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Changes in central venous-to-arterial PCO_2 difference and central venous oxygen saturation as markers to define fluid responsiveness in critically ill patients: a pot-hoc analysis of a multi-center prospective study

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Abstract

Background The main aim of the study whether changes in central venous-to-arterial CO_2 difference ($\Delta P(v–a)CO_2$) and central venous oxygen saturation ($\Delta ScvO_2$) induced by volume expansion (VE) are reliable parameters to define fluid responsiveness (FR) in sedated and mechanically ventilated septic patients. We also sought to determine whether the degree of FR was related to baseline $ScvO_2$ and $P(v–a)CO_2$ levels.

Methods This was a post-hoc analysis of a multicenter prospective study. We included 205 mechanically ventilated patients with acute circulatory failure. Cardiac index (CI), $P(v–a)CO_2$, $ScvO_2$, and other hemodynamic variables were measured before and after VE. A VE-induced increase in CI > 15% defined fluid responders. Areas under the receiver operating characteristic curves (AUCs) and the gray zones were determined for $\Delta P(v–a)CO_2$ and $\Delta ScvO_2$.

Results One hundred fifteen patients (56.1%) were classified as fluid responders. The AUCs for $\Delta P(v–a)CO_2$ and $\Delta ScvO_2$ to define FR were 0.831 (95% CI 0.772–0.880) ($p < 0.001$) and 0.801 (95% CI 0.739–0.853) ($p < 0.001$), respectively. $\Delta P(v–a)CO_2 \leq 2.1$ mmHg and $\Delta ScvO_2 \geq 3.4\%$ after VE allowed the categorization between responders and non-responders with positive predictive values of 90% and 86% and negative predictive values of 58% and 64%, respectively. The gray zones for $\Delta P(v–a)CO_2$ (−2 to 0 mmHg) and $\Delta ScvO_2$ (−1 to 5%) included 22% and 40.5% of patients, respectively. $\Delta P(v–a)CO_2$ and $\Delta ScvO_2$ were independently associated with FR in multivariable analysis. No significant relationships were found between pre-infusion $ScvO_2$ and $P(v–a)CO_2$ levels and FR.

Conclusion In mechanically critically ill patients, $\Delta P(v–a)CO_2$ and $\Delta ScvO_2$ are reliable parameters to define FR and can be used in the absence of CI measurement. The response to VE was independent of baseline $ScvO_2$ and $P(v–a)CO_2$ levels.

Clinical trial registration The study was registered in the ClinicalTrials.gov registry: NCT03225378, date: July 20, 2017.

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Keywords Central venous-to-arterial PCO_2 gap, Central venous oxygen saturation, Fluid responsiveness, Volume expansion, Heart–lung interaction, Oxygen consumption, Tissue hypoperfusion, Tissue hypoxia, Circulatory failure

Introduction

The aim of volume expansion (VE) is to increase oxygen delivery (DO_2) by increasing cardiac index (CI) and, finally, to improve tissue oxygenation in critically ill patients with acute circulatory failure. However, excessive fluid therapy is associated with bad outcomes [1, 2]. Thus, it is crucial to identify patients who would benefit from VE, which remains challenging [3] and is often dependent on measuring CI [4, 5]. Recently, it has been demonstrated that the changes in pulse pressure variation (PPV) induced by a passive leg-raising test (PLR) [6, 7] or after a tidal volume challenge [8, 9] and other non-invasive tests reliably predict fluid responsiveness (FR) in mechanically ventilated patients without requiring CI measurements [10, 11]. However, special devices are required to measure PPV continuously.

Central venous oxygen saturation ($ScvO_2$), which reflects the adequacy between DO_2 and oxygen consumption (VO_2), has been widely used to assess FR. Indeed, in a recent meta-analysis that included five studies and 240 mechanically ventilated patients, the change in $ScvO_2$ ($\Delta ScvO_2$) during VE was a reliable indicator of FR [12]. However, the included studies [13–17] had small sample sizes, which might have overestimated the effect size. Moreover, it has been shown that the range of mixed venous oxygen saturation (SvO_2) baseline values was not associated with the FR status in septic patients [18]. However, this was a single-center retrospective study that included a small sample size of patients. Therefore, the relationship between $ScvO_2$ and FR still needs further investigation.

Central venous-to-arterial CO_2 tension difference ($P(v–a)CO_2$) reflects the balance between CO_2 production and CO_2 delivery to the lungs, a surrogate of the CI [19, 20]. Only one study has shown that the change in $P(v–a)CO_2$ during VE ($\Delta P(v–a)CO_2$) had a moderate ability to identify FR in septic shock patients [16]. However, this was a single-center study that included a small sample size. Also, no data have been reported on the relationship between the different baseline range values of $P(v–a)CO_2$ and FR status. Therefore, the primary aim of the study was to investigate if $\Delta P(v–a)CO_2$ and $\Delta ScvO_2$ are reliable parameters to define FR in critically ill mechanically ventilated patients with acute circulatory failure. The secondary aims were: (1) to investigate if $\Delta P(v–a)CO_2$ and $\Delta ScvO_2$ are independently associated with FR after adjusting for confounding variables, and (2) to assess the relationship between baseline $P(v–a)CO_2$, $ScvO_2$ values, and FR.

Methods

This was a secondary analysis of the prospective multicentre study that was conducted in eleven adult intensive care units in France from September 21st, 2017, to September 21st, 2021 (ClinicalTrials.gov NCT03225378) [7]. The French "Comité de Protéction des Personnes Ouest IV Nantes" approved the study (number: 2017-A01273-50). Informed consent was obtained from all patients or their next of kin.

Patients

Patients aged 18 years and older under invasive mechanical ventilation with acute circulatory failure for whom the attending physician decided to perform the PLR test and VE were eligible to participate. Acute circulatory failure was defined as previously described [21] (Additional-Methods-Patients). All included patients needed to have an arterial line. Exclusion criteria were as follows: cardiac arrhythmias, contraindication to PLR maneuver (intracranial hypertension, fracture of lower extremities), pregnancy, moribund patients, changes in vasopressors and sedation doses during the study period, and risk of fluid-loading-induced pulmonary edema.

This secondary analysis study included only patients whose arterial and central venous blood gas were performed at baseline and after VE.

Measurements

Patient characteristics, acute circulatory failure etiology, vasopressors, and/or inotropic use were collected on the day of enrolment. Hemodynamic variables, including CI (Additional-Methods-Measurements), were also obtained at different study periods.

Arterial and central venous blood gases were measured using the GEM Premier 4000 (Instrumentation Laboratory Co, Paris, France). $P(v–a)CO_2$ was calculated as the difference between the central venous carbon dioxide tension and the arterial carbon dioxide tension.

CI was measured with transthoracic echocardiography (TTE) or by thermodilution (PiCCO device, Pulsion Medical System, Munich, Germany) by injecting cold 0.9% saline (15 mL) through the central line catheter in triplicate and then averaged. TTE was performed by experienced physicians (at least 3 years training period). The same physician performed the measurements on

each patient during the different study periods. Stroke volume index (SVI) and CI were determined as previously described (Additional-Methods-Measurements).

Study protocol

A set of hemodynamic and oxygen-CO_2 derived variables measurements was obtained at baseline with the patients in the 45° semi-recumbent position, including CI (TTE or thermodilution), $ScvO_2$, and $P(v–a)CO_2$. Then, a VE (500 mL of crystalloid solution) was administered over 15 min, and the second set of measurements (CI measured using TTE or thermodilution) was obtained. Ventilation parameters and infusions of norepinephrine and sedation drugs remained unchanged during the VE. The TTE data were analyzed offline.

Changes in CI (ΔCI) and SVI (SVI) induced by the VE test were expressed as relative changes (((parameter at the end of VE − parameter at baseline)/parameter at baseline) × 100). $\Delta ScvO_2$ and $\Delta P(v–a)CO_2$ induced by the VE test were calculated as absolute changes ($\Delta ScvO_2$: $ScvO_2$ at the end of VE − $ScvO_2$ at baseline, $\Delta P(v–a)CO_2$: $P(v–a)CO_2$ at the end of VE − $P(v–a)CO_2$ at baseline).

Primary aim

To investigate if $\Delta P(v–a)CO_2$ and $\Delta ScvO_2$ are reliable parameters to define FR.

Secondary aims

1) To investigate if $\Delta P(v–a)CO_2$ and $\Delta ScvO_2$ are independently associated with FR and ΔCI after adjusting for confounding variables
2) To assess the relationships between baseline $ScvO_2$ values and baseline $P(v–a)CO_2$ values with FR

Statistical analysis

Patients in whom 500-mL VE increased CI (measured by TTE or thermodilution) > 15% were classified as responders and the remaining ones as non-responders. All data are expressed as mean (SD) or as median (25–75%, interquartile range, [IQR]), as appropriate. The normality of data distribution was assessed using the Shapiro–Wilk test. Comparisons of values between responders and non-responders were performed by two-tailed Student's t test, or Wilcoxon rank-sum test, as appropriate. Pairwise comparisons between different study times were assessed using paired Student's t test or Wilcoxon signed-rank test, as appropriate. Analysis of categorical data was performed using the Chi2 and Fisher's exact tests. Correlations were tested by using the Pearson or the Spearman test, as appropriate.

Receiver operating characteristic (ROC) curves were constructed to evaluate the ability of each parameter to predict fluid responsiveness after fluid challenge. The AUCs were compared using the nonparametric technique described by DeLong et al. [22]. Previously, we have shown that the smallest detectable differences (SDDs), which are the minimum changes that needed to be measured by a laboratory analyzer in order to recognize a real change of measurement, for $P(v–a)CO_2$ and $ScvO_2$ were ± 2 mmHg and ± 3% respectively [23]. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR^+), negative likelihood ratio (LR^-), and their 95% confidence intervals were calculated for $\Delta - \Delta PCO_2$ and $\Delta ScvO_2$.

Gray zones were calculated using the method that defines three levels of response: positive, uncertain, and negative. Uncertain responses were cutoff values with a sensitivity of < 90% or a specificity of < 90% (diagnosis tolerance of 10%) [24]. The gray zones were determined for each variable from the values that did not allow having of 10% diagnosis tolerance (Additional-Statistical analysis).

Multivariable logistic regression analysis was used to determine whether $\Delta P(v–a)CO_2$ and $\Delta ScvO_2$ were independent predictors of FR after adjusting for potential confounders, including center, shock etiology, baseline mean arterial pressure, baseline CI, norepinephrine and dobutamine uses, CI measurement technique, and severity score. The model's goodness-of-fit was assessed using the Hosmer–Lemeshow test.

Multivariable regression analysis was used to determine whether $\Delta P(v–a)CO_2$ and $\Delta ScvO_2$ were independent predictors of ΔCI after adjusting for the same potential confounders.

Statistical analysis was performed using STATA 17.0 (StataCorp LP, College Station, Texas, USA) and MedCalc 15.8 (MedCalc Software, Ostend, Belgium). $p < 0.05$ was considered statistically significant. All reported p values are 2-sided.

Results

Patient characteristics

Two hundred and five patients were included in this post-hoc analysis study. Table 1 summarizes the characteristics of the patients. Norepinephrine was given to 160 patients (78%). The major causes of acute circulatory failure were septic shock (60%) and hypovolemic shock (31.7%).

Effect of VE on hemodynamic variables

There were 115 (56.1%) responders defined by an increase in CI > 15% after VE of 500 mL.

At baseline, CI, and SVI were significantly lower in the responders' group (Table 2). $ScvO_2$ significantly

Table 1 Baseline characteristics of the population (n = 205)

Characteristics	
Age, median [IQR] (year)	68 [59–73]
Body mass index, median [IQR] (kg m^{-2})	27.4 [23.9–32.4]
Male, n (%)	128 (62.7)
SAPS II score, mean ± SD	56 ± 19
SOFA score, mean ± SD	9.5 ± 3.7
ICU mortality, n (%)	48 (23.4)
Norepinephrine, n (%)	160 (78.0)
Dose of norepinephrine, median [IQR] (µg kg^{-1} min^{-1})	0.3 [0.1–0.7]
Dobutamine, n (%)	41 (20.0)
Dose of dobutamine, median [IQR] (µg kg^{-1} min^{-1})	7.5 [5–10]
Lactate, median [IQR] (mmol L^{-1})	2.0 [1.2–3.5]
Septic shock, n (%)	123 (60.0)
Hypovolemic shock, n (%)	74 (36.1)
Cardiogenic shock, n (%)	8 (3.9)
Invasive mechanical ventilation, n (%)	205 (100)
CMV/PSV	187/18
Sedation, n (%)	192 (93.7)
Vt IBW, median [IQR] (kg)	7.0 [6.5–7.3]
Total PEEP, median [IQR] (cmH_2O)	6 [5–8]
Plateau pressure, median [IQR] (cmH_2O)	20 [16–23]
Driving pressure, median [IQR] (cmH_2O)	13 [10–15]
PaO_2/FiO_2, median [IQR] (mmHg)	266 [172–358]
Cardiac output monitoring method (echocardiography/TPTD)	126/79

FiO_2 inspired oxygen fraction, *HR* heart rate, *IBW* ideal body weight, *PaO_2* arterial oxygen partial pressure, *SAPS* simplified acute physiology score, *SOFA* sequential organ failure assessment, *Vt* tidal volume, *CMV* controlled mechanical ventilation, *PSV* pressure support ventilation, *PEEP* positive end-expiratory pressure, *TPTD* transpulmonary thermodilution, *ARDS* acute respiratory distress syndrome

Data are expressed as mean (SD), median [25–75% interquartile range], or count (%)

increased, and $P(v–a)CO_2$ significantly decreased only in the responders' group after VE.

Relationship between baseline $ScvO_2$, baseline $P(v–a)CO_2$, and FR

Baseline $ScvO_2$ and $P(v–a)CO_2$ values were not significantly different between the two groups (Table 2). Figure 1 shows that the proportions of fluid responders were not significantly different between the different ranges of baseline $ScvO_2$ values ($p = 0.38$). The AUC to predict FR for baseline $ScvO_2$ was 0.547 (95% CI 0.476–0.616) ($p = 0.26$). Figure 2 shows that the proportions of fluid responders were not significantly different between the different ranges of baseline $P(v–a)CO_2$ values ($p = 0.78$). The AUC to predict FR for baseline $P(v–a)CO_2$ was 0.553 (95% CI 0.482–0.622) ($p = 0.19$). The AUC to predict FR for baseline pulse pressure variation was 0.66 (95% CI 0.59–0.73) ($p < 0.001$). Additional data are reported in the Additional-Results.

Relationship between $\Delta ScvO_2$, $\Delta P(v–a)CO_2$ after VE, and FR

The correlation coefficients between $\Delta ScvO_2$ and changes in ΔCI (Additional-Figure S1-A) and ΔSVI after VE were 0.55 ($p < 0.001$) and 0.52 ($p < 0.001$), respectively. The correlation coefficients between $\Delta P(v–a)CO_2$ and changes in ΔCI (Additional-Figure S1-B) and ΔSVI after VE were −0.61 ($p < 0.001$) and −0.62 ($p < 0.001$), respectively.

The AUCs to identify fluid responsiveness for $\Delta ScvO_2$ and $\Delta P(v–a)CO_2$ were 0.801 (95% CI 0.739–0.853) ($p < 0.001$) and 0.831 (95% CI 0.772–0.880) ($p < 0.001$) (Fig. 3). There were no significant differences between the AUCs for $\Delta ScvO_2$ and $\Delta P(v–a)CO_2$ ($p = 0.27$).

The best cutoff value (according to Youden index) for $\Delta ScvO_2$ was ≥ 2.4% (sensitivity = 71% and specificity = 80%), which was lower than its SDD (± 3%). Taking into account the repeatability (SDD), the best cutoff value was ≥ 3.4% (sensitivity = 63%, specificity = 87%, PPV = 86%, NPV = 64%, $LR^+ = 4.7$, and $LR^- = 0.4$) (Additional-Results). Only 4 patients (3.5%) who had an increase in CI > 15% experienced a decrease in $ScvO_2$ (< − 3%) after VE (Additional-Figure S2).

The best cutoff value (according to Youden index) for $\Delta P(v–a)CO_2$ was ≤ −0.4 mmHg (sensitivity = 86% and specificity = 67% [95% CI 57–77%]), which was lower than its SDD (± 2 mmHg). Taking into account the repeatability (SDD), the best cutoff value was ≤ −2.1 mmHg (sensitivity = 47%, specificity = 93%, PPV = 90%, NPV = 58%, $LR^+ = 7.0$, and $LR^- = 0.6$) (Additional-Results). None of the patients who had an increase in CI > 15% experienced an increase in $P(v–a)CO_2$ (> 2 mmHg) after VE (Additional-Figure S2).

The combination of $\Delta ScvO_2$ and $\Delta P(v–a)CO_2$ led to a slight improvement in FR detection, with an AUC of 0.858 (95% CI 0.802–0.903) that was significantly better than that observed for $\Delta ScvO_2$ ($p = 0.002$) and $\Delta P(v–a)CO_2$ ($p = 0.04$). However, the combination of $\Delta P(v–a)CO_2 \leq -2.1$ mmHg and $\Delta ScvO_2 \geq 3.4\%$ could identify FR with a sensitivity of 37%, a specificity of 94, an NPV of 54%, and a PPV of 90% (Additional-Results).

Gray zone limits

The gray zone range for $\Delta ScvO_2$ was −1% to 5% (Fig. 3), and 40.5% of patients were within this inconclusive zone. The gray zone range for $\Delta P(v–a)CO_2$ was −2 to −0 mmHg (Fig. 3), which included 45 patients (22%).

Factors associated with FR

$\Delta ScvO_2$ and $\Delta P(v–a)CO_2$ were independently associated with FR after adjusting for many potential confounders in the multivariable logistic regression analysis,

Table 2 Hemodynamic and acid–base variables before and after 500 ml of volume expansion (n = 205)

	Responders (n = 115)			Non-responders (n = 90)		
	Before VE	After VE	*p*	Before VE	After VE	*p*
HR, beats/min	91 [73–108]	89 [73–103]	< 0.001	94 [81–114]	90 [79–110]	< 0.001
SAP, mmHg	104 ± 19	114 ± 25*	< 0.001	106 ± 22	122 ± 25	< 0.001
DAP, mmHg	55 [48–63]	59 [52–67]	< 0.001	55 [48–64]	58 [51–65]	< 0.001
MAP, mmHg	71 ± 14	80 ± 15	< 0.001	72 ± 12	76 ± 14	< 0.001
PP, mmHg	46 [37–60]	63 [45–75]*	< 0.001	48 [35–61]	51 [38–71]	0.001
CVP, mmHg	9 [6–13]*	10 [8–15]*	< 0.001	11 [8–16]	14 [8–18]	< 0.001
CI, L.min/m^2	2.1 [1.6–2.7]*	2.9 [2.2–3.7]	< 0.001	2.7 [2.1–3.8]	2.7 [2.2–3.8]	0.003
SVI, mL/m^2	23.8 [19.4–30.3]*	33.3 [26.7–42.7]	< 0.001	29.7 [22.4–41.9]	31.5 [23.8–43.5]	< 0.001
Arterial pH	7.35 [7.29–7.40]	7.35 [7.28–7.39]	0.255	7.34 [7.25–7.40]	7.36 [7.26–7.41]	0.436
Central venous pH	7.30 [7.24–7.35]	7.30 [7.24–7.35]	0.385	7.30 [7.22–7.36]	7.31 [7.23–7.37]	0.184
Arterial lactate, mmol/L	1.9 [1.1–3.3]	1.8 [1.2–4]	0.155	2.0 [1.4–3.7]	1.9 [1.3–3.8]	0.147
$ScvO_2$, (%)	71 [61–76]	75 [67–81]	< 0.001	71 [63–79]	71 [62–79]	0.385
$PaCO_2$, mmHg	37 [32–41]	37 [32–41]	0.780	38 [33–43]	38 [32–42]	0.09
$PcvCO_2$, mmHg	45 [38–50]	42 [36–46]*	< 0.001	45 [39–50]	44 [39–49]	0.027
$P(v–a)CO_2$, mmHg	7 [5–10]	5 [4–6]*	< 0.001	6 [5–9]	7 [5–9]	0.961
PPV, (%)	10 [7–12]*	5 [3–7]*	< 0.001	7 [6–10]	6 [5–9]	0.013

Data are expressed as mean ± SD or median [25–75% interquartile range]

HR heart rate, *MAP* mean arterial pressure, *SAP* systolic arterial pressure, *DAP* diastolic arterial pressure, *PP* pulse pressure, *CI* cardiac index, *SVI* stroke volume index, *CVP* central venous pressure, $ScvO_2$ central venous oxygen saturation, $PaCO_2$ arterial partial pressure of carbon dioxide, $PcvCO_2$ central venous partial pressure of carbon dioxide, $P(v–a)CO_2$ difference between central venous partial pressure of carbon dioxide and arterial partial pressure of carbon dioxide, *VE* volume expansion

*$p < 0.05$ between responders and non-res

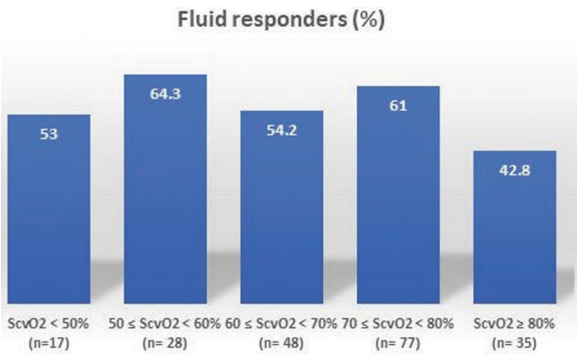

Fig. 1 Percentage of fluid responders among the different ranges of baseline central venous oxygen saturation ($ScvO_2$) values

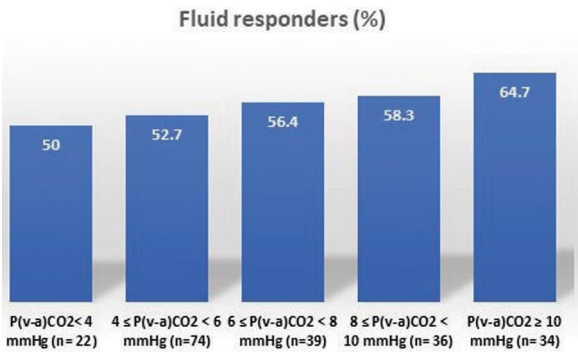

Fig. 2 Percentage of fluid responders among the different ranges of baseline difference between venous-to-arterial carbon dioxide tension difference ($P(v–a)CO_2$) values

with the responder's and non-responder's groups taken as the dependent variable (Table 3). We also found that $\Delta ScvO_2$ and $\Delta P(v–a)CO_2$ were independently associated with ΔCI after VE after adjusting for many potential confounders (Additional-Table S1).

Discussion

The main findings of our study can be summarized as follows: (1) the abilities of $\Delta ScvO_2$ and $\Delta P(v–a)CO_2$ were similar and excellent at identifying FR; (2) $\Delta P(v–a)CO_2$ and $\Delta ScvO_2$ were independently associated with FR detection and with ΔCI after VE. A $\Delta ScvO_2 \geq 3.4\%$ or $\Delta P(v–a)CO_2 \leq -2.1$ mmHg had excellent PPV to identify fluid responders after VE; (3) the combination of $\Delta ScvO_2$ and $\Delta P(v–a)CO_2$ did not offer clinical advantages at identifying FR compared to each parameter alone in terms of NPV and PPV; (4) the response to a VE was independent of baseline $ScvO_2$ and $P(v–a)CO_2$ values.

Applying the modified Fick method to CO_2 shows that the difference between mixed venous blood

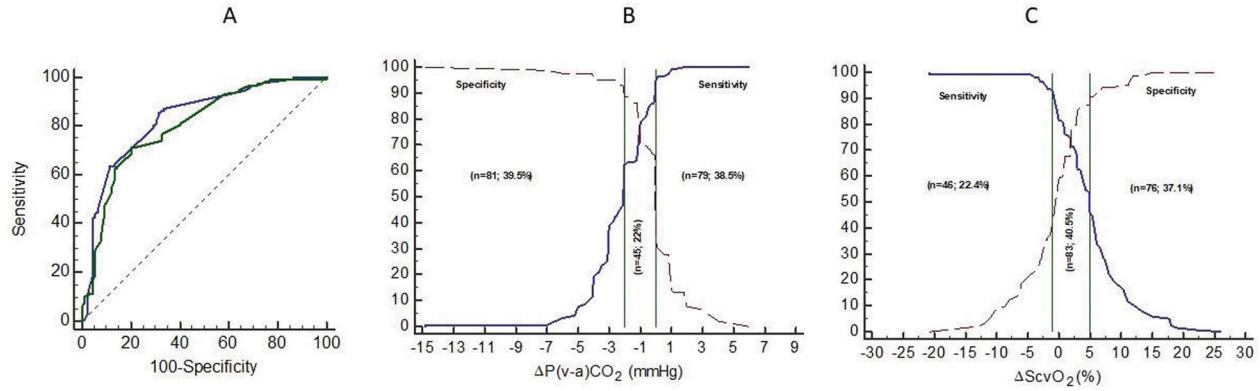

Fig. 3 Receiver operating characteristic (ROC) curve for changes in central venous-to-arterial PCO_2 difference ($\Delta P(v–a)CO_2$) (blue curve) and for changes in central venous oxygen saturation ($\Delta ScvO_2$) induced by volume expansion (green curve) (**A**). Two-graph ROC curves: sensitivity and specificity of $\Delta P(v–a)CO_2$ (**B**), and $\Delta ScvO_2$ (**C**) according to the cutoff value for the detection of more than 15% increase in cardiac index after volume expansion. The inconclusive zone, which is > 10% of diagnosis tolerance, is between the two vertical red lines

Table 3 Multivariable logistic regression analysis to determine the risk factors associated with fluid responsiveness

Variables	Odds ratio (95% CI)	*p* value
Centre	1.10 (0.96 to 1.25)	0.18
Shock etiology	1.74 (0.65 to 4.61)	0.65
Baseline mean arterial pressure	1.02 (0.97 to 1.06)	0.44
Baseline cardiac index	0.69 (0.46 to 1.05)	0.09
Norepinephrine use	2.83 (0.92 to 8.70)	0.07
Dobutamine use	2.51 (0.62 to 10.2)	0.20
Baseline central venous pressure	1.007 (0.901 to 1.116)	0.89
Cardiac output monitoring method	0.60 (0.21 to 1.72)	0.11
$\Delta ScvO_2$	1.11 (1.007 to 1.224)	0.036
$\Delta P(v–a)CO_2$	0.64 (0.46 to 0.89)	0.008
SAPS II	1.005 (0.979 to 1.031)	0.72

Goodness-of-fit test (Hosmer–Lemeshow Chi^2): *p* value = 0.50

$\Delta ScvO_2$ changes in central venous oxygen saturation induced by volume expansion; *$\Delta P(v–a)CO_2$*, changes in the difference between venous-to-arterial partial pressure of carbon dioxide induced by volume expansion, *SAPS* simplified acute physiology score, *shock etiology* hypovolemic, septic, and cardiogenic; cardiac output monitoring method: echocardiography, transpulmonary thermodilution/pulse contour; *CI* confidence interval

CO_2 content (CCO_2) and arterial blood CO_2 content depends on the cardiac output and total CO_2 production. Several experimental studies have demonstrated the primary role of decreased tissue blood flow in the increased PCO_2 gap [19, 25, 26]. A high PCO_2 gap (> 6 mmHg) reflects that blood flow is not sufficiently high to wash out the CO_2 produced by the tissues, and it is a marker of tissue hypoperfusion [20]. Interestingly, persistent high $P(v–a)CO_2$ levels (> 6 mmHg) were associated with poor outcomes, and it has been suggested that $P(v–a)CO_2$ might be an interesting target for resuscitation in critically ill patients [27–29].

A few studies have investigated the behaviors of $P(v–a)CO_2$ after VE [30, 31]. In 42 critically ill patients, Pierrakos et al. observed that VE decreased high $P(v–a)CO_2$ levels independently of pre-infusion CI [31]. However, to the best of our knowledge, no studies have investigated the relationship between baseline $P(v–a)CO_2$ and FR. We found that baseline $P(v–a)CO_2$ was a poor predictor of FR. Also, the proportions of fluid responders did not significantly differ among the different baseline $P(v–a)CO_2$ values (Fig. 2). Interestingly, between 35.3 and 43.6% of patients with high to very high baseline $P(v–a)CO_2$ values did not respond to VE. On the other hand, 50% of patients with very low baseline $P(v–a)CO_2$ values still responded to VE by increasing their CI > 15% (Fig. 2). These findings suggest that even extreme baseline $P(v–a)CO_2$ values cannot be used to predict FR in critically ill patients and the decision of VE should not be based only on $P(v–a)CO_2$ levels. Different mechanisms can explain this phenomenon.

The relationship between $P(v–a)CO_2$ and CI is curvilinear and influenced by CO2 production [20, 32]. Similarly, the CCO_2-PCO_2 relationship is also curvilinear and affected by factors like metabolic acidosis, hematocrit, and oxygen saturation (Haldane effect) [20, 33]. However, these factors likely did not impact our patients, as baseline pH and ScvO2 were not significantly altered (Table 2). These results are in agreement with the physiology of $P(v–a)CO_2$. Indeed, high $P(v–a)CO_2$ in situations of tissue hypoperfusion indicates that the best therapeutic approach would be to increase CI, which does not necessarily mean through VE. Other interventions to increase CI and improve tissue perfusion, such as dobutamine, might be indicated [34, 35]. Low $P(v–a)CO_2$ does not mean that patients would not respond to VE by increasing their CI. However, in such situations where

blood flow is sufficiently high to remove the CO_2 production from the peripheral circulation, interventions aiming at increasing CI, including VE, might not be indicated, even in the presence of tissue hypoperfusion[20]. However, this should be further evaluated in future studies.

Only one study investigated the role of $\Delta P(v-a)CO_2$ induced by VE in identifying FR [16]. In that study, which included 49 septic shock patients, the authors observed that the AUC for $\Delta P(v-a)CO_2$ to define FR was 0.76. However, the ability of $\Delta P(v-a)CO_2$ to define FR improved when patients with tissue hypoxia (VO_2/DO_2 dependency) were excluded (AUC:0.83) [16]. Indeed, it is known that in situations with VO_2/DO_2 dependency and anaerobic CO_2 production, the rise in CI would increase VO_2 and VCO_2. This would attenuate the decrease in $P(v-a)CO_2$ related to the increase in blood flow [20, 32]. We observed that $\Delta P(v-a)CO_2$ had an excellent ability to define FR. Also, a decrease in $P(v-a)CO_2$ (≤ -2 mmHg) after VE had excellent PPV (=90%) to identify fluid responders. However, the NPV (=58%) was poor. These findings suggest that after VE, if $P(v-a)CO_2$ decreases more than 2 mmHg, the physician can be almost confident that the patient has responded to VE. However, if no changes in $P(v-a)CO_2$ happened after VE, nothing can be said about the response in terms of CI. Indeed, CI can still increase > 15% after VE with no changes in $P(v-a)CO_2$ if patients are in situations of tissue hypoxia because of the anaerobic CO_2 production (VO_2/DO_2 dependency) [36, 37]. Moreover, we found that $\Delta P(v-a)CO_2$ was independently associated with FR (Table 3). Also, applying a continuous approach to the identification of FR, i.e., how much the CI is expected to increase after VE, rather than the classic binary one, i.e., [38] we found that $\Delta P(v-a)CO_2$ was independently associated with ΔCI after VE in the multivariable linear regression analysis (Additional-Table S1).

Venous oxygen saturation is a global marker of adequacy between VO_2 and DO_2 [39]. We observed that $ScvO_2$ levels (low and high values) before VE were poor predictors of FR in critically ill patients (Fig. 1). Indeed, overall, 40.1% of patients with baseline $ScvO_2 < 70\%$ did not respond to VE. On the other side, 55.4% of patients with baseline $ScvO_2 > 70\%$ did respond to VE. $ScvO_2$ depends on CI, but also on different other parameters. Low $ScvO_2$ is often associated with an inadequate CI, but it also can be associated with low arterial oxygen content (CaO_2) or increased VO_2 by the tissues. Indeed, a low $ScvO_2$ value is a warning sign of the potential inadequacy of DO_2 for tissue demands, indicating the need to increase DO_2 to the tissues that could be with VE, or transfusions, or dobutamine administration. Contrarily, a normal or high $ScvO_2$ level does not necessarily indicate that oxygen metabolism is entirely normalized and does not exclude the presence of persisting tissue hypoperfusion and hypoxia, mainly in septic shock patients due to microcirculatory shunting and mitochondrial dysfunction [27, 28]. Indeed, supranormal $ScvO_2$ values were associated with multiple organ failure and death in septic patients [40, 41]. Our results are in line with a previous retrospective study [18] that included 65 septic patients; the authors reported that the response to a VE was independent of baseline SvO_2. Indeed, 52% of patients with $SvO_2 > 70\%$ responded to a VE, and 47.5% of patients with low $SvO_2 < 70\%$ did not respond to a VE in that study [18].

Usually, changes in $ScvO_2$ are more informative than absolute $ScvO_2$ values. The changes in $ScvO_2$ after VE can theoretically track the fluid-induced changes in CI as long as the other determinant parameters remain unchanged during VE. We observed that $\Delta ScvO_2$ after VE was good at defining fluid responsiveness (Fig. 3). A $\Delta ScvO_2 \geq 3.4\%$ had a very good PPV to rule in a positive response to VE. Of note, the NPV was poor, and cannot rule out a positive response to VE. This might be due to different factors that could attenuate the increases in $ScvO_2$ after VE. Indeed, VE might induce a hemodilution effect with a decrease in hemoglobin levels and CaO_2 [42]. Also, in situations of VO_2/DO_2 dependency, the increase in CI would induce an increase in VO_2 [36, 37]. We also found that $\Delta ScvO_2$ was an independent factor associated with FR (Table 3). Our findings agree with a recent meta-analysis of 5 observational studies comprising 240 critically ill patients [12]. The authors found that the pooled AUC for $\Delta ScvO_2$ defining FR was 0.86. However, this meta-analysis did not include granular data and the cutoff values of CI to define FR were different between the included studies with different types of fluid administration.

We did not find a significant difference between $\Delta ScvO_2$ and $\Delta P(v-a)CO_2$ regarding their abilities to define FR (Fig. 3). $P(v-a)CO_2$ and $\Delta ScvO_2$ reflect different pathophysiological mechanisms. Indeed, $\Delta ScvO_2$ reflects the balance between VO_2 and DO_2 [43], whereas $P(v-a)CO_2$ is related to tissue perfusion independently of the presence of tissue hypoxia [44]. It has been shown that $P(v-a)CO_2$ may provide additional information for evaluating the adequacy of resuscitation in critically ill patients when $ScvO_2$ is normal or high [27, 28, 45, 46]. However, we found that the combination of $\Delta ScvO_2$ and $\Delta P(v-a)CO_2$ did not offer clinical advantages in defining FR compared to each parameter alone.

Our results are of clinical importance for several reasons. First, baseline values of $P(v-a)CO_2$ or $ScvO_2$ (low or high) cannot be used to predict FR. Second, in situations where CI measurement is unavailable or pulse pressure variation use is inappropriate, changes in $P(v-a)CO_2$ or $ScvO_2$ can be used to assess the effects of VE in terms

of FR. If $P(v–a)CO_2$ decreased by more than 2 mmHg or $ScvO_2$ increased by more than 3.4%, the clinician could be almost sure that VE significantly increased CI by more than 15%. However, nothing can be said about the effects of VE on CI in the cases where there were no or minor changes in $P(v–a)CO_2$ or $ScvO_2$. Our results suggest that the changes in $P(v–a)CO_2$ should be preferred over those in $ScvO_2$ because of the smaller gray zone.

This study has several strengths. First, to the best of our knowledge, our study is the first multicenter prospective study that has investigated the usefulness of $ScvO_2$ and $P(v–a)CO_2$ changes in defining FR. The multicenter design extends the generalizability of our findings. Second, we included a large number of patients with different etiologies of shock. Third, we used the gray zone approach, which circumvents the binary limitations of a "black-or-white" decision of the ROC curve method that often is not appropriate for the reality of clinical practice [24, 47]. Fourth, we performed a multivariable analysis to ascertain the association between $\Delta P(v–a)CO_2$, $\Delta ScvO_2$, and FR.

Our study also presents some limitations. First, it was a post-hoc analysis so that ΔPCO_2, $\Delta P(v–a)CO_2$, and $\Delta ScvO_2$ were calculated retrospectively. However, collecting these variables was performed prospectively since they were part of the planned protocol in the original study [7]. Second, different techniques of CI measurement were used in this study that could have affected the classification of fluid responders and non-responders. However, CI measurement technique was not independently associated with FR classification. Third, we were not able to calculate VO_2, DO_2, and tissue hypoxia markers since hemoglobin levels were not collected.

Conclusions

In mechanically ventilated ICU patients, $ScvO_2$ and $P(v–a)CO_2$ levels (even extreme values) before VE are poor predictors of FR. $\Delta P(v–a)CO_2$ and $\Delta ScvO_2$ are reliable parameters to define FR and can be used in the absence of CI measurement.

Abbreviations

FR	Fluid responsiveness
CI	Cardiac index
VE	Volume expansion
PLR	Passive leg raising
VE	Volume expansion
ROC	Receiver operating characteristic
AUC	Area under the ROC curve
TTE	Transthoracic echocardiography
CO_2	Carbon dioxide
VO_2	Oxygen consumption
DO_2	Oxygen delivery
$P(v–a)CO_2$	Venous-to-arterial carbon dioxide tension difference
$PaCO_2$	Partial arterial carbon dioxide tension
$PcvCO_2$	Central venous carbon dioxide tension
$ScvO_2$	Central venous oxygen saturation
SvO_2	Mixed venous oxygen saturation
CI	Cardiac index
SDD	Smallest detectable differences
PPV	Positive predictive value
NPV	Negative predictive value
LR	Likelihood ratio
HR	Heart rate
ICU	Intensive care unit
PPV	Pulse pressure variation

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

Author contributions

Study concept: JM, PGG, OAA, and MOF Data acquisition: ML, OAA, MOF, JM, and PGG Data collection: ML, OAA, MOF, and PGG Data analysis: JM, MOF, PGG, and OAA Statistical analysis: JM Drafting of the manuscript: JM, MOF, OAA, DS, and PGG Revision of the final manuscript: JM, ML, OAA, MOF, DS, and PGG All authors read and approved the manuscript.

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Declarations

Ethics approval

This study was approved by the French "Comité de Protéction des Personnes Ouest IV Nantes" approved the study on July 5th, 2017 (number: 2017-A01273-50).

Consent to participate

Informed consent was obtained from all patients or their next of kin.

Competing of interest

The authors declare that they have no conflict of interests.

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References

1. Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, Connors AF Jr, Hite RD, Harabin AL. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med. 2006;354(24):2564–75.
2. Acheampong A, Vincent JL. A positive fluid balance is an independent prognostic factor in patients with sepsis. Crit Care. 2015;19(1):251.
3. Michard F, Teboul JL. Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. Chest. 2002;121(6):2000–8.

4. Vincent JL, Weil MH. Fluid challenge revisited. Crit Care Med. 2006;34(5):1333–7.
5. Cecconi M, Parsons AK, Rhodes A. What is a fluid challenge? Curr Opin Crit Care. 2011;17(3):290–5.
6. Taccheri T, Gavelli F, Teboul JL, Shi R, Monnet X. Do changes in pulse pressure variation and inferior vena cava distensibility during passive leg raising and tidal volume challenge detect preload responsiveness in case of low tidal volume ventilation? Crit Care. 2021;25(1):110.
7. Mallat J, Fischer MO, Granier M, Vinsonneau C, Jonard M, Mahjoub Y, Baghdadi FA, Préau S, Poher F, Rebet O, et al. Passive leg raising-induced changes in pulse pressure variation to assess fluid responsiveness in mechanically ventilated patients: a multicentre prospective observational study. Br J Anaesth. 2022;129(3):308–16.
8. Myatra SN, Prabu NR, Divatia JV, Monnet X, Kulkarni AP, Teboul JL. The changes in pulse pressure variation or stroke volume variation after a "tidal volume challenge" reliably predict fluid responsiveness during low tidal volume ventilation. Crit Care Med. 2017;45(3):415–21.
9. Wang X, Liu S, Gao J, Zhang Y, Huang T. Does tidal volume challenge improve the feasibility of pulse pressure variation in patients mechanically ventilated at low tidal volumes? A systematic review and meta-analysis. Crit Care. 2023;27(1):45.
10. Mallat J, Lemyze M, Fischer MO. Passive leg raising test induced changes in plethysmographic variability index to assess fluid responsiveness in critically ill mechanically ventilated patients with acute circulatory failure. J Crit Care. 2024;79: 154449.
11. Beurton A, Gavelli F, Teboul JL, De Vita N, Monnet X. Changes in the plethysmographic perfusion index during an end-expiratory occlusion detect a positive passive leg raising test. Crit Care Med. 2021;49(2):e151–60.
12. Pan J, Sun Y, Xu Z, Dong P, Zhou X. Variation in central venous oxygen saturation to evaluate fluid responsiveness: a systematic review and meta-analysis. Crit Care. 2023;27(1):203.
13. Giraud R, Siegenthaler N, Gayet-Ageron A, Combescure C, Romand JA, Bendjelid K. ScvO(2) as a marker to define fluid responsiveness. J Trauma. 2011;70(4):802–7.
14. Xu B, Yang X, Wang C, Jiang W, Weng L, Hu X, Peng J, Du B. Changes of central venous oxygen saturation define fluid responsiveness in patients with septic shock: a prospective observational study. J Crit Care. 2017;38:13–9.
15. Khalil MH, Sekma A, Zhani W, Zorgati A, Ben Soltane H, Nouira S. Variation in central venous oxygen saturation to assess volume responsiveness in hemodynamically unstable patients under mechanical ventilation: a prospective cohort study. Crit Care. 2021;25(1):245.
16. Nassar B, Badr M, Van Grunderbeeck N, Temime J, Pepy F, Gasan G, Tronchon L, Thevenin D, Mallat J. Central venous-to-arterial PCO(2) difference as a marker to identify fluid responsiveness in septic shock. Sci Rep. 2021;11(1):17256.
17. Giraud R, Vujovic B, Assouline B, Neto Silva I, Bendjelid K. Do ScvO(2) variations induced by passive leg raising predict fluid responsiveness? A prospective study. Physiol Rep. 2021;9(17): e15012.
18. Velissaris D, Pierrakos C, Scolletta S, De Backer D, Vincent JL. High mixed venous oxygen saturation levels do not exclude fluid responsiveness in critically ill septic patients. Crit Care. 2011;15(4):R177.
19. Vallet B, Teboul JL, Cain S, Curtis S. Venoarterial CO(2) difference during regional ischemic or hypoxic hypoxia. J Appl Physiol (1985). 2000;89(4):1317–21.
20. Mallat J, Lemyze M, Tronchon L, Vallet B, Thevenin D. Use of venous-to-arterial carbon dioxide tension difference to guide resuscitation therapy in septic shock. World J Crit Care Med. 2016;5(1):47–56.
21. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med. 2017;43(3):304–77.
22. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics. 1988;44(3):837–45.
23. Mallat J, Lazkani A, Lemyze M, Pepy F, Meddour M, Gasan G, Temime J, Vangrunderbeeck N, Tronchon L, Thevenin D. Repeatability of blood gas parameters, PCO_2 gap, and $_{PCO2}$ gap to arterial-to-venous oxygen content difference in critically ill adult patients. Medicine (Baltimore). 2015;94(3): e415.
24. Cannesson M, Le Manach Y, Hofer CK, Goarin JP, Lehot JJ, Vallet B, Tavernier B. Assessing the diagnostic accuracy of pulse pressure variations for the prediction of fluid responsiveness: a "gray zone" approach. Anesthesiology. 2011;115(2):231–41.
25. Nevière R, Chagnon JL, Teboul JL, Vallet B, Wattel F. Small intestine intramucosal PCO(2) and microvascular blood flow during hypoxic and ischemic hypoxia. Crit Care Med. 2002;30(2):379–84.
26. Dubin A, Murias G, Estenssoro E, Canales H, Badie J, Pozo M, Sottile JP, Barán M, Pálizas F, Laporte M. Intramucosal-arterial PCO_2 gap fails to reflect intestinal dysoxia in hypoxic hypoxia. Crit Care. 2002;6(6):514–20.
27. Mallat J, Pepy F, Lemyze M, Gasan G, Vangrunderbeeck N, Tronchon L, Vallet B, Thevenin D. Central venous-to-arterial carbon dioxide partial pressure difference in early resuscitation from septic shock: a prospective observational study. Eur J Anaesthesiol. 2014;31(7):371–80.
28. Vallée F, Vallet B, Mathe O, Parraguette J, Mari A, Silva S, Samii K, Fourcade O, Genestal M. Central venous-to-arterial carbon dioxide difference: An additional target for goal-directed therapy in septic shock? Intensive Care Med. 2008;34(12):2218–25.
29. Ospina-Tascón GA, Bautista-Rincón DF, Umaña M, Tafur JD, Gutiérrez A, García AF, Bermúdez W, Granados M, Arango-Dávila C, Hernández G. Persistently high venous-to-arterial carbon dioxide differences during early resuscitation are associated with poor outcomes in septic shock. Crit Care. 2013;17(6):R294.
30. Mecher CE, Rackow EC, Astiz ME, Weil MH. Venous hypercarbia associated with severe sepsis and systemic hypoperfusion. Crit Care Med. 1990;18(6):585–9.
31. Pierrakos C, De Bels D, Nguyen T, Velissaris D, Attou R, Devriendt J, Honore PM, Taccone FS, De Backer D. Changes in central venous-to-arterial carbon dioxide tension induced by fluid bolus in critically ill patients. PLoS ONE. 2021;16(9): e0257314.
32. Lamia B, Monnet X, Teboul JL. Meaning of arterio-venous PCO_2 difference in circulatory shock. Minerva Anestesiol. 2006;72(6):597–604.
33. Teboul JL, Scheeren T. Understanding the Haldane effect. Intensive Care Med. 2017;43(1):91–3.
34. Mallat J, Benzidi Y, Salleron J, Lemyze M, Gasan G, Vangrunderbeeck N, Pepy F, Tronchon L, Vallet B, Thevenin D. Time course of central venous-to-arterial carbon dioxide tension difference in septic shock patients receiving incremental doses of dobutamine. Intensive Care Med. 2014;40(3):404–11.
35. Teboul JL, Mercat A, Lenique F, Berton C, Richard C. Value of the venous-arterial PCO_2 gradient to reflect the oxygen supply to demand in humans: effects of dobutamine. Crit Care Med. 1998;26(6):1007–10.
36. Monnet X, Julien F, Ait-Hamou N, Lequoy M, Gosset C, Jozwiak M, Persichini R, Anguel N, Richard C, Teboul JL. Lactate and venoarterial carbon dioxide difference/arterial-venous oxygen difference ratio, but not central venous oxygen saturation, predict increase in oxygen consumption in fluid responders. Crit Care Med. 2013;41(6):1412–20.
37. Mallat J, Lemyze M, Meddour M, Pepy F, Gasan G, Barrailler S, Durville E, Temime J, Vangrunderbeeck N, Tronchon L, et al. Ratios of central venous-to-arterial carbon dioxide content or tension to arteriovenous oxygen content are better markers of global anaerobic metabolism than lactate in septic shock patients. Ann Intensive Care. 2016;6(1):10.
38. Aneman A, Schulz L, Prat G, Slama M, Vignon P, Vieillard-Baron A. Volume responsiveness revisited: an observational multicenter study of continuous versus binary outcomes combining echocardiography and venous return physiology. Am J Physiol Heart Circ Physiol. 2023;325(5):H1069-h1080.
39. Squara P. Central venous oxygenation: when physiology explains apparent discrepancies. Crit Care. 2014;18(6):579.
40. Pope JV, Jones AE, Gaieski DF, Arnold RC, Trzeciak S, Shapiro NI. Multicenter study of central venous oxygen saturation (ScvO(2)) as a predictor of mortality in patients with sepsis. Ann Emerg Med. 2010;55(1):40-46. e41.
41. Textoris J, Fouché L, Wiramus S, Antonini F, Tho S, Martin C, Leone M. High central venous oxygen saturation in the latter stages of septic shock is associated with increased mortality. Crit Care. 2011;15(4):R176.
42. Quispe-Cornejo AA, Alves da Cunha AL, Njimi H, Mongkolpun W, Valle-Martins AL, Arébalo-López M, Creteur J, Vincent JL. Effects of rapid fluid infusion on hemoglobin concentration: a systematic review and meta-analysis. Crit Care. 2022;26(1):324.

43. Németh M, Tánczos K, Demeter G, Erces D, Kaszaki J, Mikor A, Molnár Z. Central venous oxygen saturation and carbon dioxide gap as resuscitation targets in a hemorrhagic shock. Acta Anaesthesiol Scand. 2014;58(5):611–9.
44. Zhang H, Vincent JL. Arteriovenous differences in PCO_2 and pH are good indicators of critical hypoperfusion. Am Rev Respir Dis. 1993;148(4 Pt 1):867–71.
45. Habicher M, von Heymann C, Spies CD, Wernecke KD, Sander M. Central venous-arterial pCO_2 difference identifies microcirculatory hypoperfusion in cardiac surgical patients with normal central venous oxygen saturation: a retrospective analysis. J Cardiothorac Vasc Anesth. 2015;29(3):646–55.
46. Robin E, Futier E, Pires O, Fleyfel M, Tavernier B, Lebuffe G, Vallet B. Central venous-to-arterial carbon dioxide difference as a prognostic tool in high-risk surgical patients. Crit Care. 2015;19(1):227.
47. Ray P, Le Manach Y, Riou B, Houle TT. Statistical evaluation of a biomarker. Anesthesiology. 2010;112(4):1023–40.

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