Ability of Change in End-Tidal Carbon Dioxide to Assess Fluid Responsiveness After a Volume Expansion of 250 ml of Crystalloid in the Operating Room (REVCO$_2$): A prospective observational study

Running Title: Changes in End-Tidal Carbon Dioxide to assess fluid responsiveness

Hugues de COURSON[1,2], Julie CHAUVET[1], Lisa LE GALL[1], Delphine GEORGES[1], Philippe BOYER[1] , Eric VERCHÈRE[1], Karine NOUETTE-GAULAIN[1,3], Matthieu BIAIS[1,4*]

ADRESS AND AFFILIATION

[1]Bordeaux University Hospital, Department of Anaesthesiology and Critical Care Pellegrin, Bordeaux, France

[2]Université de Bordeaux, Institut National de la Santé et de la Recherche Médicale, UMR 1219, Bordeaux Population Health Research Center, CHU Bordeaux, Bordeaux, France

[3]Institut National de la Santé et de la Recherche Médicale, U12-11, Laboratoire de Maladies Rares: Génétique et Métabolisme, Bordeaux, France

[4]Institut National de la Santé et de la Recherche Médicale, U1034, Biology of Cardiovascular Diseases, Pessac, France

CORRESPONDING AUTHOR

*Pr Matthieu BIAIS, Service d'Anesthésie-Réanimation, Groupe Hospitalier Pellegrin, Place Amélie Raba Léon – 33000 Bordeaux. @ : matthieu.biais@chu-bordeaux.fr Tel : 05 57 82 10 19, ext +33

EDITOR'S KEY POINTS

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

ABSTRACT

Background: From a physiological view, changes in end-tidal carbon dioxide ($EtCO_2$) could be a simple, non-invasive and inexpensive way to monitor changes in cardiac index (CI). This study aimed to assess the utility of changes in $EtCO_2$ as a marker of fluid responsiveness following 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. Hundred nine non-consecutive, mechanically ventilated adults undergoing neurosurgery in the supine position and equipped with cardiac output monitors were included. Patients with major respiratory disease, arrhythmia or heart failure were excluded. Volume expansion with 250 ml of 0.9% saline was performed for 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 (SVI) of more than 10% from baseline. Changes in SVI (monitored using pulse contour analysis) and $EtCO_2$ were recorded before and after infusion.

Results: A total of 242 fluid challenges were performed (26.9% positive challenges). Changes in $EtCO_2$ greater than 1.1% induced by infusions had utility for identifying fluid responsiveness, with a sensitivity of 62.9% (95% CI: 62.5 to 63.3%) and a specificity of 77.8% (95% CI: 77.6 to 78.1%). The area under the receiver operating curve for changes in $EtCO_2$ after volume expansion was 0.683 (95% CI: 0.680 to 0.686).

Conclusions: Changes in $EtCO_2$ induced by rapid infusion of 250 ml 0.9% saline lacked accuracy for identifying fluid responsiveness in mechanically ventilated patients in the operating room.

Clinical registration : <u>NCT03635307</u>

INTRODUCTION

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, while hypervolemia may induce peripheral oedema and cardiac overload.[4–6] Volume expansion only induces an increase in stroke volume 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 predicting volume expansion responsiveness through dynamic indices based on heart-lung interactions, such as pulse pressure variation (PPV) and stroke volume variation (SVV). However, the use of these parameters is limited due to 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 non-invasive 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 following 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 intensive care units.[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 as 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 0.9% saline in the operating room.

METHODS

Ethics approval

Ethical approval for this study (Ethical Committee N° ID-RCB 2018-A01197-48) was granted by the Comité de Protection des Personnes du Sud-Est IV, France, on 28th May, 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]

Trial Registration : This study was registered on Clinicaltrials.gov with 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 years, 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 dyspnea scale ≥ 3, arrhythmia, right or left heart failure (systolic and/or diastolic) and refusal to participate.

Perioperative Management

Standard monitoring included continuous electrocardiogram, non-invasive 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 respiratory rate 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 cmH$_2$0.

Haemodynamic Monitoring

A radial arterial catheter was connected to a Pulsioflex® monitor (Maquet, Rastatt, Germany) via a specific transducer (ProAQT®; Maquet) for 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 mmHg. Other ventilatory measurements included tidal volume, respiratory rate, inspired oxygen fraction and positive expiratory pressure. Minute ventilation was obtained by multiplying the tidal volume by the respiratory rate.

Study Design

Volume expansion was achieved by infusion of 250 ml 0.9% saline 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 in order 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 (SD) or median [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 chi-square 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 1,000 estimated parameters for each sample.[32] Comparison between AUCROCs also took into account repeated measurements by

using 2000 bootstrap sample with replacement of individuals to estimate the standard deviation of the difference between AUCROCs.[33] A *P*-value less than 0.05 was considered to be statistically significant. Statistical analysis was performed using R software.[34]

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, 5 of them received ephedrine, phenylephrine or norepinephrine during all volume expansions and were then excluded from analysis. A total of 242 volume expansion including 65 positive fluid challenges (26.9%) and 177 negative fluid challenges (73.1%) were so analysed (Supplementary Figure 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 prior to 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, are shown in Table 3. The increase in SVI was higher for positive versus 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) %; $P<0.001$) (Figure 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).

Relationship between changes in SVI or changes CI and changes in EtCO$_2$ induced by volume expansion

Changes in EtCO$_2$ and SVI were weakly statistically correlated (r = 0.260, *P*=0.002). Changes in EtCO2 and CI 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 to 0.686) (Figure 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 CI by 10% or more, the AUCROC of ΔCO$_2$ was 0.738 (95% CI: 0.735 to 0.740) (Figure 2) and the best threshold was a 3.08%, corresponding to a sensitivity of 58.7% and a specificity of 84.5%. AUCROC 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 accurately identify the SVI or CI response to volume expansion. Several studies performed in prehospital setting[35], operating room and intensive care have evaluated variations in EtCO2 as a surrogate for changes cardiac output during volume expansion, passive leg raising or increase in positive end-expiratory pressure 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 mmHg 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 non-cardiac procedures, of whom 30% were in a septic state, showed that an increase of more than 2 mmHg of $EtCO_2$ (i.e. an increase of > 5.8%) accurately predicted a positive response to a 500 ml colloid volume expansion (AUC = 0.80, 95% CI: 0.65 to 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 and/or receiving vasopressors. This is of major importance because the pathophysiological conditions that led to the prescription of volume expansion are not comparable. The objective of haemodynamic optimization in the operating room is to maximize stroke volume and cardiac output in a patient without haemodynamic failure, while fluid challenge done in a patient with acute circulatory failure aims to restore an impaired haemodynamic system. Furthermore, we performed a fluid challenge using 250ml of crystalloid whereas other studies used larger amount of fluid (passive leg raising or 500 mL) and/or different fluid (colloids) 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. Tusmann et al. reported positive results when using VCO2 which include by definition more values of instanteous expired CO2 measurements.[36]

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 smalls 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 Pulsioflex monitor was able to detect a small increase in the stroke volume during an occlusion test and that the least significant changes of the SV and CI were low.[38] [39]. Thirdly, we did not calculate the LSC 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 mmHg. 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 versus negative fluid challenges. Finally, as the clinician recording EtCO2 and CI was the same, the study was not "blind". This can be a source of bias.

We conclude that we were not able to demonstrate the utility of $\Delta EtCO_2$ as a marker of variation in the SVI or CI after a volume expansion of 250 ml of crystalloid in mechanically ventilated patients undergoing neurosurgery.

REFERENCES

1.	Benes J, Chytra I, Altmann P, Hluchy M, Kasal E, Svitak R, et al. Intraoperative fluid optimization using stroke volume variation in high risk surgical patients: Results of prospective randomized study. *Crit Care* 2010; **14**

2.	Marik PE. Perioperative hemodynamic optimization: A revised approach. *J Clin Anesth* [Internet] Elsevier Inc.; 2014; **26**: 500–5 Available from: http://dx.doi.org/10.1016/j.jclinane.2014.06.008

3.	Michard F, Biais M. Rational fluid management: Dissecting facts from fiction. *Br J Anaesth* 2012; **108**: 369–71

4.	Bednarczyk JM, Fridfinnson JA, Kumar A, Blanchard L, Rabbani R, Bell D, et al. Incorporating Dynamic Assessment of Fluid Responsiveness into Goal-Directed Therapy: A Systematic Review and Meta-Analysis. *Crit Care Med* 2017; **45**: 1538–45

5.	Bellamy MC. Wet, dry or something else? *Br J Anaesth* 2006; **97**: 755–7

6.	Thacker JKM, Mountford WK, Ernst FR, Krukas MR, Mythen M (Monty) G. Perioperative Fluid Utilization Variability and Association With Outcomes. *Ann Surg* [Internet] 2016; **263**: 502–10 Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00000658-201603000-00013

7.	Michard F, Teboul JL. Predicting fluid responsiveness in ICU patients: A critical analysis of the evidence. *Chest* 2002; **121**: 2000–8

8.	MacDonald N, Ahmad T, Mohr O, Kirk-Bayley J, Moppett I, Hinds CJ, et al. Dynamic preload markers to predict fluid responsiveness during and after major gastrointestinal surgery: An observational substudy of the OPTIMISE trial. *Br J Anaesth* 2015; **114**: 598–604

9.	Benes J, Giglio M, Brienza N, Michard F. The effects of goal-directed fluid therapy based on dynamic parameters on post-surgical outcome: a meta-analysis of randomized controlled trials. *Crit Care* 2014; **18**: 584

10.	Michard F. Changes in Arterial Pressure during Mechanical Ventilation. *Anesthesiology* 2005; 419–28

11.	Futier E, Constantin J-M, Paugam-Burtz C, Pascal J, Eurin M, Neuschwander A, et al. A Trial of Intraoperative Low-Tidal-Volume Ventilation in Abdominal Surgery. *N Engl J Med* 2013; **369**: 428–37

12.	Prove T, Investigators N, Trial C. High versus low positive end-expiratory pressure during general anaesthesia for open abdominal surgery (PROVHILO trial): a multicentre randomised controlled trial. *Lancet* 2014; **384**: 495–503

13.	Pearse RM, Harrison DA, MacDonald N, Gillies MA, Blunt M, Ackland G, et al. Effect of a Perioperative, Cardiac Output–Guided Hemodynamic Therapy Algorithm on Outcomes Following Major Gastrointestinal Surgery. *Jama* 2014; **311**: 2181

14.	Hamilton MA, Cecconi M, Rhodes A. A systematic review and meta-analysis on the use of preemptive hemodynamic intervention to improve postoperative outcomes in moderate and high-risk surgical patients. *Anesth Analg* 2011; **112**: 1392–402

15. Vallet B, Blanloeil Y, Cholley B, Orliaguet G, Pierre S, Tavernier B, et al. Guidelines for perioperative haemodynamic Stratégie du remplissage vasculaire périopératoire. *Ann Fr Anesth Reanim* 2013; **32**: e151–8

16. Guidance N medical technology. CardioQ-ODM oesophageal doppler monitor. *NHS Natl Inst Heal Clin Excell* 2011;

17. Cannesson M, Pestel G, Ricks C, Hoeft A, Perel A. Hemodynamic monitoring and management in patients undergoing high risk surgery: a survey among North American and European anesthesiologists. *Crit Care* 2011; **15**: R197

18. Anderson CT, Breen PH. Carbon dioxide kinetics and capnography during critical care. *Crit Care* 2000; **4**: 207–15

19. Ornato JP, Garnett AR, Glauser FL. Relationship between cardiac output and the end-trial carbon dioxide tension. *Ann Emerg Med* 1990; **19**: 1104–6

20. Shibutani K, Muraoka M, Shirasaki S, Kubal K, Sanchala VT, Gupte P. Do Changes in End-Tidal Pco, Quantitatively Reflect Changes in Cardiac Output? *Anesth Analg* 1994; **79**: 829–33

21. Monge García MI, Cano AG, Romero MG, Pintado RM, Madueño VP, Díaz Monrové JC. Non-invasive assessment of fluid responsiveness by changes in partial end-tidal CO_2 pressure during a passive leg-raising maneuver. *Ann Intensive Care* 2012; **2**: 2–9

22. Monnet X, Bataille A, Magalhaes E, Barrois J, Le Corre M, Gosset C, et al. End-tidal carbon dioxide is better than arterial pressure for predicting volume responsiveness by the passive leg raising test. *Intensive Care Med* 2013; **39**: 93–100

23. Young A, Marik PE, Sibole S, Grooms D, Levitov A. Changes in end-tidal carbon dioxide and volumetric carbon dioxide as predictors of volume responsiveness in hemodynamically unstable patients. *J Cardiothorac Vasc Anesth* 2013; **27**: 681–4

24. Lakhal K, Nay MA, Kamel T, Lortat-Jacob B, Ehrmann S, Rozec B, et al. Change in end-tidal carbon dioxide outperforms other surrogates for change in cardiac output during fluid challenge. *Br J Anaesth* 2017; **118**: 355–62

25. Toupin F, Clairoux A, Deschamps A, Lebon J-S, Lamarche Y, Lambert J, et al. Assessment of fluid responsiveness with end-tidal carbon dioxide using a simplified passive leg raising maneuver: a prospective observational study. *Can J Anesth Can d'anesthésie* 2016; **63**: 1033–41

26. Jacquet-Lagrèze M, Baudin F, David JS, Fellahi JL, Hu PB, Lilot M, et al. End-tidal carbon dioxide variation after a 100- and a 500-ml fluid challenge to assess fluid responsiveness. *Ann Intensive Care* Springer Paris; 2016; **6**

27. Toulouse E, Masseguin C, Lafont B, McGurk G, Harbonn A, A Roberts J, et al. French legal approach to clinical research. *Anaesth Crit Care Pain Med*; 2018; **37**: 607–14

28. Cohen JF, Korevaar DA, Altman DG, Bruns DE, Gatsonis CA, Hooft L, et al. STARD 2015 guidelines for reporting diagnostic accuracy studies: Explanation and elaboration. *BMJ Open* 2016; **6**: 1–17

29. Ray P, Ph D, Manach Y Le, Riou B, Ph D, Houle TT, et al. Statistical Evaluation of a Biomarker. *Anesthesiology* 2010; **112**: 1023–40

30. Meng L, Heerdt PM. Perioperative goal-directed haemodynamic therapy based on flow parameters: a concept in evolution. *Br J Anaesth* Elsevier; 2016; **117**: iii3–17

31. Bakdash JZ, Marusich LR. Repeated measures correlation. *Front Psychol* 2017; **8**: 1–13

32. Carpenter J, Bithell J. Bootstrap confidence intervals : when , which , what ? A practical guide for medical statisticians. *Stat Med* 2000; **19**: 1141–64

33. Turck N, Vutskits L, Sanchez-Pena P, Robin X, Hainard A, Gex-Fabry M, et al. pROC: an open-source package for R and S+ to analyze and compare ROC curves. *BMC Bioinformatics* 2011; **8**: 12–77

34. R Core Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.

35. Soar J, Nolan JP, Böttiger BW, Perkins GD, Lott C, Carli P, et al. European Resuscitation Council Guidelines for Resuscitation 2015 Section 3. Adult advanced life support on behalf of the Adult advanced life support section Collaborators 1. *Resuscitation* 2015; **95**: 100–47

36. Tusman G, Groisman I, Maidana GA, Scandurra A, Arca JM, Bohm SH, et al. The Sensitivity and Specificity of Pulmonary Carbon Dioxide Elimination for Noninvasive Assessment of Fluid Responsiveness. *Anesth Analg* 2016; **122**: 1404–11

37. Monnet X, Vaquer S, Anguel N, Jozwiak M, Cipriani F, Richard C, et al. Comparison of pulse contour analysis by Pulsioflex and Vigileo to measure and track changes of cardiac output in critically ill patients. 2015; **114**: 235–43

38. Biais M, Larghi M, Henriot J, De Courson H, Sesay M, Nouette-Gaulain K. End-expiratory occlusion test predicts fluid responsiveness in patients with protective ventilation in the operating room. *Anesth Analg* 2017;

39. de Courson H, Ferrer L, Cane G, Verchère E, Sesay M, Nouette-Gaulain K, et al. Evaluation of least significant changes of pulse contour analysis-derived parameters. *Ann Intensive Care* 2019; **9**

Table 1. Main Characteristics of all patients at baseline (*n*=114) and patients included in analysis (*n*=109).

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, %)		
- I	23 (20)	22 (20)
- II	76 (66)	71 (65)
- III	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)

Values are mean ± SD or number (*%*) as appropriate.

ASA = American Society of Anaesthesiologist; BMI = body mass index.

Table 2. Main Characteristics prior to fluid challenge (*n*=242) and number of fluid challenge per patients

Characteristics	
Tidal volume (ml)	417 (60)
Tidal volume of ideal body weight (ml kg^{-1})	6.7 (0.7)
Respiratory rate (cycles min^{-1})	13 [12-15]
Minute ventilation (L min^{-1})	5.6 (1.3)
Positive end-expiratory pressure (cmH$_2$0)	6 [6-6]
Driving pressure (cmH$_2$0)	7 [3-10]
FiO$_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)

Values are mean ± SD or median (percentile, 25–75) or number (n) as appropriate. Minute Ventilation obtained by multiplying tidal volume and respiratory rate.

Table 3. Haemodynamic and Respiratory Variables before and after Volume Expansion in Positive Fluid Challenges (*n*=65) and Negative Fluid Challenge (*n*=177)

	Before VE	After VE	*P* Value
Heart Rate, beats per minute			
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, mmHg			
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$_2$, mmHg			
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

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. VE = Volume expansion; PPV= pulse pressure variation; SVV= stroke volume variation

Table 4: Diagnostic Performance of PPV, SVV and change in EtCO$_2$ and cardiac output.

	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%							
ΔEtCO$_2$	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 or more than 10%							
ΔEtCO$_2$	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

Figure Legends

Figure 1: End-tidal carbon dioxide (EtCO$_2$) variations in negative and positive fluid challenge.

Individual values with median and interquartile 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.

Figure 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) prior to volume expansion. a fluid responsiveness defined by an increase of more than 10% of stroke volume. b fluid responsiveness defined by an increase equal or more than 10% of cardiac output.
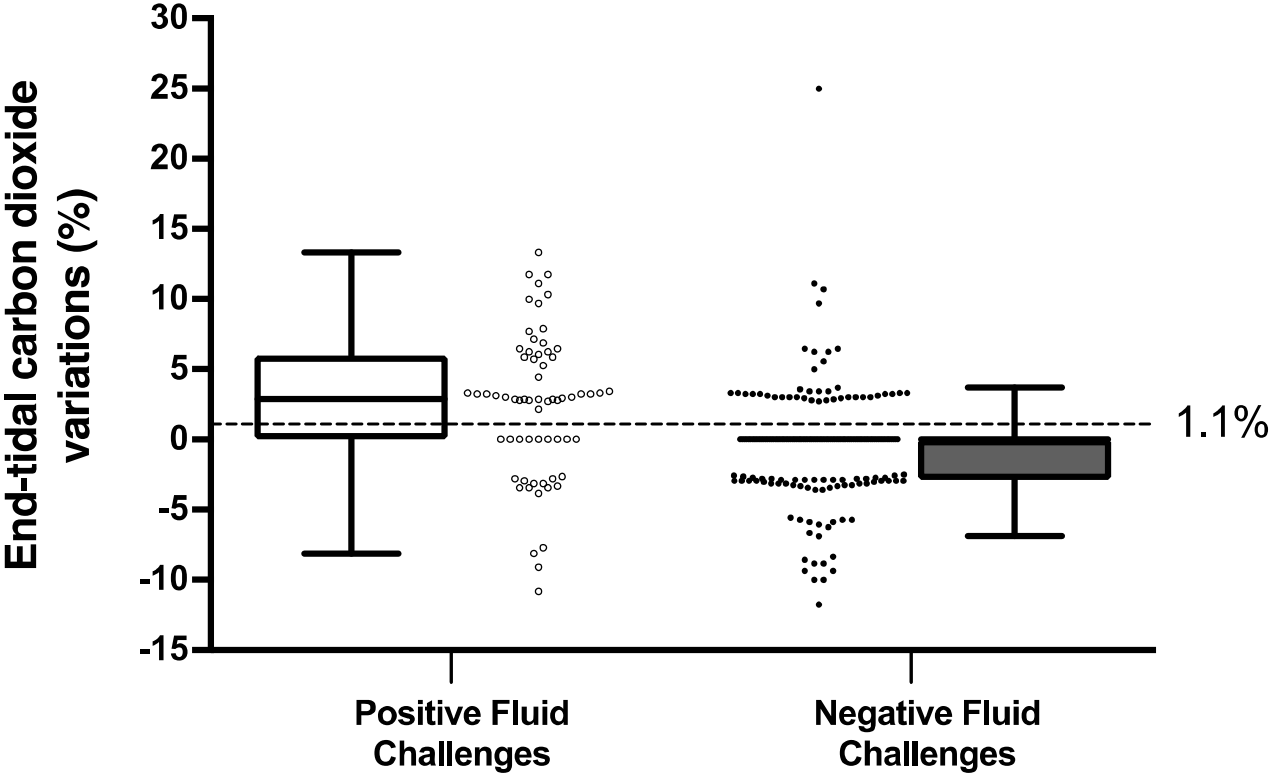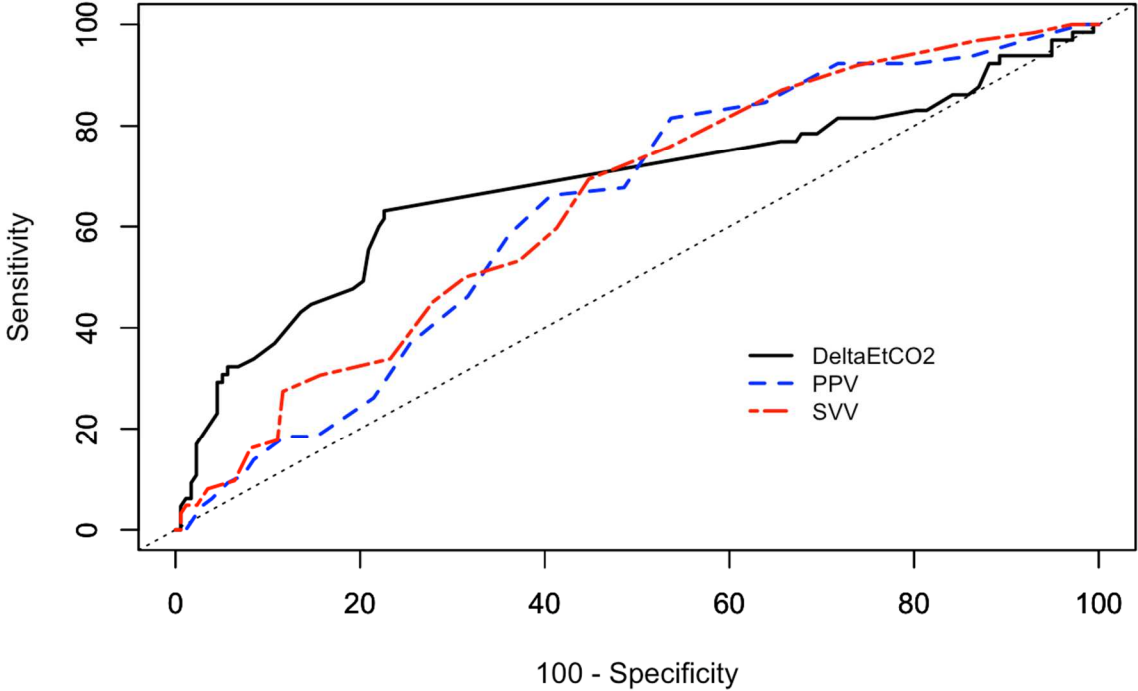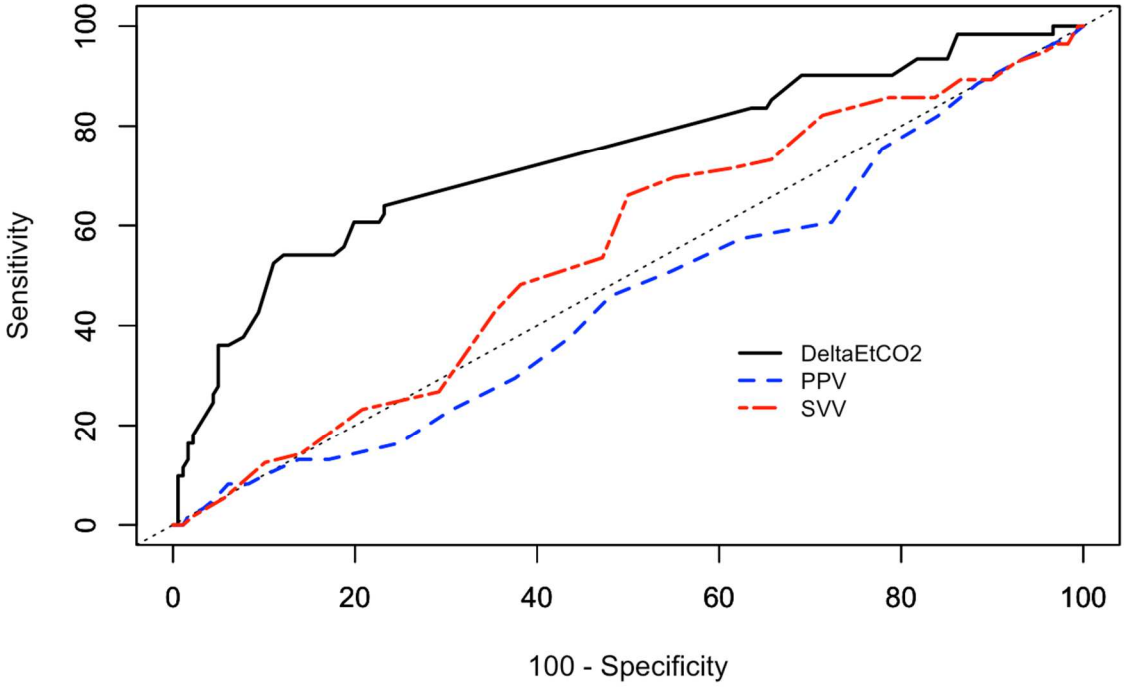
Figure 1.

Figure 2.

a.

b.