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Central venous-to-arterial PCO_2 difference as a marker to identify fluid responsiveness in septic shock

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Defining the hemodynamic response to volume therapy is integral to managing critically ill patients with acute circulatory failure, especially in the absence of cardiac index (CI) measurement. This study aimed at investigating whether changes in central venous-to-arterial CO_2 difference (Δ-ΔPCO_2) and central venous oxygen saturation ($\Delta ScvO_2$) induced by volume expansion (VE) are reliable parameters to define fluid responsiveness in sedated and mechanically ventilated septic patients. We prospectively studied 49 critically ill septic patients in whom VE was indicated because of circulatory failure and clinical indices. CI, ΔPCO_2, $ScvO_2$, and oxygen consumption (VO_2) were measured before and after VE. Responders were defined as patients with a > 10% increase in CI (transpulmonary thermodilution) after VE. We calculated areas under the receiver operating characteristic curves (AUCs) for Δ-ΔPCO_2, $\Delta ScvO_2$, and changes in CI (ΔCI) after VE in the whole population and in the subgroup of patients with an increase in VO_2 (ΔVO_2) ≤ 10% after VE (oxygen-supply independency). Twenty-five patients were fluid responders. In the whole population, Δ-ΔPCO_2 and $\Delta ScvO_2$ were significantly correlated with ΔCI after VE (r = − 0.30, $p = 0.03$ and r = 0.42, $p = 0.003$, respectively). The AUCs for Δ-ΔPCO_2 and $\Delta ScvO_2$ to define fluid responsiveness (increase in CI > 10% after VE) were 0.76 ($p < 0.001$) and 0.68 ($p = 0.02$), respectively. In patients with $\Delta VO_2 \leq 10\%$ (n = 36) after VE, the correlation between $\Delta ScvO_2$ and ΔCI was 0.62 ($p < 0.001$), and between Δ-ΔPCO_2 and ΔCI was − 0.47 ($p = 0.004$). The AUCs for Δ-ΔPCO_2 and $\Delta ScvO_2$ were 0.83 ($p < 0.001$) and 0.73 ($p = 0.006$), respectively. In these patients, Δ-$\Delta PCO_2 \leq$ -37.5% after VE allowed the categorization between responders and non-responders with a positive predictive value of 100% and a negative predictive value of 60%. In sedated and mechanically ventilated septic patients with no signs of tissue hypoxia (oxygen-supply independency), Δ-ΔPCO_2 is a reliable parameter to define fluid responsiveness.

Abbreviations

CO_2	Carbon dioxide
VO_2	Oxygen consumption
DO_2	Oxygen delivery
ΔPCO_2	Venous-to-arterial carbon dioxide tension difference
$\Delta ContO_2$	Arterial-to-venous oxygen content difference
$PaCO_2$	Partial arterial carbon dioxide tension
$PcvCO_2$	Central venous carbon dioxide tension
$ScvO_2$	Central venous oxygen saturation
SaO_2	Arterial oxygen saturation
PaO_2	Partial arterial oxygen tension
PvO_2	Partial venous oxygen tension
Hb	Hemoglobin
CI	Cardiac index
LSC	Least significant change
AUC	Area under the curve

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ROC	Receiver operating characteristic
PPV	Positive predictive value
NPV	Negative predictive value
LR	Likelihood ratio
VE	Volume expansion
HR	Heart rate
ICU	Intensive care unit

Hemodynamic optimization through fluid resuscitation is commonly used in critically ill patients with tissue hypoperfusion. The goal of volume expansion (VE) is to raise cardiac output and oxygen supply to improve tissue oxygenation. Recognizing patients who would benefit from VE remains challenging[1]. Identifying such patients is often dependent on measuring cardiac output[2,3]. Echocardiography is a skill that has made strides but not fully penetrated all critical care areas; it is limited by ultrasound availability and poor echogenicity, especially in mechanically ventilated patients. Passive leg raising test and end-expiratory occlusion methods also necessitate cardiac output measurement to asses fluid responsiveness[4,5]. Other measurements such as pulse pressure and stroke volume variations require specific technologies[6] or are restricted to certain patient populations[7]. With these limitations, defining fluid responsiveness without cardiac output measurement would be of great help to the clinician at the bedside.

Venous-to-arterial CO_2 tension difference reflects the balance between CO_2 production and CO_2 delivery to the lungs, a surrogate of the cardiac output[8,9]. Opposing changes over time in central venous-to-arterial CO_2 tension difference (ΔPCO_2) and cardiac output were reported in septic shock patients[10–12]. In post-cardiac surgery sedated and mechanically ventilated patients, Yazigi et al. observed a significant inverse correlation between changes in ΔPCO_2 (Δ-ΔPCO_2) and changes in cardiac index (ΔCI) induced by VE[13]. Moreover, in the same population, changes in central venous oxygen saturation (ΔScvO2) after VE were a reliable parameter to define fluid responsiveness[14]. However, data in the septic population is lacking.

In situations with tissue hypoxia, the increase in cardiac output and oxygen delivery (DO_2) after VE would result in an increase in CO_2 production (VCO_2) and oxygen consumption (VO_2) (oxygen supply dependency). These metabolic changes might confound fluctuations in arteriovenous O_2 and CO_2 parameters attributed solely to circulatory changes. This might reduce the changes in ΔPCO_2 and $ScvO_2$ induced by VE. Clinical studies have shown that the ratio of ΔPCO_2 over the arterial-to venous oxygen content ($\Delta PCO_2/\Delta ContO_2$) was a good indicator of oxygen supply dependency (tissue hypoxia) in critically ill patients[15,16]. This indicator could perhaps be used to identify such patients and guide the usage of CO_2 and oxygen gaps.

Therefore, our study aimed to investigate: (1) if Δ-ΔPCO_2 and $\Delta ScvO_2$ are reliable parameters to identify fluid responsiveness in overall sedated and mechanically ventilated septic patients; (2) if the reliability of these parameters would be better in the sub-group of patients with no tissue hypoxia, defined as the absence of an increase in VO_2 induced by a rise in DO_2 after VE (oxygen supply independency); (3) if baseline ΔPCO_2 / $\Delta ContO_2$ ratio is a good predictor of tissue hypoxia. Such measurements are readily available in these patients with central venous and arterial catheters.

Materials and methods

This prospective and observational study was conducted in a single, mixed medical and surgical adult intensive care unit (ICU) between April and December 2017. The study was approved by the local institutional ethics committee (Comité d'Ethique du centre hospitalier du Dr. Shaffner de Lens). Informed consent was obtained from the next of kin of each patient. All experiments were performed in accordance with relevant guidelines and regulations.

Patients. We studied mechanically ventilated patients with sepsis[17] for whom the attending physician decided to give VE due to the presence of at least one clinical sign of tissue hypoperfusion[17] as previously described[15]: (a) systolic arterial pressure < 90 mmHg, mean arterial pressure < 65 mmHg, or the requirement for vasopressor administration; (b) skin mottling; (c) lactate levels > 2 mmo/l; or urinary output < 0.5 ml/kg/h for ≥ 2 h. Also, patients had to have a PiCCO device (PiCCO, Pulsion Medical System, Munich, Germany) as part of routine management of persistent signs of inadequate tissue perfusion in our ICU. Exclusion criteria were: pregnancy, age < 18 years old, moribund, and risk of fluid loading-induced pulmonary edema.

Measurements. Demographic data, acute circulatory failure etiology, the Simplified Acute Physiology Score (SAPS) II, and the Sequential Organ Failure Assessment (SOFA) scores were obtained on the day of enrollment. CI was obtained with the PiCCO device by central venous injections of 20 ml of iced 0.9% saline solution and recorded as the average of the three measurements.

Arterial and central venous blood gases were measured using the GEM Premier 4000 (Instrumentation Laboratory Co, Paris, France). The central venous blood was collected from a central venous catheter with the tip confirmed to be in the superior vena cava, near or at the right atrium, by radiograph as previously described[15]. ΔPCO_2 was calculated as the difference between the central venous carbon dioxide tension and the arterial carbon dioxide tension. The arterial oxygen content was calculated as CaO_2 (ml) = 1.34 × Hb (g/dl) × SaO_2 + 0.003 × PaO_2 (mmHg), where SaO_2 is the oxygen saturation of arterial blood, Hb the hemoglobin concentration, and PaO_2 the arterial oxygen tension. The central venous oxygen content was calculated as $CcvO_2$ (ml) = 1.34 × Hb (g/dl) × $ScvO_2$ + 0.003 × $PcvO_2$ (mmHg), where $PcvO_2$ is the central venous oxygen tension. $\Delta ContO_2$ (ml) was calculated as $CaO_2 - CcvO_2$. DO_2 (ml/min/m^2) was calculated as $CaO_2 \times CI \times 10$. VO_2 (ml/m^2) was calculated as

Variables	All patients (n = 49)	Responders (n = 25)	Non-responders (n = 24)	*p*-value
Age (years)	67 [60–73]	62 [59–74]	68 [65–71]	0.25
Weight (kg)	79 [67–96]	80 [67–90]	78 [66–100]	0.89
BMI (kg/m^2)	27.2 [23.6–33.0]	26.5 [22.6–29.2]	27.5 [23.8–32.4]	0.32
Admission SAPS II	62 ± 15	62 ± 17	65 ± 20	0.57
SOFA score	10 [7–14]	10 [7–12]	10 [7–14]	0.54
Male, n (%)	34 (69.4)	19 (76.0)	15 (62.5)	0.30
Mechanical ventilation, n (%)	49 (100)	25 (100)	24 (100)	1.00
Infection source, n (%)				
Pneumonia	27 (55)	14 (56)	13 (54)	0.88
Peritonitis	12 (25)	7 (28)	6 (25)	0.93
Meningitis	3 (6)	2 (8)	1 (4)	0.99
Catheter related infections	2 (4)	0 (0)	2 (8)	0.46
Others	5 (10)	2 (8)	3 (12)	0.96
Norepinephrine, n (%)	37 (75.5)	19 (76)	18 (75)	0.93
Norepinephrine (μg kg min^{-1})	0.14 [0.06–0.45]	0.14 [0.05–0.46]	0.13 [0.06–0.47]	0.99

Table 1. Baseline characteristics of the study population. BMI, body mass index; SAPS II, Simplified Acute Physiologic Score; SOFA, Sequential Organ failure Assessment. Data are expressed as mean ± SD, median [25–75 interquartile range], or count.

$CI \times \Delta ContO_2 \times 10$. Oxygen extraction was defined as $OE = VO_2/DO_2$. We also calculated the $\Delta PCO_2/\Delta ContO_2$ ratio.

Study protocol. A first set of hemodynamic and oxygen-CO_2 derived variables measurements was performed at baseline, including heart rate (HR), systemic arterial pressure, CI (thermodilution), DO_2, VO_2, $ScvO_2$, arterial lactate level, and ΔPCO_2. A 500 ml of colloid solution (4% Human serum albumin, Vialebex®; LFB) was administered to the patient over 15 min via a specific venous line. The same set of measurements was repeated immediately after the end of VE infusion. Ventilation parameters and infusions of norepinephrine and sedation drugs were remained unchanged during the VE.

Changes in hemodynamic and oxygenation variables were expressed as relative changes (([parameter after volume expansion − parameter before volume expansion]/parameter before volume expansion) × 100).

Statistical analysis. Patients in whom 500-ml VE increased thermodilution-derived CI > 10% were defined as responders and the remaining ones as non-responders. Also, patients were divided into two subgroups according to their increases in VO_2 (≤ or > 10%) induced by VE. 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. Linear 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.[18]. Previously, we have shown that the upper 95% confidence interval values of the least significant changes (LSC), which are the minimum changes that needed to be measured by a laboratory analyzer in order to recognize a real change of measurement, for ΔPCO_2 and $ScvO_2$ were 36.5% and 5.0% respectively[19]. 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 Δ-ΔPCO_2 and $\Delta ScvO_2$.

Variables are usually considered of good clinical tool (having good discriminative property tests) when the inferior limits of the 95% confidence interval of their AUC are more than 0.75[20]. For this purpose, 43 patients would be sufficient for a power of 80% and an alpha risk of 0.05. Statistical analysis was performed using STATA 14.0 (StataCorp LP, College Station, Texas, USA). $p < 0.05$ was considered statistically significant. All reported *p* values are 2-sided.

Results

We studied 49 patients whose characteristics are summarized in Table 1. Twenty-five of the 49 patients (51%) were defined as responders because thermodilution CI increased by > 10% after VE of 500-ml.

There were no significant differences in patient characteristics, SOFA score, and norepinephrine between responders and non-responders (Table 1).

	Before volume expansion	After volume expansion
Heart rate (beats min^{-1})		
Responders	101 ± 26	100 ± 26
Non-responders	99 ± 25	97 ± 26
Systolic arterial pressure (mmHg)		
Responders	102 ± 21	119 ± 20#
Non-responders	107 ± 29	116 ± 28#
Diastolic arterial pressure (mmHg)		
Responders	58 ± 12	59 ± 12#
Non-responders	55 ± 12	62 ± 10#
Mean arterial pressure (mmHg)		
Responders	72 ± 13	81 ± 12#
Non-responders	72 ± 17	78 ± 17#
Pulse pressure (mmHg)		
Responders	44 ± 18	57 ± 17#
Non-responders	52 ± 21	57 ± 22#
Central venous pressure (mmHg)		
Responders	13 ± 6	16 ± 6#
Non-responders	16 ± 5	19 ± 6#
Intra-thoracic blood volume index (ml m^{-2})		
Responders	841 ± 188	951 ± 215#
Non-responders	858 ± 236	971 ± 223#
Extravascular lung water index (ml kg^{-1})		
Responders	9.1 ± 4.2	9.2 ± 4.3
Non-responders	8.9 ± 3.6	9.1 ± 3.4
Systemic vascular resistance index (DS m^{-2} cm^5)		
Responders	1702 [1218–2225]	1587 [1220–1990]#
Non-responders	1540 [957–1894]	1678 [1123–2096]
Cardiac index (l min^{-1} m^{-2})		
Responders	2.6 [2.1–3.5]	3.46 [2.59–4.16]#
Non-responders	2.9 [2.2–3.9]	2.78 [2.19–4.07]
Stroke volume index (ml m^{-2})		
Responders	29.6 ± 10.5	36.6 ± 10.7#
Non-responders	33.6 ± 13.6	33.6 ± 12.2
Hemoglobin (g/dL)		
Responders	10.3 ± 1.6	9.5 ± 1.3#
Non-responders	9.6 ± 1.8	9.1 ± 1.6#
Arterial pH		
Responders	7.35 [7.28–7.37]	7.34 [7.26–7.36]
Non-responders	7.34 [7.20–7.39]	7.31 [7.21–7.37]
Central venous pH		
Responders	7.28 [7.22–7.33]	7.30 [7.22–7.33]
Non-responders	7.30 [7.15–7.34]	7.28 [7.16–7.34]
Base excess (mmol L^{-1})		
Responders	−6.5 [−8.9 to −1.7]	−6.7 [−9.5 to −2.1]#
Non-responders	−4.7 [−12.4 to −1.1]	−5.1 [−12.1 to −1.7]#

Table 2. Hemodynamic and acid–base variables before and after 500 ml of volume expansion. Data are expressed as mean (SD) or median [25–75 interquartile range]. Responders n = 25; Non-responders n = 24. *$p < 0.05$ comparisons between responders and non-responders.#$p < 0.05$ comparisons between before and after before volume expansion.

Effect of volume expansion on hemodynamic variables. At baseline, all the tested hemodynamic variables were similar between the two groups (Table 2). VE significantly increased arterial pressures, CVP, and intrathoracic blood volume, and decreased hemoglobin in both groups. CI and stroke volume index increased significantly only in responders after VE, whereas HR and extravascular lung water did not change (Table 2). Arterial and venous pH were not significantly different between responders and non-responders' groups at baseline, and did not change significantly after VE (Table 2).

	Before volume expansion	After volume expansion
Central venous oxygen saturation (%)		
Responders	62 ± 13	68 ± 13#*
Non-responders	57 ± 15	56 ± 15
Oxygen delivery (ml min^{-1} m^{-2})		
Responders	382 ± 130	441 ± 134#
Non-responders	388 ± 163	368 ± 151
Arterial oxygen content (mL)		
Responders	13.4 ± 2.2	12.5 ± 1.8#
Non-responders	12.3 ± 2.5	11.8 ± 2.2
Central venous oxygen content (mL)		
Responders	8.6 ± 2.2	8.7 ± 2.1*
Non-responders	7.4 ± 2.6	7.1 ± 2.6
Oxygen consumption (mL min^{-1} m^{-2})		
Responders	129.6 ± 44.5	125.8 ± 45.2
Non-responders	144.3 ± 49.5	139.3 ± 51.0
Oxygen extraction (%)		
Responders	36.0 ± 12.8	30.4 ± 12.8*#
Non-responders	40.0 ± 15.0	41.1 ± 14.9
$PaCO_2$ (mmHg)		
Responders	38 [33–41]	39 [32–41]
Non-responders	38 [34–40]	38 [33–41]
$PcvCO_2$ (mmHg)		
Responders	45 [38–49]	44 [36–48]#
Non-responders	45 [42–47]	45 [41–50]
ΔPCO_2 (mmHg)		
Responders	7.0 [5.0–9.0]	5.0 [3.0–6.0]#
Non-responders	7.0 [5.0–9.0]	6.5 [5.0–9.0]
$\Delta PCO_2/\Delta ContO_2$ (mmHg/mL)		
Responders	1.59 ± 0.53	1.51 ± 0.56
Non-responders	1.60 ± 0.70	1.60 ± 0.49
Lactate (mmol/L)		
Responders	2.0 [1.1–3.6]	1.7 [1.0–3.4]#
Non-responders	1.5 [1.3–4.7]	1.6 [1.3–4.2]
Arterial oxygen saturation (%)		
Responders	96 [92–99]	96 [94–98]
Non-responders	96 [93–97]	96 [94–97]
PaO_2/FiO_2 ratio (mmHg)		
Responders	202 [149–294]	211 [157–295]
Non-responders	197 [124–273]	202 [154–265]

Table 3. Oxygenation and CO_2-derived variables before and after 500 ml of volume expansion. $PaCO_2$, arterial CO_2 tension; $PcvO_2$, central venous CO_2 tension; ΔPCO_2, central venous-to-arterial PCO_2 difference; $\Delta ContO_2$, arterial-to-venous oxygen content difference; PaO_2, arterial oxygen tension; FiO_2, inspiratory oxygen fraction. Data are expressed as mean (SD) or median [25–75 interquartile range]. Responders n = 25; Non-responders n = 24. *$p < 0.05$ comparisons between responders and non-responders.#$p < 0.05$ comparisons between before and after before volume expansion.

Effect of volume expansion on oxygenation and CO_2-derived variables. At baseline, there were no significant differences between the responders and non-responders' groups regarding all the oxygenation and CO_2-derived variable (Table 3). DO_2 and $ScvO_2$ increased significantly, and OE decreased only in responders' group after VE. VE significantly reduced ΔPCO_2 and lactate levels only in the responders' group (Table 3). VO_2 and $\Delta PCO_2/\Delta ContO_2$ ratio remained unchanged in both groups after VE.

We observed significant correlations between $\Delta ScvO_2$ and ΔCI (r = 0.42, $p = 0.003$) and between Δ-ΔPCO_2 and ΔCI (r = − 0.30, $p = 0.03$) after VE.

In patients with an increase in $VO_2 \leq 10\%$ (n = 36) after VE, the correlation between $\Delta ScvO_2$ and ΔCI was of 0.62 ($p < 0.001$). Also, in these patients, Δ-ΔPCO_2 was significantly correlated with ΔCI (r = − 0.47, $p = 0.004$).

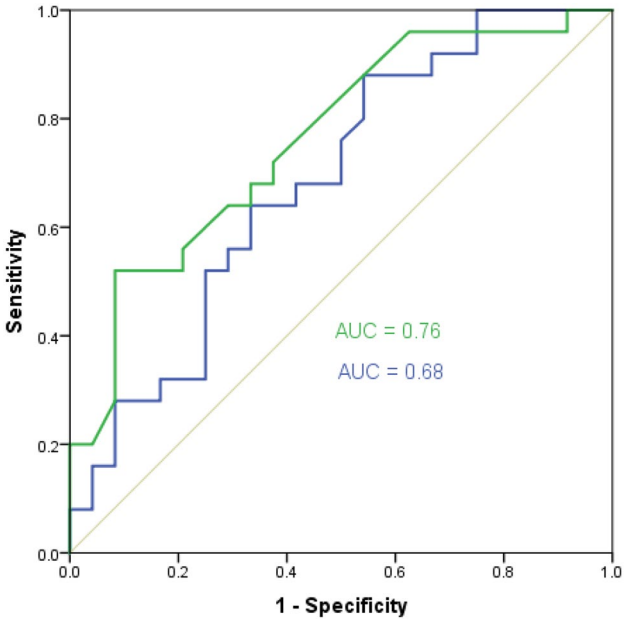

Figure 1. Receiver operating characteristic (ROC) curves showing the ability of the changes in ΔPCO_2 (Δ-ΔPCO_2) (green curve), $ScvO_2$ ($\Delta ScvO_2$) (blue curve) between before and after 500 mL of volume expansion to define fluid responsiveness (increase in cardiac index > 10% after volume expansion).

Ability of $\Delta ScvO_2$ and Δ-ΔPCO_2 to define fluid responsiveness (increase in CI > 10% after VE). The AUC for $\Delta ScvO_2$ was 0.68 (95% CI: 0.53–0.83) ($p = 0.02$) and for Δ-ΔPCO_2 was 0.76 (95% CI: 0.63–0.89) ($p < 0.001$) (Fig. 1). There were no significant differences between the AUCs for $\Delta ScvO_2$ and Δ-ΔPCO_2 ($p = 0.41$).

The best cutoff value (according to Youden index) for $\Delta ScvO_2$ was ≥ 3.5% (sensitivity = 64% [95% CI: 42–82%], specificity = 65% [95% CI: 43–84%]), which was lower than its LSC (5%). Taking into account the repeatability (LSC), the best cutoff value was ≥ 7.4% (sensitivity = 56% [95% CI: 35–76%], specificity = 71% [95% CI: 49–87%], PPV = 63% [95% CI: 39–83%], NPV = 61% [95% CI: 41–78%], $LR^+ = 1.8$ [95% CI: 0.9–3.7], and $LR^- = 0.7$ [95% CI: 0.4–1.1]).

The best cutoff value (according to Youden index) for Δ-ΔPCO_2 was ≤ -23.5% (sensitivity = 52% [95% CI: 31–72%], specificity = 87% [95% CI: 68–97%], which was lower than its LSC (36.5%). Taking into account the repeatability (LSC), the best cutoff value was ≤ -37.5% (sensitivity = 32% [95% CI:15–53%], specificity = 92% [95% CI: 73–99%], PPV = 79% [95% CI: 42–97%], NPV = 58% [95% CI: 42–74%], $LR^+ = 3.8$ [95% CI: 0.9–16.3], and $LR^- = 0.7$ [95% CI:0.6–1.0]).

In patients with an increase in $VO_2 \leq 10\%$, the AUC for $\Delta ScvO_2$ was 0.73 (95% CI: 0.57–0.90) ($p = 0.006$) and for Δ-ΔPCO_2 was 0.83 (95% CI: 0.69–0.97) ($p < 0.001$) (Fig. 2). There was no significant difference between the AUCs for $\Delta ScvO_2$ and Δ-ΔPCO_2 ($p = 0.41$).

The best cutoff value (according to Youden index) for $\Delta ScvO_2$ was ≥ 8.1% (sensitivity = 65% [95% CI: 38–86%], specificity = 74% [95% CI: 49–91%]), PPV = 73% [95% CI: 47–91%], NPV = 65% [95% CI: 40–85%], $LR^+ = 2.5$ [95% CI: 1.1–5.6], and $LR^- = 0.5$ [95% CI: 0.2–1.0]).

The best cutoff value (according to Youden index) for Δ-ΔPCO_2 was ≤ -25% (sensitivity = 59% [95% CI: 33–82%], specificity = 89% [95% CI: 65–99%], which was lower than its LSC (36.5%). Taking into account the repeatability (LSC), the best cutoff value was ≤ − 37.5% (sensitivity = 41% [95% CI: 18–67%], specificity = 100% [95% CI: 59–100%], PPV = 100% [95% CI: 62–100%], NPV = 60% [95% CI: 40–78%], $LR^+ = \infty$, and $LR^- = 0.60$ [95% CI: 0.4–0.9]).

Characteristics of patients with tissue hypoxia (ΔVO_2 > 10% after VE). At baseline, $\Delta PCO_2/\Delta ContO_2$ ratio was significantly higher in patients with $\Delta VO_2 > 10\%$ (tissue hypoxia) induced by volume expansion compared to patients with $\Delta VO_2 \leq 10\%$ (2.03 [1.73–2.27] vs. 1.39 [1.00–1.71] mmHg/mL, $p = 0.03$, respectively). We did not observe significant differences between patients with $\Delta VO_2 > 10\%$ and $\Delta VO_2 \leq 10\%$ regarding baseline lactate levels (2.35 [1.02–3.97] vs. 1.70 [1.40–3.10] mmol/L, $p = 0.89$, respectively) and baseline $ScvO_2$ levels (60 ± 17% vs. 59 ± 13%, $p = 0.78$, respectively).

The AUCs of baseline lactate and $ScvO_2$ values to predict $\Delta VO_2 > 10\%$ were 0.48 (95% CI: 0.28–0.69) ($p = 0.89$) and 0.54 (95% CI: 0.33–0.74) ($p = 0.72$), respectively. The AUC of baseline $\Delta PCO_2/\Delta ContO_2$ ratio to predict $\Delta VO_2 > 10\%$ after volume expansion was 0.84 (95% CI: 0.71–0.96) ($p < 0.001$) (Fig. 3). The best cutoff value (according to Youden index) for baseline $\Delta PCO_2/\Delta ContO_2$ ratio was > 1.70 (sensitivity = 77% [95% CI: 46–95%], specificity = 77% [95% CI: 60–90%]), PPV = 90% [95% CI: 73–98%], NPV = 55% [95% CI :31–78%], $LR^+ = 3.4$ [95% CI: 1.7–6.6], and $LR^- = 0.3$ [95% CI: 0.1–0.8]).

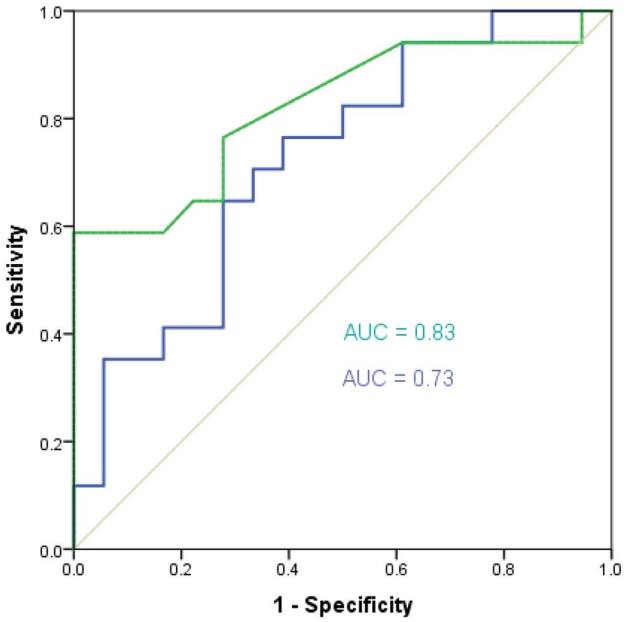

Figure 2. Receiver operating characteristic (ROC) curves showing the ability of the changes in ΔPCO_2 (Δ-ΔPCO_2) (green curve), $ScvO_2$ ($\Delta ScvO_2$) (blue curve) between before and after 500 mL of volume expansion to define fluid responsiveness (increase in cardiac index > 10% after volume expansion) in the subgroup of patients with an increase in oxygen consumption ≤ 10%.

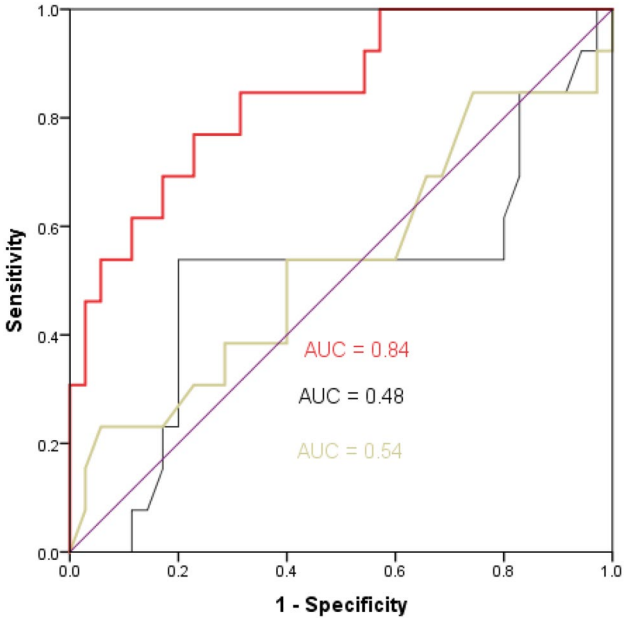

Figure 3. Receiver operating characteristic (ROC) curves showing the ability of baseline $\Delta PCO_2/\Delta ContO_2$ (red curve), $ScvO_2$ (yellow curve), and lactate (black curve) to predict an increase in oxygen consumption > 10% after 500 mL of volume expansion.

Discussion

The main findings of our study are: (1) in the whole population Δ-ΔPCO_2 induced by VE has an acceptable ability to define fluid responsiveness, but not $\Delta ScvO_2$; (2) The abilities of Δ-ΔPCO_2 and $\Delta ScvO_2$ to define fluid responsiveness improved when we considered only patients in whom changes in VO_2 were minimal ($\Delta VO_2 \leq 10\%$) after VE, i.e., patients without tissue hypoxia; 3) Baseline $\Delta PCO_2/\Delta ContO_2$ ratio has a good ability to predict the presence of tissue hypoxia (increases in $VO_2 > 10\%$ after VE).

Applying the modified Fick method to CO_2, venous-to-arterial PCO_2 difference reflects cardiac output. Several experimental studies have demonstrated the primary role of decreased tissue blood flow in the increased venous-to-arterial PCO_2 gap[8,21,22]. Similarly, a mathematical model analysis has confirmed that blood flow represents the major determinant in the elevation of venous-to-arterial PCO_2 gap[23]. A rise in mixed venous-to-arterial PCO_2 gap that was directly linked to a decrease in cardiac output has been observed in different types of circulatory failure including septic shock[24,25]. Mecher et al. found a significant negative correlation between the changes in cardiac output and mixed venous-to-arterial PCO_2 gap after fluid resuscitation in septic shock patients ($r = -0.42$, $p < 0.01$)[24]. In post-cardiac surgery sedated and mechanically ventilated patients with cardiac index < 2.5 L/min/m^2, ΔCI induced by VE (500-mL bolus of crystalloid given over 30 min) was found to be significantly correlated with Δ-ΔPCO_2 ($r = -0.53$, $p = 0.001$)[13]. However, the AUC for Δ-ΔPCO_2 to define fluid responsiveness was not determined in that study.

The correlation between Δ-ΔPCO_2 and ΔCI induced by VE was weaker in our septic patients than what was observed in post-cardiac surgery patients[13]. Also, the ability of Δ-ΔPCO_2 to define fluid responsiveness was not robust (AUC = 0.76). These findings could be explained by several factors. First, the relationship between ΔPCO_2 and CI is curvilinear[9], which means that the magnitude of changes in ΔPCO_2 is more pronounced at low CI than at normal or high CI. Second, the relationship between CO_2 content and PCO_2, which is curvilinear rather than linear, is influenced by many factors such as the degree of metabolic acidosis, hematocrit, and oxygen saturation (Haldane effect)[9,26]. However, we believe that this factor is unlikely to have occurred in our patients. Although base excess and hemoglobin significantly decreased in both groups (responders and non-responders) and $ScvO_2$ increased only in the responders' group (Tables 2, 3) after VE, it is unlikely that these clinically irrelevant changes could have affected the PCO_2/CO_2 content relationship. If these changes had affected the PCO_2/CO_2 content relationship, it would have resulted in an increase in ΔPCO_2 in both groups. Third, in situations of tissue hypoxia with VO_2/DO_2 dependency phenomenon and anaerobic CO_2 production, the rise in CI would increase VO_2 and VCO_2. This would attenuate the decrease in ΔPCO_2 related to the increase in blood flow[9,27]. We believe that this factor may have contributed to the reduction in the performance of Δ-ΔPCO_2 (AUC = 0.76) in defining an increase in CI > 10% induced by VE (fluid responsiveness) in the overall population. When we excluded patients with tissue hypoxia, patients with an increase in $VO_2 \leq 10\%$ (VO_2/DO_2 independency), we observed an improvement in the ability of Δ-ΔPCO_2 to define fluid responsiveness with a very good AUC of 0.83 (Fig. 2). A decrease in Δ-ΔPCO_2 of more or equal than 37.5% induced by VE allowed discrimination between responders and non-responders with a PPV of 100%. Also, the correlation between Δ-ΔPCO_2 and ΔCI was higher than in the overall population.

Venous oxygen saturation is a global marker of adequacy between oxygen consumption and oxygen supply[28]. Therefore, changes in venous oxygen saturation reflect changes in the balance between VO_2 and DO_2 and indicate tissue oxygenation. Giraud et al. observed, in 30 cardiogenic shock or postoperative cardiac surgery patients, that $\Delta ScvO_2$ was significantly correlated with ΔCI induced by a bolus of 500 mL of normal saline administered over 10-min ($r = 0.67$, $p < 0.001$)[14]. Also, $\Delta ScvO_2$ had an excellent ability to define an increase in CI ≥ 15% after VE (fluid responsiveness) with an AUC of 0.90. Our findings are different from those reported by Giraud et al.[14]. We observed in our whole septic population a weaker correlation between $\Delta ScvO_2$ and ΔCI ($r = 0.42$), and $\Delta ScvO_2$ had a poor ability to discriminate between responders and non-responders. In the subgroup of patients without tissue hypoxia (no significant increase in VO_2, or VO_2/DO_2 independency), even though the correlation between $\Delta ScvO_2$ and ΔCI improved, the ability of $\Delta ScvO_2$ to characterize fluid responsiveness was not good. The main explanation of the discrepancies between our findings and those of Giraud et al.[14] is that the patient populations are different. As has been previously described, venous oxygen saturation may not be a good indicator of tissue oxygenation in the setting of sepsis, due to microcirculatory shunting and mitochondrial dysfunction that can result in oxygen extraction abnormalities[29].

It has been suggested that $\Delta PCO_2/\Delta ContO_2$ ratio, considered as a surrogate of the respiratory quotient, can be used as a marker of global tissue hypoxia in critically ill patients[15,16,30]. In our study, we found that baseline $\Delta PCO_2/\Delta ContO_2$ value was significantly higher in patients with global tissue hypoxia (defined as an increase in $VO_2 > 10\%$ after VE) than those without global tissue hypoxia. Also, baseline $\Delta PCO_2/\Delta ContO_2$ ratio had a very good ability to predict the presence of VO_2/DO_2 dependency (global tissue hypoxia). Our results confirmed our previous findings[15] and those reported by Monnet et al.[16], who observed excellent predictability of baseline $\Delta PCO_2/\Delta ContO_2$ value for tissue hypoxia (AUCs = 0.96 and 0.94, respectively). Baseline lactate and $ScvO_2$ levels had poor ability to predict VO_2/DO_2 dependency (global tissue hypoxia) in our study. This finding is in line of what we observed previously in septic shock patients[15].

To the best of our knowledge, our study is the first to investigate the role of Δ-ΔPCO_2 and $\Delta ScvO_2$ in defining fluid responsiveness in septic patients. Our findings are valuable as they can be integrated in a clinical algorithm and used by the bedside provider as part of the assessment of fluid responsiveness. These values are readily available as patients in septic shock usually have arterial and central venous catheters inserted. After measuring O_2 content and CO_2 partial pressures, the $\Delta PCO_2/\Delta ContO_2$ ratio can help the provider recognize patients without tissue hypoxia. In these patients, ΔPCO_2 can be measured before and after VE and be used to appreciate if the latter has resulted in a significant increase in CI and to guide further fluid resuscitation when cardiac output monitoring is not available.

Our study presents several limitations. First, it is a single-center study, so the results might not universally apply. Second, we used central venous samples instead of mixed venous to assess oxygen and CO_2-derived variables, limiting its accuracy. However, we were interested in the changes in these variables induced by fluid challenge rather than their absolute values. Moreover, it has been shown that calculating the oxygen and CO_2-derived variables from the central venous blood permitted the detection of global tissue hypoxia in critically ill patients[15,16]. Third, our patients were sedated and mechanically ventilated with stable oxygen consumption; thus, our findings might not apply to spontaneously breathing patients with varying oxygen demands. Finally,

our study was not sufficiently powered for subgroup analyses; thus, our findings need to be replicated in a future study with larger sample size.

Conclusions

In sedated and mechanically ventilated septic patients with no signs of tissue hypoxia, Δ-ΔPCO_2 is a reliable parameter to define fluid responsiveness and can be used in the absence of CI measurement. Baseline $\Delta PCO_2/\Delta ContO_2$ ratio could help the physician recognize the presence of tissue hypoxia.

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Author contributions

J.M., B.N., and M.B. designed the study. J.M. conducted statistical analyses. N.V., G.G., F.P., and J.T. collected data. J.M., B.N., L.T., and D.T. participated in manuscript writing and reviewing. All authors read and approved the final manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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