BJA

*British Journal of Anaesthesia*, 118 (3): 355–62 (2017)

**doi: 10.1093/bja/aew478**
Cardiovascular

CARDIOVASCULAR

# Change in end-tidal carbon dioxide outperforms other surrogates for change in cardiac output during fluid challenge

K. Lakhal[1,*], M. A. Nay[2], T. Kamel[3], B. Lortat-Jacob[4], S. Ehrmann[2], B. Rozec[1] and T. Boulain[3]

[1]Réanimation chirurgicale polyvalente, service d'anesthésie-réanimation, Hôpital Laënnec, Centre Hospitalier Universitaire, Nantes, France, [2]Service de réanimation polyvalente, CHRU de Tours, Tours, France, [3]Service de réanimation médicale, Hôpital La Source, centre hospitalier régional, avenue de l'Hôpital, Orléans, France and [4]Réanimation chirurgicale polyvalente, service d'anesthésie-réanimation, Hôpital Bichat-Claude Bernard, assistance publique-hôpitaux de Paris, France

*Corresponding author. E-mail: lakhal_karim@yahoo.fr

## Abstract

**Background.** During fluid challenge, volume expansion (VE)-induced increase in cardiac output ($\Delta_{VE}CO$) is seldom measured.
**Methods.** In patients with shock undergoing strictly controlled mechanical ventilation and receiving VE, we assessed minimally invasive surrogates for $\Delta_{VE}CO$ (by transthoracic echocardiography): fluid-induced increases in end-tidal carbon dioxide ($\Delta_{VE}E'_{CO_2}$); pulse ($\Delta_{VE}PP$), systolic ($\Delta_{VE}SBP$), and mean systemic blood pressure ($\Delta_{VE}MBP$); and femoral artery Doppler flow ($\Delta_{VE}FemFlow$). In the absence of arrhythmia, fluid-induced decrease in heart rate ($\Delta_{VE}HR$) and in pulse pressure respiratory variation ($\Delta_{VE}PPV$) were also evaluated. Areas under the receiver operating characteristic curves ($AUC_{ROC}$s) reflect the ability to identify a response to VE ($\Delta_{VE}CO \geq 15\%$).
**Results.** In 86 patients, $\Delta_{VE}E'_{CO_2}$ had an $AUC_{ROC}$=0.82 [interquartile range 0.73–0.90], significantly higher than the $AUC_{ROC}$ for $\Delta_{VE}PP$, $\Delta_{VE}SBP$, $\Delta_{VE}MBP$, and $\Delta_{VE}FemFlow$ ($AUC_{ROC}$=0.61–0.65, all $P<0.05$). A value of $\Delta_{VE}E'_{CO_2}$ >1 mm Hg (>0.13 kPa) had good positive (5.0 [2.6–9.8]) and fair negative (0.29 [0.2–0.5]) likelihood ratios. The 16 patients with arrhythmia had similar relationships between $\Delta_{VE}E'_{CO_2}$ and $\Delta_{VE}CO$ to patients with regular rhythm ($r^2$=0.23 in both subgroups). In 60 patients with no arrhythmia, $\Delta_{VE}E'_{CO_2}$ ($AUC_{ROC}$=0.84 [0.72–0.92]) outperformed $\Delta_{VE}HR$ ($AUC_{ROC}$=0.52 [0.39–0.66], $P<0.05$) and tended to outperform $\Delta_{VE}PPV$ ($AUC_{ROC}$=0.73 [0.60–0.84], $P$=0.21). In the 45 patients with no arrhythmia and receiving ventilation with tidal volume <8 ml kg$^{-1}$, $\Delta_{VE}E'_{CO_2}$ performed better than $\Delta_{VE}PPV$, with $AUC_{ROC}$=0.86 [0.72–0.95] *vs* 0.66 [0.49–0.80], $P$=0.02.
**Conclusions.** $\Delta_{VE}E'_{CO_2}$ outperformed $\Delta_{VE}PP$, $\Delta_{VE}SBP$, $\Delta_{VE}MBP$, $\Delta_{VE}FemFlow$, and $\Delta_{VE}HR$ and, during protective ventilation, arrhythmia, or both, it also outperformed $\Delta_{VE}PPV$. A value of $\Delta_{VE}E'_{CO_2}$ >1 mm Hg (>0.13 kPa) indicated a likely response to VE.

**Key words:** arterial pressure/physiology; blood pressure determination; capnography; echocardiography, doppler; $E'_{CO_2}$; fluid therapy; heart rate; hypovolaemia; pulse pressure variation; intermittent positive-pressure ventilation; ultrasonography, doppler

**Editorial decision:** December 23, 2016; **Accepted:** December 29, 2016

### Editor's key points

- Volume expansion is used to improve cardiac filling and output, but changes in cardiac output are infrequently measured owing to costs, invasiveness, and poor reliability of available monitors.
- Change in end-tidal $CO_2$ was evaluated as a non-invasive surrogate measure of cardiac output in mechanically ventilated intensive care unit patients and compared with other surrogate measures.
- Change in end-tidal $CO_2$ outperformed other minimally invasive indices of fluid responsiveness in mechanically ventilated patients with shock.

During acute circulatory failure, volume expansion (VE) is often the first-line therapy[1] to increase cardiac output (CO). But either insufficient[2] or overzealous VE[3] can negatively impact patient outcome. Therefore, rational administration of fluids requires reliable identification of patients in whom VE genuinely increases CO. Prediction of fluid responsiveness is not always possible,[4 5] and most intensivists opt for administering VE and assessing its effects.[1 6] This fluid challenge strategy requires ensuring that CO has genuinely increased before considering further VE.[7 8] However, CO measurements are seldom used to guide VE.[1 6] Indeed, the use of CO measuring devices is usually limited by their cost, an unfavourable risk–benefit balance (for indwelling devices), the lack of reliability of some non-invasive devices for tracking changes in CO, the lack of expertise of some users, and pathophysiological barriers.[9] As surrogates for VE-induced increases in CO ($\Delta_{VE}CO$), indices such as increases in systolic, mean, and pulse systemic arterial blood pressure ($\Delta_{VE}SBP$, $\Delta_{VE}MBP$, and $\Delta_{VE}PP$, respectively) or decreases in heart rate ($\Delta_{VE}HR$) are often used,[1] but poorly reflect the CO response to VE.[10 11]

The VE-induced change in end-tidal carbon dioxide ($\Delta_{VE}E'_{CO_2}$) could be a surrogate for $\Delta_{VE}CO$. The amount of exhaled carbon dioxide ($CO_2$) depends on $CO_2$ production by the body, its delivery by pulmonary blood flow (CO), and its elimination by alveolar ventilation.[12] If during VE alveolar ventilation is kept unchanged, as during fully controlled ventilation, and if $CO_2$ production is relatively constant, then $\Delta_{VE}E'_{CO_2}$ would reflect $\Delta_{VE}CO$.[13 14] Contrary to indices and devices using beat-to-beat analysis, $\Delta_{VE}E'_{CO_2}$ should not be limited by cardiac arrhythmias. Doppler measurement of VE-induced increases in femoral artery flow ($\Delta_{VE}FemFlow$) could also be appealing;[15] arterial Doppler is a non-invasive, easily learned technique,[16] not limited by poor transthoracic insonation, and measures a flow rather than a pressure. In patients with an arterial catheter, pulse pressure respiratory variation (PPV) was initially proposed for prediction of fluid responsiveness rather than for the assessment of the effects of a fluid challenge.[17] Nonetheless, VE-induced decreases in PPV ($\Delta_{VE}PPV$) might be helpful in the absence of inspiratory efforts or arrhythmias.[4]

These indices ($\Delta_{VE}E'_{CO_2}$, $\Delta_{VE}FemFlow$, and $\Delta_{VE}PPV$) have rarely been evaluated to assess fluid responsiveness and have never been compared. We compared $\Delta_{VE}E'_{CO_2}$, $\Delta_{VE}FemFlow$, $\Delta_{VE}SBP$, $\Delta_{VE}MBP$, $\Delta_{VE}PP$, and when applicable, $\Delta_{VE}PPV$ and $\Delta_{VE}HR$, as surrogates for $\Delta_{VE}CO$ to to identify intensive care unit patients who have responded to VE in mechanically ventilated intensive care unit (ICU) patients.

## Methods

### Ethics

The ethics board of the French Intensive Care Society (SRLF 13-14) approved the study design and waived the need for prior and written consent because the study procedures fulfilled the criteria of a non-interventional study as defined by French law.[18] Patients' next of kin and the patients themselves (if they regained capacity) were informed of their right to refuse use of the data. The French Advisory Board on Medical Research Data Processing (CCTIRS, 14-167) and the French Personal Data Protection Authority (CNIL, DR-2015-215) also approved the study design.[19]

### Setting

Patients from three French ICUs were included: the surgical ICU of Laënnec University Hospital, Nantes, medical ICU of Tours University Hospital, and medical ICU of Orléans Hospital.

### Patients

Adult patients were included in this prospective study if they met the following criteria: (i) they already had an arterial catheter; (ii) they were receiving strictly controlled mechanical ventilation; (iii) their systemic arterial blood pressure (BP) was stable throughout 5 min [no change in vasoactive drug dosage and no significant (>10%) variation in mean BP]; (iv) the attending physician prescribed VE; and (v) at least one of the following criteria suggested circulatory shock:[20] hypotension (invasive systolic BP <90 mm Hg, mean BP <65 mm Hg, or both), oliguria (<0.5 ml $kg^{-1}$ $h^{-1}$) considered to be related to circulatory failure, arterial lactate >2.5 mmol $litre^{-1}$, skin mottling, or drug infusion of a vasopressor, inotrope, or both.

Patients were not included if pregnant or with obvious contraindication for femoral Doppler. Patients were excluded in the event of poor thoracic insonation, study protocol-induced discomfort, need for urgent therapy, or significant change in minute ventilation (arbitrary cut-off of 0.2 litres $min^{-1}$).

### Measurements

#### *Arterial blood pressure (BP)*

Before and after VE, we averaged three intra-arterial measurements of BP (at 30 s intervals) displayed via an Intellivue™ MP70 monitor (Philips Medical Systems, Best, The Netherlands) connected to a pressure transducer (T100209A; Edwards Lifesciences, Irvine, CA, USA) zeroed at the level of the mid-axillary line. Heart rate was collected in a similar manner. In instances of arrhythmia, defined as atrial fibrillation/flutter or more than one extrasystole per six cardiac cycles, five rather than three measurements were averaged. For PPV analysis, the definition for arrhythmia was more stringent, as follows: if, during 60 s, neither arrhythmia (no extrasystole) nor inspiratory efforts were detected, PPV (automatically displayed on the MP70 monitor) was collected once, 'at a glance'.

#### *Cardiac output*

Echographic measurements [Vivid S6™ or Vivid i™ (GE Healthcare, Wauwatosa, WI, USA) or Epiq 5™ (Philips, Andover, MA, USA)] were made by board-certified investigators. The velocity–time integral (VTI) of subaortic flow was computed on an apical five-chamber view using pulse Doppler.

$$CO\ (litres\ min^{-1}) = heart\ rate \times subaortic\ VTI \times (subaortic\ diameter)^2 \times \pi/4.$$

$$\Delta_{VE}CO(\%) = (CO\ before - CO\ after\ VE)/CO\ before\ VE.$$

Cardiac output was the average of two sets of three (five in the event of arrhythmia) consecutive measurements started from the VTI of higher magnitude (to minimize the impact of respiratory changes in VTI). Poor transthoracic insonation was defined *a priori* as poor alignment (angle >30°) of the ultrasonographic beam with left ventricular outflow, poor waveform visibility, or seeing fewer than three (fewer than five in the event of arrhythmia) consecutive cardiac cycles.

#### *End-tidal $CO_2$*

End-tidal $CO_2$ as displayed on the ventilator (Servo I™, Maquet, Ardon, France or Evita 4™, Dräger Medical, Lubeck, Germany) was collected once, 'at a glance', in millimetres of mercury, and is also expressed in kilopascals, for information purposes only (two decimal precision is not guaranteed with commonly used $E'_{CO_2}$ monitors).

#### *Femoral flow*

A 5 MHz linear echographic probe was gently affixed on the inguinal area, and the femoral artery diameter was measured (transverse plane). On a longitudinal axis, pulsed Doppler of femoral blood flow was obtained after placing the sample volume in the midstream of the artery lumen and moving it longitudinally to display a clear Doppler waveform of maximal magnitude.

Before and after VE, the probe was placed at the same level, perpendicular to the skin. We attempted to keep the angle between the ultrasonographic beam and arterial flow constant. However, the main source of measurement bias is underestimation of femoral VTI because of an increase in this angle. Therefore, we chose to analyse only the set of measurements, out of three sets, with the highest mean femoral VTI. Within one set, femoral VTI was the average of three (five in the event of arrhythmia) consecutive measurements. The $\Delta_{VE}$FemFlow was calculated as follows: [femoral flow before minus femoral flow after VE)/femoral flow before VE] (%). Unless specified, femoral flow was femoral VTI. Other definitions for femoral flow were tested in a similar manner: magnitude (peak) of the femoral pulse wave, consideration of femoral artery diameter, and heart rate; for instance, femoral flow=heart rate×femoral VTI×(femoral diameter)$^2\times\pi/4$.

### Study protocol

Echographic, BP, PPV, heart rate, and $E'_{CO_2}$ measurements were prospectively collected before and after VE. The amount and flow of VE were left at the discretion of the attending physician. Ventilator, posture, and vasoactive drugs were kept unchanged during the study period.

### Statistics

#### *Definition of fluid responsiveness*

Patients with $\Delta_{VE}$CO ≥15% were classified as responders. This commonly used cut-off for echocardiographic measurements is slightly higher than twice the intra-observer variability of echographic measurements of CO and therefore reliably reflects that a change genuinely occurred.[21] For validation, we calculated the least significant change for each set of CO measurements in each patient before fluid challenge [(1.96√2)CV/√number of measurements within one set], where CV=coefficient of variation (SD/mean).[22]

#### *Statistical tests*

Normal distribution of variables was tested using the Kolmogorov–Smirnov test and logarithmic transformation if needed. Variables are expressed as *n* (%), mean (SD) or median [interquartile range] as appropriate. Correlations were assessed by linear regression. Areas under the receiver operating characteristic curve ($AUC_{ROC}$s) for detection of fluid responsiveness were compared.[23] Other comparisons relied on $\chi^2$, Student's paired and unpaired *t*, and Wilcoxon rank tests as appropriate. All statistical tests were two tailed, performed using MedCalc 13.1.0.0 (MedCalc Software, bvba, Ostend, Belgium). We did not correct *P*-values for multiple testing, and a value of $P<0.05$ was considered significant.

A minimal value of 5 for the positive likelihood ratio (or a maximal value of 0.2 for the negative likelihood ratio) was used *a priori* to define a test that had 'good' positive (negative) diagnostic performance.[24]

## Results

Of 109 patients included, poor transthoracic insonation prevented CO measurements in 22 (20%). One patient was excluded because of a change in minute ventilation >0.2 litres min$^{-1}$ during the study protocol (Fig. 1). Thus, 86 patients were analysed and 33 (38%) responded to VE (500 [500–500] ml in 12 [10–15] min; Tables 1 and 2). Reasons for VE were hypotension or vasopressor administration in 80 (93%) patients, oliguria considered to be related to circulatory failure in 40 (47%), arterial lactate >2.5 mmol litre$^{-1}$ in 33 (38%), and skin mottling in 43 (50%). The mean least significant change of CO measurements was 9% at baseline, and the observed increase in CO was above the individual least significant change for all responders.

### Volume expansion-induced change in end-tidal $CO_2$

The $AUC_{ROC}$ for $\Delta_{VE}E'_{CO_2}$ was 0.82 [0.73–0.90]. A value of $\Delta_{VE}E'_{CO_2}$ >1 mm Hg (>0.13 kPa) was associated with a positive likelihood ratio of 5.0 [2.6–9.8]. In other words, $\Delta_{VE}E'_{CO_2}$ >1 mm Hg (>0.13 kPa) was of good performance (as stated *a priori*)[24] to indicate that the patient responded to VE. The negative likelihood ratio was 0.29 [0.2–0.5] (i.e. higher than 0.20) indicating that $\Delta_{VE}E'_{CO_2}$ ≤1 mm Hg (≤0.13 kPa) was of lower performance to rule out the absence of response (Fig. 2). In 16 patients with arrhythmia, the relationship between $\Delta_{VE}E'_{CO_2}$ and $\Delta_{VE}$CO was similar to that observed in patients with a normal rhythm ($r^2$=0.23 and $P<0.0001$ in both subgroups).

### Comparison of $\Delta_{VE}E'_{CO_2}$ with other indices

The $\Delta_{VE}E'_{CO_2}$ ($AUC_{ROC}$=0.82 [0.73–0.90]) significantly ($P<0.05$) outperformed $\Delta_{VE}$PP ($AUC_{ROC}$=0.65 [0.54–0.75]), $\Delta_{VE}$SBP ($AUC_{ROC}$=0.65 [0.54–0.76]), $\Delta_{VE}$MBP ($AUC_{ROC}$=0.63 [0.51–0.73]), and $\Delta_{VE}$FemFlow ($AUC_{ROC}$=0.59 [0.48–0.70]). Other definitions tested for femoral flow did not yield $AUC_{ROC}$ >0.61, significantly below that of $\Delta_{VE}E'_{CO_2}$.

In 60 patients (25 responders) with both regular cardiac rhythm and absence of missing data, $\Delta_{VE}E'_{CO_2}$ could also be compared with $\Delta_{VE}$HR and $\Delta_{VE}$PPV (Fig. 3). The $\Delta_{VE}E'_{CO_2}$ ($AUC_{ROC}$=0.84 [0.72–0.92]) significantly outperformed $\Delta_{VE}$HR ($AUC_{ROC}$=0.52 [0.39–0.66], $P<0.05$), but not $\Delta_{VE}$PPV ($AUC_{ROC}$=0.73 [0.60–0.84], $P$=0.21) or baseline PPV ($AUC_{ROC}$=0.84 [0.72–0.92] *vs* 0.67 [0.54–0.79], $P$=0.053).

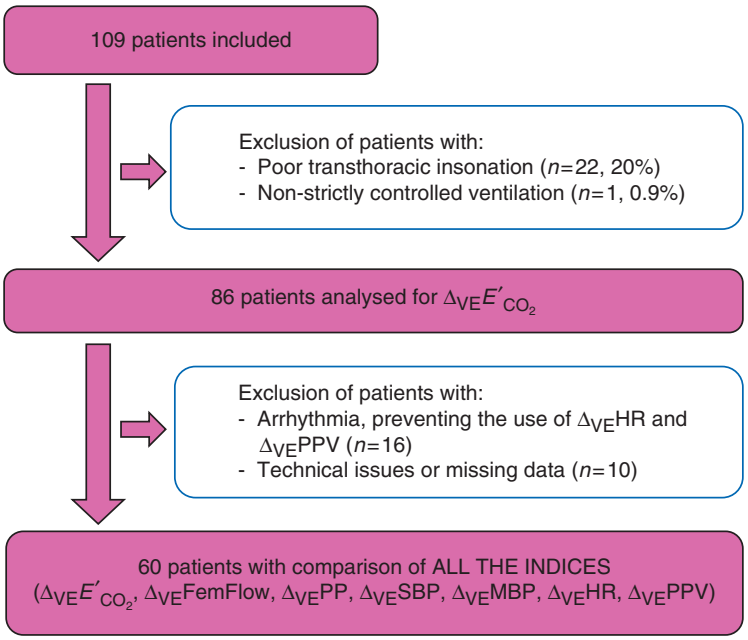


Fig 1 Study flow chart. $\Delta_{VE}E'_{CO_2}$, volume expansion-induced increase in end-tidal carbon dioxide; $\Delta_{VE}$FemFlow, volume expansion-induced increase in femoral artery flow; $\Delta_{VE}$HR, volume expansion-induced decrease in heart rate; $\Delta_{VE}$MBP, volume expansion-induced increase in mean arterial blood pressure; $\Delta_{VE}$PP, volume expansion-induced increase in arterial pulse pressure; $\Delta_{VE}$PPV, volume expansion-induced decrease in respiratory pulse pressure; $\Delta_{VE}$SBP, volume expansion-induced increase in systolic arterial blood pressure.

### Impact of tidal volume on $\Delta_{VE}$PPV

Low tidal volume (Vt) can result in a low baseline value of PPV[4] and therefore in a low $\Delta_{VE}$PPV, even in responders. Therefore, subgroup analysis according to Vt, above or below 8 ml kg$^{-1}$ of ideal body weight (IBW), was undertaken.[25] In the 15 patients with Vt≥8 ml kg$^{-1}$ IBW, the $AUC_{ROC}$ for baseline PPV was higher, but not significantly, than in the 45 patients with lower Vt (0.86 [0.59–0.98] *vs* 0.64 [0.48–0.79], $P$=0.13). There was also a non significantly higher $AUC_{ROC}$ in patients with higher Vt (0.80 [0.52–0.96] *vs* 0.66 [0.49–0.80], $P$=0.35). Importantly, in the 45 patients receiving a Vt<8 ml kg$^{-1}$ IBW, $\Delta_{VE}E'_{CO_2}$ significantly outperformed both baseline PPV and $\Delta_{VE}$PPV: $AUC_{ROC}$=0.86 [0.72–0.95] *vs* 0.64 [0.48–0.79], $P$=0.039, and 0.66 [0.49–0.80], $P$=0.024, respectively.

## Discussion

The main finding of this study is that, in volume-controlled ventilation, $\Delta_{VE}E'_{CO_2}$ outperformed widely used indices ($\Delta_{VE}$PP, $\Delta_{VE}$SBP, $\Delta_{VE}$MBP, and $\Delta_{VE}$HR) and femoral Doppler indices in assessing fluid responsiveness. In the presence of arrhythmia, protective ventilation (Vt <8 m kg$^{-1}$ IBW), or both, $\Delta_{VE}E'_{CO_2}$ also significantly outperformed $\Delta_{VE}$PPV and baseline PPV.

The amount of exhaled $CO_2$ depends on production by body tissues, pulmonary blood flow (i.e. CO), and alveolar ventilation.[12] Hence, $\Delta_{VE}E'_{CO_2}$ parallels $\Delta_{VE}$CO if alveolar ventilation is constant, as in patients with fully controlled mechanical ventilation, and if cell metabolism is stable (i.e. not altered by the VE itself). We found, as reported by others,[13 14] that $\Delta_{VE}E'_{CO_2}$ and $\Delta_{VE}$CO are significantly correlated ($r^2$=0.23; $P$<0.0001). Others have reported the ability of changes in $E'_{CO_2}$ during a postural manoeuvre or a mini-fluid challenge to predict fluid responsiveness, not for assessment of the effects of a fluid challenge.[13 14 26] To our knowledge, only two studies have reported the ability of $\Delta_{VE}E'_{CO_2}$ to assess responsiveness to VE. Their limited size ($n$=34 and $n$=40) and their conflicting findings ($AUC_{ROC}$ of 0.67 [0.48–0.80] and 0.80 [0.65–0.96], respectively)[27 28] indicated the need for a larger study. Furthermore, the former study suffers from the use of a CO determination method (bioreactance) of questioned reliability.[9] Our findings are in line with the results of the latter study, undertaken in the specific setting of the operating room.[28] In ICU patients, we found that if $\Delta_{VE}E'_{CO_2}$ was ≤1 mm Hg (≤0.13 kPa), no firm conclusion could be drawn about fluid responsiveness (negative likelihood ratio of 0.29). However, $\Delta_{VE}E'_{CO_2}$ >1 mm Hg (>0.13 kPa) indicated a very likely response to VE (positive likelihood ratio of 5.0). Hence, detection of fluid responders was more reliable than detection of non-responders. This might be attributable to VE-induced recruitment of collapsed pulmonary capillaries, which could have improved elimination of $CO_2$ in responders. Besides increasing $CO_2$ delivery to the lungs, the VE-induced increase in CO in responders might also allow an increase in cell metabolism and then in $CO_2$ production.

Use of peripheral arterial changes in pressure or flow as surrogates for $\Delta_{VE}$CO relies on the hypothesis that arterial properties are not significantly modified by the VE itself. This would be the case if the arterial system behaved as inert pipes. However, VE changes not only arterial tone but also pulse wave transmission and reflection characteristics.[29] In addition, in fluid responders, changes in regional rather than global arterial tone cause heterogeneous distribution of the increased CO.[30] For

**Table 1** Patient characteristics ($n$=86), after exclusion of patients with poor transthoracic insonation (see Methods) preventing the valid measurement of cardiac output. *Established diagnosis by means of a dedicated radiological procedure, which is likely to underestimate the real prevalence of these arterial diseases in our population, as some patients did not undergo exploration. †Number of patients with atrial fibrillation/flutter, atrial extrasystoles, or ventricular extrasystoles (more than one extrasystole per six cardiac cycles) were 12, 2, and 2, respectively

| Characteristic | $n$ (%), mean (SD) or median [interquartile range] |
|---|---|
| Age (yr) | 62 (51–69) |
| Sex [male/female; $n$ (%)] | 54 (63)/32(37) |
| BMI (kg m$^{-2}$) | 25 (23–28) |
| Simplified acute physiology score 2 | 50 (18) |
| Ramsay sedation scale [$n$ (%)] | |
| >4 | 69 (80) |
| 4 | 12 (14) |
| ≤3 | 5 (6) |
| Vascular disease* [$n$ (%)] | 26 (30) |
| Atherosclerosis of the lower limbs | 7 |
| Carotid stenosis | 8 |
| Coronary artery disease | 20 |
| Aortic calcifications | 5 |
| Radial/femoral intra-arterial catheter [$n$ (%)] | 76 (88)/10 (12) |
| Main cause of circulatory failure at study entry [$n$ (%)] | |
| Septic shock | 48 (56) |
| Haemorrhagic shock | 6 (7) |
| Cardiogenic shock | 3 (4) |
| Other shock | 6 (7) |
| Combination of mechanical ventilation and drug-induced circulatory impairment | 16 (19) |
| Other | 7 (8) |
| Acute respiratory distress syndrome [$n$ (%)] | 22 (26) |
| Tidal volume (ml kg$^{-1}$ of ideal body weight) | 7.1 [6.5–8.0] |
| Respiratory rate (cycles min$^{-1}$) | 20 (18–24) |
| Cardiac arrhythmia [$n$ (%)]† | 16 (19) |
| Capillary refill time >4 s [$n$ (%)] | 36 (42%) |
| Tissue oedema [$n$ (%)] | |
| None | 58 (67) |
| Moderate (only ankles, hands, elbows, sides) | 18 (21) |
| Important | 10 (11) |
| Trunk elevation [$n$ (%)] | |
| 0° | 17 (20) |
| <30° | 29 (34) |
| 30–45° | 40 (46) |
| Catecholamines [$n$ (%)] | 74 (86) |
| Norepinephrine (μg kg$^{-1}$ min$^{-1}$) | 0.48 (0.22–0.93) $n$=69 (80%) |
| Dobutamine (μg kg$^{-1}$ min$^{-1}$) | 4.1 (3.0–8.6) $n$=11 (13%) |
| Epinephrine (μg kg$^{-1}$ min$^{-1}$) | 0.4 (0.2–1.4) $n$=5 (6%) |
| Delay between intensive care unit admission and measurements (days) | 1 (0–2.5) |
| Delay between onset of circulatory failure and measurements (days) | 1 (0–1) |

these reasons, $\Delta_{VE}$PP, $\Delta_{VE}$SBP, and $\Delta_{VE}$MBP are known to be imperfect surrogates for $\Delta_{VE}$CO.[10 11] We tested whether these limitations apply also to flow, rather than pressure, measured in a large vessel, such as the femoral artery. We found that $\Delta_{VE}$FemFlow, whatever definition we used, was of no added value compared with widely used BP-derived indices to assess the effects of VE.[1] Doppler measurements at the femoral level are probably too distal and then exposed to the above-mentioned limitations. Therefore, femoral Doppler is not a reliable alternative to more proximal measurements of systemic flow, such as descending aorta flow (via oesophageal Doppler) or CO. Carotid blood flow measurements were recently proposed as an alternative. In 34 patients undergoing a postural change, carotid blood flow paralleled changes in CO.[30]

Two previous studies reported an encouraging relationship between $\Delta_{VE}$FemFlow and $\Delta_{VE}$CO.[15 31] Apart from their limited size (34 and 52 patients) and use of a postural change rather than fluid infusion in one study,[15] these studies differ from ours because the analysed population was likely to have different arterial tree properties (patients were younger, less sick, etc.).

In a large panel of patients in the perioperative setting, $\Delta_{VE}$PPV was reported to be a reliable tool to detect VE responsiveness.[11] As Vt is the stimulus for respiratory PPV, the lower the Vt, the lower the baseline PPV and thus $\Delta_{VE}$PPV, therefore leading to measurement

**Table 2** Haemodynamic parameters at baseline and after volume expansion. $E'_{CO_2}$, end-tidal carbon dioxide; PPV, respiratory pulse pressure variation; SBP, MBP, and DBP, systolic, mean, and diastolic arterial blood pressure (measured invasively). Variables are expressed as the mean (SD) or median [interquartile range]. *P<0.05 for comparison between responders and non-responders. †P<0.05 for comparison between before and after volume expansion. ‡If the left ventricular outflow chamber diameter could not be measured (poor insonation on parasternal view), a value of 2.1 mm for males and 1.9 mm for females was attributed. As this diameter was constant during the study protocol, its value did not impact the volume expansion-induced increase in cardiac output ($\Delta_{VE}$CO). ¶In patients with regular rhythm

| Haemodynamic parameter | Before volume expansion | | After volume expansion | |
|---|---|---|---|---|
| | Responders | Non-responders | Responders | Non-responders |
| Cardiac output (litres $min^{-1}$)‡ | 5.1 (1.7)* | 5.7 (1.8)* | 6.4 (1.9)† | 6.0 (1.9) |
| Cardiac index (litres $min^{-1}$ $m^{-2}$)‡ | 2.8 (1.0)* | 3.2 (1.1)* | 3.5 (1.2)† | 3.3 (1.1) |
| Heart rate (beats $min^{-1}$)¶ | 95 (29) | 98 (27) | 93 (27)† | 94 (24)† |
| SBP (mm Hg) | 105 (24) | 107 (21) | 128 (23)† | 120 (25)† |
| MBP (mm Hg) | 71 (12) | 71 (11) | 83 (12)† | 79 (15)† |
| DBP (mm Hg) | 55 (9) | 54 (9) | 63 (10)† | 58 (11)† |
| Pulse pressure (mm Hg) | 50 (22) | 53 (19) | 65 (20)† | 62 (20)† |
| Femoral flow (ml $min^{-1}$) | 479 [335–759] | 339 [222–580] | 675 [407–840]† | 419 [261–693]† |
| $E'_{CO_2}$ (kPa) | 4.0 [3.3–4.8] | 4.3 [3.4–4.8]* | 4.3 [3.8–5.1]*† | 4.2 [3.5–4.9] |
| PPV (%)¶ | 17 (10)* | 11 (7)* | 8 (5)† | 6 (3)† |

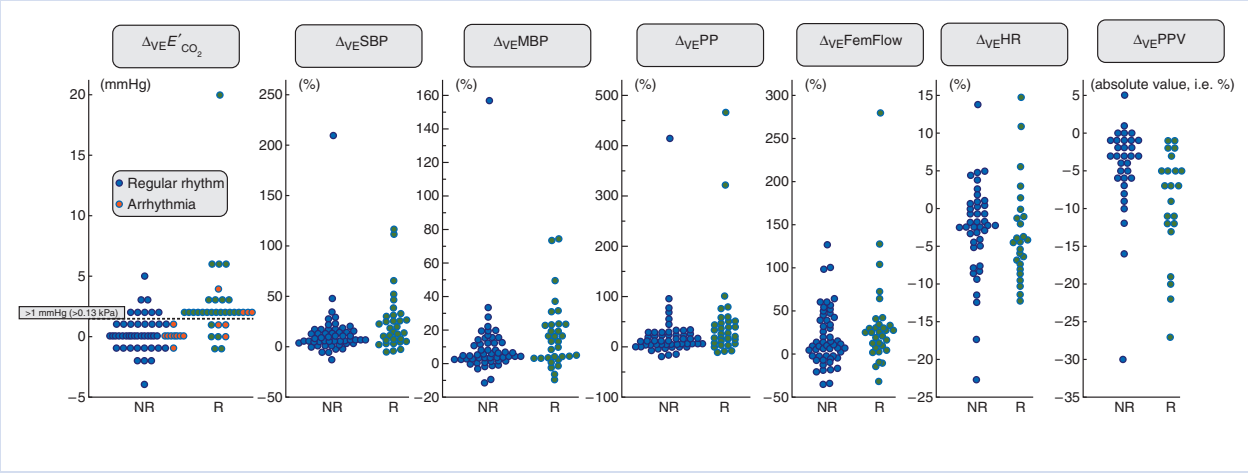


**Fig 2** Individual values of each index. $\Delta_{VE}E'_{CO_2}$, volume expansion-induced increase in end-tidal carbon dioxide; $\Delta_{VE}$FemFlow, volume expansion-induced increase in femoral artery flow; $\Delta_{VE}$HR, volume expansion-induced decrease in heart rate; $\Delta_{VE}$MBP, volume expansion-induced increase in mean arterial blood pressure; $\Delta_{VE}$PP, volume expansion-induced increase in arterial pulse pressure; $\Delta_{VE}$PPV, volume expansion-induced decrease in respiratory pulse pressure; $\Delta_{VE}$SBP, volume expansion-induced increase in systolic arterial blood pressure; NR, non-responders to volume expansion; R, responders to volume expansion. $n$=86 patients for $\Delta_{VE}E'_{CO_2}$, 84 patients for $\Delta_{VE}$PP, $\Delta_{VE}$SBP, $\Delta_{VE}$MBP, and $\Delta_{VE}$FemFlow, and $n$=60 patients with no arrhythmia for $\Delta_{VE}$PPV and $\Delta_{VE}$HR. A marked overlap of values of responders and non-responders was observed, except for $\Delta_{VE}E'_{CO_2}$. $\Delta_{VE}E'_{CO_2}$ >1 mm Hg (>0.13 kPa) was associated with a good positive and a fair negative likelihood ratio of 5.0 [2.6–9.8] and 0.29 [0.2–0.5], respectively.

errors. The use of lower Vt in the present study (7.1 [6.5–8.0] ml $kg^{-1}$ IBW *vs* 7.9 (1.3) ml $kg^{-1}$) could explain the poor performance for $\Delta_{VE}$PPV in our study ($AUC_{ROC}$ of 0.73 [0.60–0.84] *vs* 0.89 [0.85–0.91]). Indeed, there was a suggestion of better performance of $\Delta_{VE}$PPV in patients with higher Vt. Of note, another work also reported a poor performance for $\Delta_{VE}$PPV in ICU patients receiving low Vt ($AUC_{ROC}$ of 0.66 [0.85–0.91]).[10] As for baseline PPV alone, use of $\Delta_{VE}$PPV should probably be restricted to patients with neither arrhythmia nor inspiratory efforts and not receiving protective ventilation.[32]

## Study limitations

We did not assess baseline variability of $E'_{CO_2}$ measurements. However, in patients with $\Delta_{VE}E'_{CO_2}$ >1 mm Hg (>0.13 kPa), the lowest percentage increase observed in $E'_{CO_2}$ was 4%. Considering that the least significant change of $E'_{CO_2}$ was previously estimated to be 1.84% [1.47–2.41] in similar conditions,[13] a $\Delta_{VE}E'_{CO_2}$ >1 mm Hg (>0.13 kPa) is likely to be indicative of a true increase in $E'_{CO_2}$. In addition, as the cut-off of 1 mm Hg is small, it exposes to misclassification of responders and non-responders when using $E'_{CO_2}$ measuring devices less accurate than the one we used.

The use of a reference technique of CO determination by cold-bolus thermodilution instead of cardiac ultrasound might have yielded even better performance of the tested indices.[33] It is, however, noteworthy that our CO measurements were very rigorous, and we used very stringent criteria to define poor transthoracic insonation.

The widely used cut-off of 15% for $\Delta_{VE}$CO to discriminate responders from non-responders could be too high in some patients. In several non-responders, we observed, along with a small

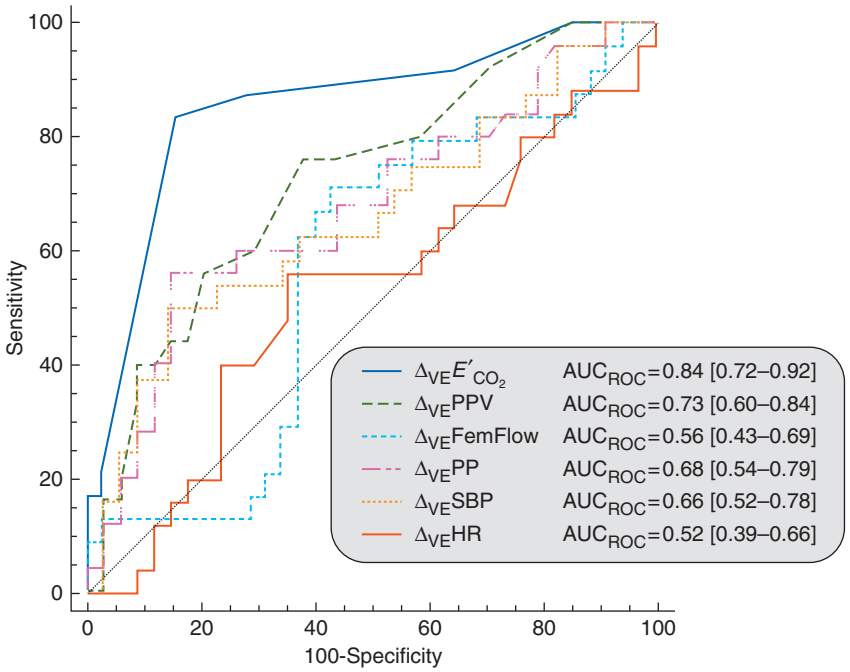


Fig 3 Comparison of the performance of the tested indices. Receiver operating characteristic curve analysis for each index to detect fluid responsiveness in 60 patients analysed for all the tested indices (i.e. in patients with neither inspiratory efforts nor arrhythmia). $\Delta_{VE}E'_{CO_2}$, volume expansion-induced increase in end-tidal carbon dioxide; $\Delta_{VE}$FemFlow, volume expansion-induced increase in femoral artery flow; $\Delta_{VE}$HR, volume expansion-induced decrease in heart rate; $\Delta_{VE}$PP, volume expansion-induced increase in arterial pulse pressure; $\Delta_{VE}$PPV, volume expansion-induced decrease in respiratory pulse pressure; $\Delta_{VE}$SBP, volume expansion-induced increase in systolic arterial blood pressure.

(<15%) increase in CO, a significant increase in arterial pressure and femoral flow and a significant decrease in PPV (Table 2 and Fig. 2). This finding has been previously reported.[10 34]

Volume expansion was left at the discretion of the attending physician and therefore not standardized. However, we believe that this represents a strength of this pragmatic study, allowing our findings to apply to real-life practice. Of note, the median VE was 500 ml, identical to the median VE reported in two recent observational studies,[1,6] with a [500 to 500 ml] interquartile range, such that standardization of VE is unlikely to have changed our findings.

We tested $\Delta_{VE}E'_{CO_2}$ during controlled ventilation only. Therefore, the included patients were often deeply sedated (Ramsay sedation scale was at least 4 in 94%). Thus, our results might not apply to mildly sedated or unsedated patients exhibiting inspiratory efforts.

The range of the tested indices was relatively narrow, exposing to misclassification of patients (Fig. 2). Indeed, many patients who were already resuscitated were non-responders or only mild responders. Earlier in the resuscitation phase, performance of the tested indices could be higher. This is particularly true for $\Delta_{VE}E'_{CO_2}$ because the relationship between $E'_{CO_2}$ and CO is logarithmic[35] such that $\Delta_{VE}E'_{CO_2}$ is markedly high if baseline CO is low.

## Conclusions

During volume-controlled ventilation, $\Delta_{VE}E'_{CO_2}$ outperformed the other minimally invasive indices we tested. A value of $\Delta_{VE}E'_{CO_2}$ >1 mm Hg (>0.13 kPa) indicates a likely response to fluids. This could trigger additional fluid infusion if signs of shock persist.

## Authors' contributions

Conception and design: K.L.
Collection of data: K.L., M.A.N., T.K., T.B.
Statistical analysis: T.B.
Drafting, revision, and final approval of the manuscript: K.L., M.A.N., B.L.-J., S.E., B.R., T.B.

## Declaration of interest

None declared.

## References

1. Boulain T, Boisrame-Helms J, Ehrmann S, *et al*. Volume expansion in the first 4 days of shock: a prospective multicentre study in 19 French intensive care units. *Intensive Care Med* 2015; **41**: 248–56
2. Jones AE, Brown MD, Trzeciak S, *et al*. The effect of a quantitative resuscitation strategy on mortality in patients with sepsis: a meta-analysis. *Crit Care Med* 2008; **36**: 2734–9
3. Boyd JH, Forbes J, Nakada TA, Walley KR, Russell JA. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. *Crit Care Med* 2011; **39**: 259–65

4. Lakhal K, Biais M. Pulse pressure respiratory variation to predict fluid responsiveness: from an enthusiastic to a rational view. *Anaesth Crit Care Pain Med* 2015; **34**: 9–10
5. Monnet X, Teboul JL. Passive leg raising: five rules, not a drop of fluid! *Crit Care* 2015; **19**: 18
6. Cecconi M, Hofer C, Teboul JL, *et al*. Fluid challenges in intensive care: the FENICE study: a global inception cohort study. *Intensive Care Med* 2015; **41**: 1529–37
7. Vallet B, Blanloeil Y, Cholley B, Orliaguet G, Pierre S, Tavernier B. Guidelines for perioperative haemodynamic optimization. *Ann Fr Anesth Reanim* 2013; **32**: e151–8
8. Vincent JL, Weil MH. Fluid challenge revisited. *Crit Care Med* 2006; **34**: 1333–7
9. Thiele RH, Bartels K, Gan TJ. Cardiac output monitoring: a contemporary assessment and review. *Crit Care Med* 2015; **43**: 177–85
10. Lakhal K, Ehrmann S, Perrotin D, Wolff M, Boulain T. Fluid challenge: tracking changes in cardiac output with blood pressure monitoring (invasive or non-invasive). *Intensive Care Med* 2013; **39**: 1953–62
11. Le Manach Y, Hofer CK, Lehot JJ, *et al*. Can changes in arterial pressure be used to detect changes in cardiac output during volume expansion in the perioperative period? *Anesthesiology* 2012; **117**: 1165–74
12. Anderson CT, Breen PH. Carbon dioxide kinetics and capnography during critical care. *Crit Care* 2000; **4**: 207–15
13. Monge Garcia MI, Gil Cano A, Gracia Romero M, Monterroso Pintado R, Pérez Madueño V, 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**: 9
14. Monnet X, Bataille A, Magalhaes E, *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
15. Preau S, Saulnier F, Dewavrin F, Durocher A, Chagnon JL. Passive leg raising is predictive of fluid responsiveness in spontaneously breathing patients with severe sepsis or acute pancreatitis. *Crit Care Med* 2010; **38**: 819–25
16. Brennan JM, Blair JE, Hampole C, *et al*. Radial artery pulse pressure variation correlates with brachial artery peak velocity variation in ventilated subjects when measured by internal medicine residents using hand-carried ultrasound devices. *Chest* 2007; **131**: 1301–7
17. Pinsky MR. Heart lung interactions during mechanical ventilation. *Curr Opin Crit Care* 2012; **18**: 256–60
18. French government. Loi 2004-806 (August 9, 2004) relative à la politique de santé publique. *J French Repub* 2004; **185**: 14277
19. Riou C, Fresson J, Serre JL, Avillach P, Leneveut L, Quantin C. Guide to good practices to ensure privacy protection in secondary use of medical records. *Rev Epidemiol Sante Publique* 2014; **62**: 207–14
20. Vincent JL, De Backer D. Circulatory shock. *N Engl J Med* 2013; **369**: 1726–34
21. Lewis JF, Kuo LC, Nelson JG, Limacher MC, Quinones MA. Pulsed Doppler echocardiographic determination of stroke volume and cardiac output: clinical validation of two new methods using the apical window. *Circulation* 1984; **70**: 425–31
22. Lodder MC, Lems WF, Ader HJ, *et al*. Reproducibility of bone mineral density measurement in daily practice. *Ann Rheum Dis* 2004; **63**: 285–9
23. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982; **143**: 29–36
24. Grimes DA, Schulz KF. Refining clinical diagnosis with likelihood ratios. *Lancet* 2005; **365**: 1500–5
25. De Backer D, Heenen S, Piagnerelli M, Koch M, Vincent JL. Pulse pressure variations to predict fluid responsiveness: influence of tidal volume. *Intensive Care Med* 2005; **31**: 517–23
26. Xiao-Ting W, Hua Z, Da-Wei L, *et al*. Changes in end-tidal $CO_2$ could predict fluid responsiveness in the passive leg raising test but not in the mini-fluid challenge test: a prospective and observational study. *J Crit Care* 2015; **30**: 1061–6
27. 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 Cardiothoracic Vasc Anesth* 2013; **27**: 681–4
28. Jacquet-Lagrèze M, Baudin F, David JS, *et al*. End-tidal carbon dioxide variation after a 100- and a 500-ml fluid challenge to assess fluid responsiveness. *Ann Intensive Care* 2016; **6**: 37
29. Lamia B, Chemla D, Richard C, Teboul JL. Clinical review: interpretation of arterial pressure wave in shock states. *Crit Care* 2005; **9**: 601–6
30. Marik PE, Levitov A, Young A, Andrews L. The use of bioreactance and carotid Doppler to determine volume responsiveness and blood flow redistribution following passive leg raising in hemodynamically unstable patients. *Chest* 2013; **143**: 364–70
31. Luzi A, Marty P, Mari A, *et al*. Noninvasive assessment of hemodynamic response to a fluid challenge using femoral Doppler in critically ill ventilated patients. *J Crit Care* 2013; **28**: 902–7
32. Mahjoub Y, Lejeune V, Muller L, *et al*. Evaluation of pulse pressure variation validity criteria in critically ill patients: a prospective observational multicentre point-prevalence study. *Br J Anaesth* 2014; **112**: 681–5
33. Wetterslev M, Møller-Sørensen H, Johansen RR, Perner A. Systematic review of cardiac output measurements by echocardiography vs. thermodilution: the techniques are not interchangeable. *Intensive Care Med* 2016; **42**: 1223–33
34. Monnet X, Letierce A, Hamzaoui O, *et al*. Arterial pressure allows monitoring the changes in cardiac output induced by volume expansion but not by norepinephrine. *Crit Care Med* 2011; **39**: 1394–9
35. Ornato JP, Garnett AR, Glauser FL. Relationship between cardiac output and the end-tidal carbon dioxide tension. *Ann Emerg Med* 1990; **19**: 1104–6


*Handling editor: H. C Hemmings Jr*