysiological conditions that led to the prescription of volume expansion are not comparable. The objective of haemodynamic optimisation in the operating room is to maximise SV and cardiac output in a patient without haemodynamic failure, whereas fluid challenge done in a patient with acute circulatory failure aims to restore an impaired haemodynamic system. Furthermore, we performed a fluid challenge using 250 ml of crystalloid whereas other studies used a larger amount of fluid (passive leg raising or 500 ml), different fluid (colloids), or both, resulting in different effects on venous return and cardiac output. This may also explain our negative results and the very low best threshold value found for $\Delta EtCO_2$.

In order to be close to the real life and to the conditions of use of the $EtCO_2$, we have chosen to select only one value of $EtCO_2$. This may have resulted in a decrease in the accuracy of the $EtCO_2$ measurement. Tusman and colleagues[36] reported positive results when using VCO_2, which include by definition more values of instantaneous expired CO_2 measurements.

Another factor that could explain our results is that the best threshold value found for $\Delta EtCO_2$ is close to the least significant change of $EtCO_2$. In other words, the variations in $EtCO_2$ that we have found are perhaps too small to be reliably detected.

The present study had several limitations. Firstly, our results apply only to adult patients without arrhythmia, right or left heart failure, or major acute or chronic lung disease, in the supine position and scheduled for neurosurgery. Secondly, we chose to use pulse contour analysis with an initial autocalibration,[37] which, unlike external calibration, may be not effective in cases of vasoplegia. However, recent studies demonstrated that the Pulsioflex monitor was able to detect a small increase in SV during an occlusion test and that the least significant changes of SV and cardiac index were low.[38,39] Thirdly, we did not calculate the least significant change of the $EtCO_2$; this was estimated to be between 1.8% and 3.2% in previous studies,[21,22,26] which corresponds to a variation in the absolute value of $EtCO_2$ of 1–2 mm Hg. This narrow range increases the risk of misclassification of responders and non-responders. Fourthly, most of the fluid challenges were performed after anaesthesia induction to ensure haemodynamic optimisation before starting the surgical procedure. Furthermore, considering the observational nature of our study, the use of vasoconstrictors during anaesthesia was left to the discretion of the physician. This may have influenced the response to volume expansion; however, the only significant difference was in the rate of administration of ephedrine, which was greater for positive *vs* negative fluid challenges. Finally, as the clinician recording $EtCO_2$ and cardiac index was the same, the study was not 'blind'. This can be a source of bias.

In conclusion, we were not able to show utility of $\Delta EtCO_2$ as a marker of variation in the SVI or cardiac index after a volume expansion of 250 ml of crystalloid in mechanically ventilated patients undergoing neurosurgery.

Authors' contributions

Study design: HdC, LlG, KNG, MB
Data analysis: HdC, LlG, MB
Patient recruitment: HdC, JC, LlG, DG, PB, EV, MB
Drafting of the manuscript: HdC, JC, LlG, KNG, MB

Declarations of interest

MB received honoraria from Edwards Lifesciences, Irvine, California, and Pulsion Medical System, Munich, Germany, for lectures. The other authors declare no competing interests.

Presentation

Preliminary data were submitted for eligibility for presentation to a communication session of French Society of Anaesthesia & Critical Care Medicine congress, September 19–21, 2019.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.07.018.

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