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Central venous-to-arterial carbon dioxide difference combined with arterial-to-venous oxygen content difference ($P_{cva}CO_2/C_{av}O_2$) reflects microcirculatory oxygenation alterations in early septic shock

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ABSTRACT

Purpose: To explore the relationship between central venous-to-arterial carbon dioxide difference ($P_{cva}CO_2$), $P_{cva}CO_2$/arterial-venous oxygen content difference ratio ($P_{cva}CO_2/C_{av}O_2$) and the microcirculatory status, evaluated by using near-infrared spectroscopy, in septic shock patients.

Methods: Observational study in a 30-bed mixed ICU. Fifty septic shock patients within the first 24 h of ICU admission were studied. After restoration of mean arterial pressure, hemodynamic, metabolic and microcirculatory parameters were simultaneously evaluated. Local tissue oxygen saturation (StO_2), and local hemoglobin index (THI) were measured on the thenar eminence by means of near-infrared spectroscopy. A transient vascular occlusion test was performed in order to obtain StO_2 deoxygenation rate (DeO_2), local oxygen consumption ($nirVO_2$), and reoxgenation rate (ReO_2).

Results: At inclusion, increased $P_{cva}CO_2$ values were associated with lower StO_2 and THI, whereas increased $P_{cva}CO_2/C_{av}O_2$ values were associated with lower DeO_2, $nirVO_2$, and ReO_2. Multiple regression models confirmed the association between $P_{cva}CO_2/C_{av}O_2$ and $nirVO_2$, while $P_{cva}CO_2$ was only related to CI, and not to microcirculatory parameters.

Conclusions: In a population of early septic shock patients, increases in $P_{cva}CO_2$ and $P_{cva}CO_2/C_{av}O_2$ reflected different alterations at the microcirculatory level. While $P_{cva}CO_2$ was related to global flow, the $P_{cva}CO_2/C_{av}O_2$ ratio was associated to impaired local oxygen utilization and diminished microvascular reactivity.

1. Introduction

The recognition and correction of tissue hypoperfusion are fundamental in the management of septic shock patients. Currently, resuscitation strategies aim at correcting global oxygenation variables, such as lactate and central venous oxygen saturations ($S_{cv}O_2$) [1,2]. However, the negative results of large multicenter studies using $S_{cv}O_2$ as resuscitation endpoint [3] have highlighted the need for more appropriate targets [4]. On that behalf, several authors support targeting the microcirculation as the ultimate resuscitation endpoint [5,6]. The growing evidence on the prognostic value of microcirculatory alterations, independently of the macrohemodynamic status [7], strengthens the idea that the appropriate monitoring of the microcirculatory status might help improve resuscitation results in septic patients. Despite the advances in different technologies, monitoring the microcirculation at the bedside is still far from its incorporation into clinical practice, and the quest for better and readily available metabolic surrogates of the microcirculatory status is a research priority.

Recently, parameters derived from carbon dioxide metabolism have been proposed as useful tools in order to detect those patients with persisting tissue hypoperfusion despite normalization of $S_{cv}O_2$. In fact, current expert recommendations propose that resuscitation efforts should be maintained when normalized $S_{cv}O_2$ values coexist with central venous-to-arterial carbon dioxide differences ($P_{cva}CO_2$) > 6 mmHg

Abbreviations: C_aO_2, Arterial oxygen content; $C_{av}O_2$, Arterial-to-venous oxygen content difference; $C_{cva}CO_2$, Central venous-to-arterial carbon dioxide content difference; $C_{cva}CO_2/C_{av}O_2$, Central venous-to-arterial carbon dioxide content difference/arterial-venous oxygen content difference ratio; DeO_2, VOT-derived StO_2 de-oxygenation rate; DO_2, Global oxygen delivery; Hb, Hemoglobin.; MAP, Mean arterial pressure; $nirVO_2$, NIRS-derived thenar muscle oxygen consumption; P_aCO_2, Arterial carbon dioxide tension; $P_{cv}CO_2$, Central venous carbon dioxide tension; $P_{cva}CO_2$, Central venous-to-arterial carbon dioxide difference; $P_{cva}CO_2/C_{av}O_2$, Central venous-to-arterial carbon dioxide difference/arterial-venous oxygen content difference ratio; ReO_2, VOT-derived StO_2 re-oxygenation rate; SAPS II, Simplified Acute Physiology Score II; S_aO_2, Arterial oxygen saturation; $S_{cv}O_2$, Central venous oxygen saturation; StO_2, Tissue oxygen saturation; THI, Tissue hemoglobin index; VO_2, Global oxygen consumption; VOT, Vascular occlusion test.

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[2]. This recommendation would be reinforced as results of a recent study, where a nice correlation between $P_{cva}CO_2$ and microcirculatory flow was demonstrated[8]. Interestingly, $P_{cva}CO_2$ evolutionary changes were related to microvascular flow variables, such as the proportion of perfused small vessels (PPV), and not related to changes in cardiac output (CO) [8]. The authors concluded that during early phases of septic shock, $P_{cva}CO_2$ could reflect the adequacy of microvascular blood flow. However, since $P_{cva}CO_2$ seems highly related to flow, either global [8], or microcirculatory [9], some authors have also advocated for the correction of $P_{cva}CO_2$ by the arterial-to-central venous oxygen content difference ($P_{cva}CO_2/C_{av}O_2$), an estimation of the respiratory quotient, as a more reliable tool to detect the presence of tissue dysoxia [10-12]. Of note, the relationship between microcirculatory flow and the estimation of the respiratory quotient seems quite poor [8]. Since microcirculatory flow might not be equal to the metabolic status at the tissue level, the aim of the present study was to explore the relationship between global CO_2-derived parameters and microcirculatory oxygenation, evaluated by near-infrared spectroscopy.

2. Material and methods

2.1. Setting

We conducted a prospective observational study in a 30-bed mixed Intensive Care Unit (ICU) at a University Hospital (Parc Taulí Hospital Universitari. Sabadell, Spain). The local Ethics Committee approved the study (Comitè Ètic d'Investigació Clínica. Institut d'Investigació i Innovació Parc Taulí I^{3}PT. Reference CEIC 2016/044). Informed consent was obtained from each patient next of kin. This study is presented following the STROBE recommendations for reporting observational studies [13].

2.2. Patients and data collection

Septic shock patients within the first 24 h of ICU admission, and elected by the attending physician to use a cardiac output monitoring system ($PiCCO_2$ system. Pulsion Medical Systems, Feldkirchen, Germany) were studied. Septic shock was defined according to international sepsis definitions [14]. All patients were resuscitated following the *Surviving Sepsis Campaign* guidelines [1]. Exclusion criteria were: Age under 18 years old, the presence of uncontrolled source of infection, and impossibility to measure NIRS-derived tissue oxygenation parameters due to local conditions, such as skin and/or vascular injuries.

2.3. Protocol

Once normalized values of mean arterial pressure (MAP ≥65 mmHg) were achieved, simultaneous measurements of hemodynamic, metabolic and microcirculatory parameters were made.

1) Hemodynamic variables were acquired using the $PiCCO_2$ system. Cardiac output (CO) values were obtained by the transpulmonary thermodilution (TPTD) technique, described elsewhere [15]. Briefly, three successive cold boluses of 15 mL of 0.9% saline were injected through the distal port of a central venous catheter. The injections were performed as rapid as possible, irrespective of the respiratory cycle. The thermodilution curves recorded by the arterial thermistance were automatically analyzed by the $PiCCO_2$ device, allowing for the calculation of the value of cardiac output. The three boluses were performed one after another, as soon as the blood temperature returned to its baseline, as indicated by the device. The mean value of the three determinations was calculated in order to provide the final CO value.
2) Blood samples were obtained from a central venous line and an arterial catheter. The investigators confirmed the correct positioning of the venous catheter tip on chest X-Ray exams. Arterial and central venous blood samples were analyzed using point-of-care equipment (ABL 800 Flex; Radiometer Medical, Copenhagen, Denmark). Measured variables included: arterial oxygen tension (P_aO_2), arterial carbon dioxide tension (P_aCO_2), central venous oxygen tension ($P_{cv}O_2$), central venous carbon dioxide tension ($P_{cv}CO_2$). Arterial oxygen saturation (S_aO_2) and central venous oxygen saturation ($S_{cv}O_2$) were calculated from the oxy-hemoglobin dissociation curve. Arterial and central venous lactate, and hemoglobin concentration (Hb) were also measured. Central venous ($C_{cv}CO_2$) and arterial (C_aCO_2) carbon dioxide contents were determined according to Douglas et al. [16] (Supplementary material. Appendix 1), and the central venous-to-arterial carbon dioxide content difference was computed ($C_{cva}CO_2$). The arterial oxygen content (C_aO_2), central venous oxygen content ($C_{cv}O_2$), arterial-to-venous oxygen content difference ($C_{av}O_2$), the $P_{cva}CO_2$, the $P_{cva}CO_2/C_{av}O_2$ ratio, the $C_{cva}CO_2/C_{av}O_2$ ratio, and the difference between $P_{cva}CO_2/C_{av}O_2$ and $C_{cva}CO_2/C_{av}O_2$ were calculated according to the following formulas:

$$C_aO_2 = (1.34 \times S_aO_2 \times Hb) + (0.003 \times P_aO_2).$$

$$C_{cv}O_2 = (1.34 \times S_{cv}O_2 \times Hb) + (0.003 \times P_{cv}O_2).$$

$$C_{av}O_2 = C_aO_2 - C_{cv}O_2.$$

$$P_{cva}CO_2 = P_{cv}CO_2 - P_aCO_2.$$

$$(P_{cv}CO_2 - P_aCO_2) - (C_aO_2 - C_{cv}O_2) = (P_{cva}CO_2 - C_{cva}CO_2)/C_{av}O_2.$$

3) Tissue oxygen saturation (StO_2) was recorded continuously using the InSpectra™ 650 Tissue Spectrometer (Hutchinson Tech., Hutchinson, Minnessotta). The StO_2 15-mm optical surface probe was placed on intact skin on the thenar eminence; it was never placed adjacent to the site of a radial artery cannulation. The InSpectra™ 650 Tissue Spectrometer also measures relative hemoglobin concentration in the NIR field of view, which is presented as the tissue hemoglobin index (THI). In addition to the steady-state StO_2 value, the response to a transient ischemic challenge was also computed. The ischemic challenge consisted in a standardized Vascular Occlusion Test (VOT), and was performed as previously described by Gómez et al. [17]. Briefly, a blood pressure cuff was placed proximal to the hand on the forearm and rapidly inflated at 40 mmHg above systolic pressure and kept inflated until StO_2 decreased to 40%. Then the cuff was rapidly deflated and the rate of increase in StO_2 was noted. The resulting deoxygenation (DeO_2) and reoxygenation (ReO_2) slopes are reported as change in O_2 saturation over time. Since DeO_2 represents the progressive desaturation of hemoglobin, it has been proposed as a marker of local oxygen extraction [18]. Using the DeO_2 slope and the THI values at the beginning and at the end of the VOT we also calculated the NIRS-derived thenar muscle oxygen consumption ($nirVO_2$), as described by Skarda et al. [19]:

$$nirVO_2 = (DeO_2\ slope)^{-1}/[(THI_{start} + THI_{end})/2].$$

On the other hand, ReO_2 reflects the increase in saturated hemoglobin, which depends on blood inflow and capillary recruitment after the hypoxic stimulus, and therefore has been proposed as a marker of endothelial function [18].

Absolute StO_2 and VOT-derived variables were obtained using the InSpectra Research Software® v4.01 (Hutchinson Tech.).

Patient demographics, diagnosis at ICU admission, sepsis origin, Acute Physiology and Chronic Health disease Classification System II (APACHE II), Simplified Acute Physiology Score 3 (SAPS 3), and Sequential Organ Failure Assessment (SOFA) Score were recorded at inclusion.

2.4. Outcome measures

The primary outcome was the correlation between $P_{cva}CO_2/C_{av}O_2$ and StO_2-derived oxygen utilization ($nirVO_2$). Secondary outcomes included the relationships between $P_{cva}CO_2$ and $P_{cva}CO_2/C_{av}O_2$ with other measured microcirculatory and global hemodynamic variables.

2.5. Sample size calculation

In order to detect a significant correlation coefficient of 0.4 or higher between $P_{cva}CO_2/C_{av}O_2$ and $nirVO_2$, accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, we determined a required sample size of 47 patients.

2.6. Statistical analysis

Statistical analysis was performed by means of IBM SPSS statistics 20.0 software (IBM Corporation). Normal distribution of the studied variables was confirmed using the Kolmogorov-Smirnov test. Accordingly, continuous variables were expressed as mean ± standard deviation (SD), and categorical variables were expressed as absolute number and proportions (%). A descriptive analysis was performed. Correlations between hemodynamic, metabolic and microcirculatory variables were explored using the Pearson correlation test. Three pre-defined groups according to $P_{cva}CO_2$, in agreement with previous studies, were defined [9]: (1) <6 mmHg, (2) 6–9.9 mmHg, and (3) ≥10 mmHg. Three groups were also pre-defined for $P_{cva}CO_2/C_{av}O_2$ in agreement with previous observations [10,11]: (1) <1, (2) 1–1.8, and (3) >1.8. Differences among groups were assessed using the Kruskal-Wallis test, with a post hoc Mann-Whitney analysis. Stepwise multiple linear regression models were used to determine the association of CO_2-derived parameters with macrocirculatory and microcirculatory variables. A two-tailed p value of <0.05 was taken to indicate statistical significance.

3. Results

Fifty septic shock patients were studied. Demographic, hemodynamic, metabolic, and microcirculatory characteristics are shown in Table 1. At inclusion, all patients were under mechanical ventilation and receiving norepinephrine infusion for maintaining normalized MAP values (79 ± 11 mmHg).

The obtained $P_{cva}CO_2$ showed a significant negative correlation with CI ($r = -0.74$, $p < 0.001$), and $ScvO_2$ ($r = -0.54$, $p < 0.001$). The $P_{cva}CO_2/C_{av}O_2$ ratio significantly correlated with lactate ($r = 0.65$, $p < 0.001$), $ScvO_2$ ($r = 0.5$, $p < 0.01$), pH ($r = -0.54$, $p < 0.01$), and norepinephrine dose ($r = 0.4$, $p < 0.03$), but not with CI. When referred to microcirculatory parameters, $P_{cva}CO_2$ values negatively correlated with StO_2 ($r = -0.4$, $p < 0.03$) and THI ($r = -0.54$, $p < 0.01$). The $P_{cva}CO_2/C_{av}O_2$ ratio negatively correlated with $nirVO_2$ ($r = -0.53$, $p < 0.01$) and ReO_2 ($r = -0.4$, $p < 0.04$). Lactate values inversely correlated with $nirVO_2$ and ReO_2 (Fig. 1). The $C_{cva}CO_2/C_{av}O_2$ ratio did not show any significant correlation with any of the studied hemodynamic, metabolic, or microcirculatory parameters. The difference between $P_{cva}CO_2/C_{av}O_2$ and $C_{cva}CO_2/C_{av}O_2$ significantly correlated with DeO_2 ($r = 0.4$, $p < 0.04$), $nirVO_2$ ($r = -0.6$, $p < 0.001$), and ReO_2 ($r = -0.6$, $p < 0.001$).

For the pre-defined groups of $P_{cva}CO_2$, we observed significant higher StO_2 values in those patients with $P_{cva}CO_2$ below 6 mmHg (Fig. 2). No differences in the dynamic StO_2-derived parameters were observed. For the three pre-defined groups of $P_{cva}CO_2/C_{av}O_2$, while no differences in StO_2 were detected, progressively higher alterations in DeO_2, $nirVO_2$ and ReO_2 were observed at progressively higher $P_{cva}CO_2/C_{av}O_2$ values (Fig. 3).

Stepwise multiple linear regression models showed that $P_{cva}CO_2$ was significantly associated with CI, but not with microcirculatory parameters (Table 2). The best predictive model for $P_{cva}CO_2/C_{av}O_2$ was obtained with $C_{cva}CO_2/C_{av}O_2$, pH, and $nirVO_2$ (R^2 0.88, $p < 0.001$). No associations were found between $C_{cva}CO_2/C_{av}O_2$ and both, macro and microcirculatory parameters. When exploring the relationship between $(P_{cva}CO_2 - C_{cva}CO_2)/C_{av}O_2$ and other variables, the stepwise regression model detected a significant association with pH and $nirVO_2$, but not with macrocirculatory parameters.

Table 1
Demographic, hemodynamic, metabolic and microcirculatory characteristics of the studied population at inclusion. A descriptive analysis of the patients at inclusion is presented.

	All (n = 50)
Age (years)	64 ± 15
Male (n, %)	34 (68)
Source of infection (n, %)	
Pneumonia	12 (24)
Abdominal	18 (36)
Urinary tract	4 (8)
Soft tissue	6 (12)
Other	10 (20)
APACHE II	21 ± 8
SAPS 3	67 ± 13
SOFA (day 1)	11 ± 3
MV (n, %)	50 (100)
HR (min^{-1})	101 ± 17
MAP (mmHg)	79 ± 11
CI ($L/min/m^2$)	3.3 ± 1.2
NE use (%)	50 (100)
NE dose (mcg/kg/min)	0.9 ± 1.14
pH	7.34 ± 0.11
Bicarbonate (mmol/L)	19.9 ± 4.9
BE (mmol/L)	−5.9 ± 6.1
Hb (g/dL)	10.7 ± 2.3
$S_{cv}O_2$ (%)	68 ± 11
Lactate (mmol/L)	4.3 ± 4.2
$P_{cva}CO_2$ (mmHg)	5.8 ± 2.6
$P_{cva}CO_2/C_{av}O_2$ (mmHg·dL/mL O_2)	1.55 ± 0.72
$C_{cva}CO_2/C_{av}O_2$	1.44 ± 0.6
StO_2 (%)	77 ± 10
DeO_2 (%/min)	−11.0 ± 4.0
$nirVO_2$	115 ± 48
ReO_2 (%/*sec*)	2.95 ± 1.75
THI	8.2 ± 4.1

APACHE II, Acute Physiology and Chronic Health Evaluation score II; *SAPS 3*, Simplified Acute Physiological Score 3; *SOFA*, Sequential Organ Failure Assessment score; MV, Mechanical ventilation; HR, heart rate; *MAP*, mean arterial pressure; *CI*, Cardiac Index; *NE*, norepinephrine; *BE*, Base excess; *Hb*, hemoglobin; *$ScvO_2$*, central venous oxygen saturation; *$P_{cva}CO_2$*, central venous-to-arterial carbon dioxide difference; *$P_{cva}CO_2/C_{av}O_2$ ratio*, central venous-to-arterial carbon dioxide difference/arterial-to-central venous oxygen content difference ratio; *$C_{cva}CO_2/C_{av}O_2$ ratio*, central venous-to-arterial carbon dioxide content difference/arterial-to-central venous oxygen content difference ratio; *StO_2*, thenar oxygen saturation; *DeO_2*, StO_2-deoxygenation slope; *$nirVO_2$*, NIRS-derived thenar muscle oxygen consumption; *ReO_2*, StO_2-reoxygenation slope; *THI*, Tissue hemoglobin index.

4. Discussion

The main result of our study is that, in a population of early septic shock patients, increases in $P_{cva}CO_2$ and in $P_{cva}CO_2/C_{av}O_2$ were associated with alterations at the microcirculatory level. While $P_{cva}CO_2/C_{av}O_2$ was independently associated with microcirculatory functional parameters, such as impaired tissue oxygen utilization, the relationship between $P_{cva}CO_2$ and the microcirculation was only independently determined by global flow, but not by local flow parameters, such as StO_2 and THI.

Recently, $P_{cva}CO_2$ has been included as an additional resuscitation endpoint in the international consensus recommendations on hemodynamic monitoring [2]. Observational data on the prognostic value of persistently elevated $P_{cva}CO_2$ [20-22], and the existing evidence supporting that high $P_{cva}CO_2$ values are closely related to low cardiac index (CI) situations, have derived in the actual recommendation of further increasing CI when $P_{cva}CO_2$ is above 6 mmHg [2]. No prospective

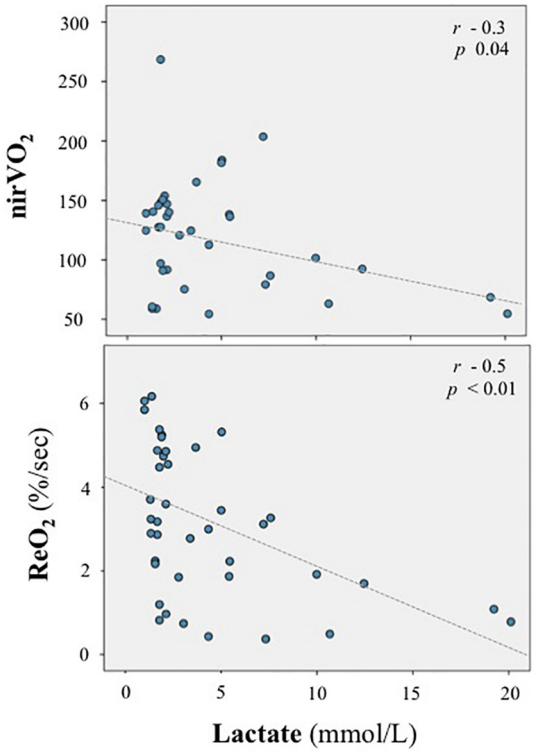

Fig. 1. Correlation between microcirculatory parameters and lactate values at inclusion. Lactate values inversely correlated with StO_2-derived parameters reflecting tissue metabolic status ($nirVO_2$) and endothelial reactivity (ReO_2).

evidence supporting the benefit of integrating this parameter in the decision tree has been published to date. In a recent study, Ospina-Tascon and colleagues investigated the relationship of $P_{cva}CO_2$ and microcirculatory flow, and demonstrated that high $P_{cva}CO_2$ values are associated with low proportion of perfused small vessels (PPV) [9]. Interestingly, evolutionary changes in $P_{cva}CO_2$ were better explained by changes in PPV than by changes in CI. These observations would support the need for further resuscitating the "hypovolemic" microcirculation in high $P_{cva}CO_2$ situations. Although we explored a different microcirculatory bed, and a completely different technology, our observations of the association between high $P_{cva}CO_2$ values with lower StO_2 and THI values are in accordance with the observations by Ospina-Tascon and colleagues. Previously published data already detected the relationship between these two NIRS-derived parameters with progressive reductions in stroke volume in a model of central hypovolemia [23-25]. However, our data suggest that the association between $P_{cva}CO_2$ and these microcirculatory flow parameters is determined by global flow, and not necessarily reflects the metabolic compromise of the microcirculation. It is crucial to bear in mind that adequate microvascular flow does not imply preserved tissue metabolism, which can be compromised by other mechanisms, such as impaired utilization of the oxygen due to tissue edema or to mitochondrial dysfunction. The lack of association between $P_{cva}CO_2$ and the StO_2-derived dynamic tissue oxygenation and endothelial reactivity parameters would point towards a significant differentiation between microcirculatory flow and microcirculatory metabolic status. Therefore, despite high $P_{cva}CO_2$ values, further resuscitation efforts should be only considered when there is evidence of metabolic compromise.

It is noteworthy that Ospina-Tascon and colleagues observed that microcirculatory flow was poorly correlated with the $C_{cva}CO_2/C_{av}O_2$ [9]. Since several authors have demonstrated that $C_{cva}CO_2/C_{av}O_2$ and $P_{cva}CO_2/C_{av}O_2$ better reflect the ongoing metabolic status than $P_{cva}CO_2$ [10-12,26], the observations by Ospina-Tascon and colleagues are not surprising, and would again reinforce the fact that microcirculatory flow and microcirculatory metabolism might be related, but they are not equivalent. A close relationship would be anticipated in profound hypoxic conditions, in patients with extremely low CI values, for instance. But low global and/or microcirculatory flow might not cause

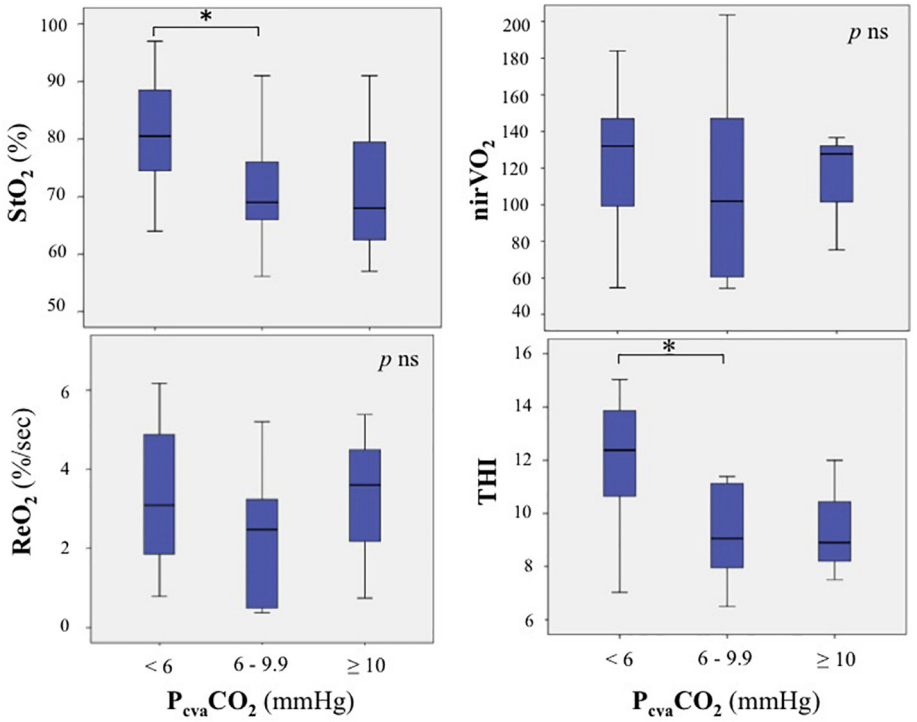

Fig. 2. NIRS-derived tissue oxygenation variables for the predefined $P_{cva}CO_2$ groups. (A) Tissue oxygen saturation (StO_2), (B) $nirVO_2$, (C) ReO_2, and (D) THI for the three $P_{cva}CO_2$ groups (<6 mmHg; 6–9.9 mmHg; and ≥10 mmHg). *Boxes* denote interquartile range, *horizontal lines* in the boxes represents the median values, and *whiskers* extend 1.5 times the interquartile range above and below the 25th and 75th percentiles. *post-hoc Mann-Whitney analysis: $p < 0.05$ for group comparisons.

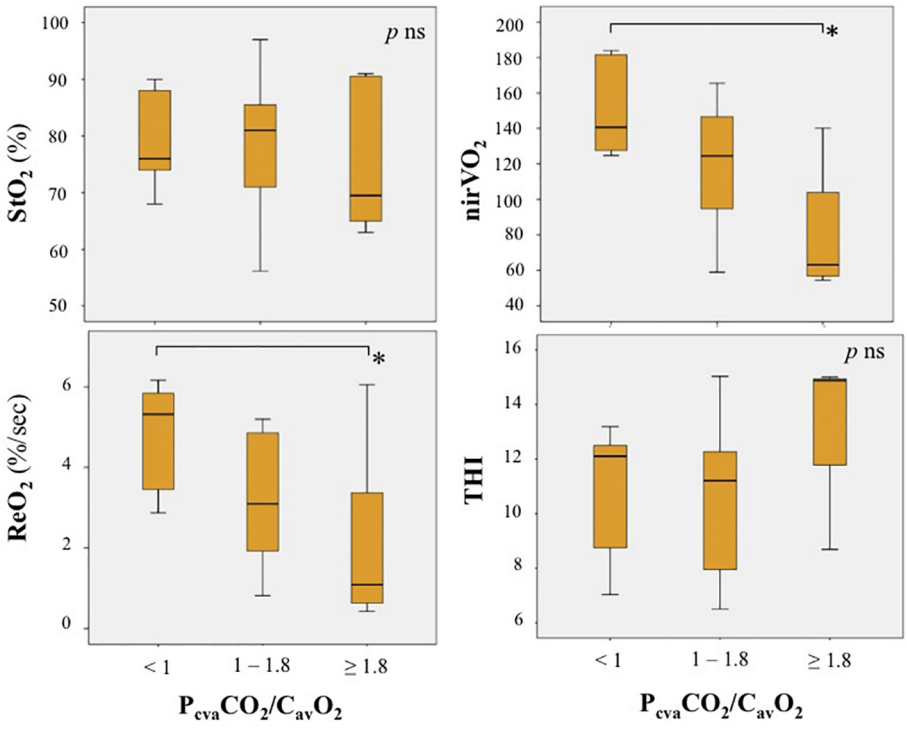

Fig. 3. NIRS-derived tissue oxygenation variables for the predefined $P_{cva}CO_2/C_{av}O_2$ groups. (A) Tissue oxygen saturation (StO_2), (B) $nirVO_2$, (C) ReO_2, and (D) THI for the three $P_{cva}CO_2/C_{av}O_2$ groups (<1 mmHg·dL/mL O_2; 1–1.8 mmHg·dL/mL O_2; and ≥1.8 mmHg·dL/mL O_2). *Boxes* denote interquartile range, *horizontal lines* in the boxes represents the median values, and *whiskers* extend 1.5 times the interquartile range above and below the 25th and 75th percentiles. *post-hoc Mann-Whitney analysis: $p < 0.05$ for group comparisons.

microcirculatory hypoxia when local oxygen demands are already met. On the other hand, despite the normalization of microcirculatory flow, alterations in oxygen utilization and anaerobic metabolism might coexist as a consequence of alterations in the diffusive transportation of oxygen, and/or due to mitochondrial dysfunction. Our data confirm the association between increases in $P_{cva}CO_2/C_{av}O_2$ and alterations in local oxygen utilization, such as DeO_2 and $nirVO_2$. In healthy subjects, normal values of DeO_2 and $nirVO_2$ are close to −13%/min and 350 U, respectively [17,27]. In septic patients, both parameters are altered, and abolished extraction (DeO_2 below −10%/min) and lower oxygen consumption ($nirVO_2$ as low as 100 U) have been repeatedly reported [27,28]. Importantly, more profound metabolic alterations have been associated with increased morbidity and mortality [18,28]. The same observations are also true for endothelial integrity. While in healthy conditions normal ReO_2 values are close to 5%/*sec* [17,27], the response to ischemia is blunted in septic patients (ReO_2 below 3%/sec in septic shock patients), and the degree of impairment has also demonstrated prognostic value [18,27,28]. In our population, alterations in these variables were more profound in the group of $P_{cva}CO_2/C_{av}O_2 > 1.8$, suggesting higher impairment in the metabolic status of the tissue and in the endothelial function in these patients. The values of DeO_2, $nirVO_2$ and ReO_2 did not differ among the different $P_{cva}CO_2$ groups. As a whole, our data suggest that $P_{cva}CO_2/C_{av}O_2$ is a more reliable marker of the metabolic status than $P_{cva}CO_2$. In accordance with previous observations [29,30], we might consider that alterations in $P_{cva}CO_2/C_{av}O_2$ can not be interpreted as a marker of oxygen consumption (VO_2)/oxygen delivery (DO_2) dependency, but just as a marker of tissue dysoxia. Whether tissue dysoxia derives from VO_2/DO_2 dependency or from impaired oxygen utilization can not be properly answered with a single $P_{cva}CO_2/C_{av}O_2$ measurement.

Finally, our findings suggest that the current approach to microcirculatory manipulation and optimization, highly linked to the use of videomicroscopic techniques, might be partial, and its complementation with tissue metabolic variables might be more adequate.

4.1. Study limitations

Several limitations might be taken into account when considering our results. Firstly, this is a single-center study, so our results might

Table 2
Multiple linear regression models for variables related to $P_{cva}CO_2$, $P_{cva}CO_2/C_{av}O_2$, and $(P_{cva}CO_2 - C_{cva}CO_2)/C_{av}O_2$.

Response variable	Explanatory variables	Unstandardized coefficient (B)	95% Confidence Interval	*p*	R^2
$P_{cva}CO_2$	CI	−1.41	−2.1, −0.75	<0.001	0.6
	StO_2	–	–	0.5	–
	THI	–	–	0.5	–
$P_{cva}CO_2/C_{av}O_2$	$C_{cva}CO_2/C_{av}O_2$	0.94	5.6, 23.7	<0.001	0.66
	pH	−1.89	−3.13, −0.64	<0.01	0.82
	$nirVO_2$	−0.01	−0.01, −0.002	<0.01	0.88
$(P_{cva}CO_2-C_{cva}CO_2)/C_{av}O_2$	pH	−1.83	−3.03, −0.63	<0.001	0.48
	$nirVO_2$	−0.01	−0.01, −0.002	<0.01	0.65

$P_{cva}CO_2$, central venous-to-arterial carbon dioxide pressure difference; $C_{cva}CO_2$, central venous-to-arterial carbon dioxide content difference; $C_{av}O_2$, arterial-to-venous oxygen content difference; *CI*, cardiac index; StO_2, tissue oxygen saturation; tissue hemoglobin index; $nirVO_2$, StO_2-derived thenar muscle oxygen consumption. R^2 represents the R square for each model, progressively including the explanatory variables in the stepwise regression model.

have limitations when trying to generalize for other ICUs, or other settings. On the other hand, the homogeneity of our resuscitation process would strengthen the value of the observed results.

Secondly, our associations correspond to a single time point observation, and therefore we can not infer any hypotheses regarding the evolutionary behavior of the different parameters.

We used central venous blood for the calculation of O_2 and CO_2-derived parameters. Thus, our results might not apply when mixed venous blood is used. Although a reasonable agreement has been reported for oxygen saturation values, the agreement between carbon dioxide gradients has not been widely evaluated. There are numerous potential causes of error in the calculation of the CO_2-derived parameters, mainly derived from the variability of the different parameters measured [31], and this is especially relevant when using the Douglas formula, where the accumulation of even slight variations of the variables in the equation might be amplified.

5. Conclusions

In a population of early septic shock patients with normalized MAP, increases in $P_{cva}CO_2/CavO_2$, but not in $P_{cva}CO_2$, were associated with alterations at the microcirculatory level. While $P_{cva}CO_2$ was related to global flow, the $P_{cva}CO_2/C_{av}O_2$ ratio reflected tissue dysoxia and impaired microvascular reactivity.

Conflict of interests

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics approval and consent to participate

The local Ethics Committee (Comitè Ètic d'Investigació Clínica, Fundació Parc Taulí) approved the study (protocol reference CEIC-2016/044). Signed informed consent was obtained from each patient's next of kin.

Competing interests

The authors declare that they have no competing interests.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Authors' contributions

All the authors contributed to the elaboration of this manuscript. JM, CE, and GG conceived, designed, and coordinated the study. JM, CE, PS, GG, EC, and APM performed data extraction. JM, CE and GG analyzed the data, and drafted the manuscript. All authors read and approved the final version of the manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2019.06.013.

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