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Evaluating tissue hypoxia and the response to fluid administration in septic shock patients: a metabolic cluster analysis

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Abstract

Background The selection of adequate indicators of tissue hypoxia for guiding the resuscitation process of septic patients is a highly relevant issue. Current guidelines advocate for the use of lactate as sole metabolic marker, which may be markedly limited, and the integration of different variables seems more adequate. In this study, we explored the metabolic profile and its implications in the response to the administration of a fluid challenge in early septic shock patients.

Methods Observational study including septic shock patients within 24 h of ICU admission, monitored with a cardiac output estimation system, with ongoing resuscitation. Hemodynamic and metabolic variables were measured before and after a fluid challenge (FC). A two-step cluster analysis was used to define the baseline metabolic profile, including lactate, central venous oxygen saturation ($ScvO_2$), central venous-to-arterial carbon dioxide difference ($PcvaCO_2$), and $PcvaCO_2$ corrected by the difference in arterial-to-venous oxygen content ($PcvaCO_2/CavO_2$).

Results Seventy-seven fluid challenges were analyzed. Cluster analysis revealed two distinct metabolic profiles at baseline. Cluster A exhibited lower $ScvO_2$, higher $PcvaCO_2$, and lower $PcvaCO_2/CavO_2$. Increases in cardiac output (CO) were associated with increases in VO_2 exclusively in cluster A. Baseline isolated metabolic variables did not correlate with VO_2 response, and changes in $ScvO_2$ and $PcvaCO_2$ were associated to VO_2 increase only in cluster A.

Conclusions In a population of early septic shock patients, two distinct metabolic profiles were identified, suggesting tissue hypoxia or dysoxia. Integrating metabolic variables enhances the ability to detect those patients whose VO_2 might increase as results of fluid administration.

Keywords Lactate, Venous oxygen saturation, Venous-to-arterial carbon dioxide difference, Fluid responsiveness, Circulatory shock, Hemodynamic monitoring

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Background

In septic shock patients, the process of hemodynamic resuscitation pivots in the detection and correction of tissue hypoxia resulting from cardiovascular insufficiency [1]. Circulatory tissue hypoxia is defined as a situation of inadequate availability of oxygen in the tissues, causing impaired oxygen consumption (VO_2), that may be remedied by increasing global oxygen delivery (DO_2) [2, 3]. Nevertheless, the optimal metabolic marker of such VO_2/DO_2-dependent tissue hypoxia fordriving the resuscitation process remains a subject of ongoing debate. The recent Surviving Sepsis Guidelines advocate for prioritising lactate kinetics in hemodynamic resuscitation, whilst de-emphasising the use of other physiological markers, such as central venous oxygen saturation ($ScvO_2$) [4]. However, lactate kinetics may be altered not only in tissue hypoxic conditions, but also in situations of abnormal utilization of oxygen not dependent on tissue perfusion – such as the existence of mitochondrial dysfunction -, a situation known as tissue dysoxia [5–7]. In these later situations, further increasing cardiac output would not be linked to a metabolic improvement, and might be even detrimental for the patient, as results of increased fluid balance, for instance [8, 9].

In addition to lactate and $ScvO_2$, central venous-to-arterial carbon dioxide ($PcvaCO_2$) variables have recently emerged as valuable tools for detecting ongoing tissue hypoxia/hypoperfusion. Elevated $PcvaCO_2$ seems to reflect low flow conditions [10], whereas correcting $PcvaCO_2$ by the difference in arterial-to-venous oxygen content ($CavO_2$) provides an estimation of the respiratory quotient, indicating real-time anaerobic metabolism [11–13].

Since every single metabolic marker has its drawbacks, an integrative approach, combining different variables, would seem appropriate to better understand the metabolic status of the patient, with special interest in whether this metabolic status would benefit from increasing cardiac output. Our initial hypothesis was that an integrative approach, combining several metabolic markers, would improve the detection of VO_2/DO_2 dependency and, therefore, would lead to a better understanding of the presence of tissue hypoxia, with direct impact on resuscitation interventions.

The main objective of the present study was to analyse the usefulness of integrating different metabolic markers to detect tissue hypoxia that could benefit from hemodynamic interventions. Tissue hypoxia was defined as an increase in VO_2 following an increase in cardiac output (CO) via a fluid challenge [2, 3].

Materials and methods

Setting

A prospective observational study was conducted in a 30-bed mixed Intensive Care Unit (ICU) at a University Hospital (Parc Taulí Hospital Universitari. Sabadell, Spain), from January 2017 to January 2020. The local Ethics Committee approved the study (Comitè Ètic d'Investigació Clínica. Institut d'Investigació i Innovació Parc Taulí I^3PT. Reference CEIC 2016/044). Informed consent to participate was obtained from each patient next of kin. This study is presented following the STROBE recommendations for reporting observational studies [14].

Patients and data collection

We studied septic shock patients within the first 24 h of ICU admission, already monitored with a cardiac output monitoring system ($PiCCO_2$ system. Pulsion Medical Systems, Feldkirchen, Germany), and selected by the attending physician for performing a fluid challenge (FC) due to suspected tissue hypoperfusion [15]. Septic shock was defined according to international sepsis definitions [16]. Exclusion criteria were: Age under 18 years old, and uncontrolled hemodynamic instability, defined as the need for significant changes in vasopressor support (>10% from baseline dose) within the 15-minute period prior to, and/or during the administration of fluids. Patients receiving continuous renal replacement therapies were also excluded, since the CO values obtained from the thermodilution techniques might be potentially affected [17].

Protocol

Upon confirmation of normalised and stable mean arterial pressure (MAP≥65 mmHg), simultaneous baseline measurements of hemodynamic and metabolic variables were taken. Once the first set of measurements was completed, a fluid challenge (FC) was performed, defined as a rapid infusion of 500 mL of crystalloids (<20 min). Immediately after completion of the fluid expansion, a second set of hemodynamic and metabolic variables was collected.

1) Hemodynamic variables were acquired using the $PiCCO_2$ system. Cardiac output (CO) values were obtained by the transpulmonary thermodilution (TPTD) technique, described elsewhere [17]. 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 to provide the final CO value.

2) Blood samples were procured from both a central venous line and an arterial catheter. The investigators confirmed the correct positioning of the venous catheter tip in the superior vena cava 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). Venous blood samples were obtained from the distal port of the central venous line. 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. 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 $P_{cva}CO_2$, and the $P_{cva}CO_2/C_{av}O_2$ ratio were calculated according to the following formulas:

- $C_aO_2 = (1.34 \times S_aO_2 \times Hb) + (0.003 \times P_aO_2)$.
- $C_{cv}O_2 = (1.34 \times S_{cv}O_2 \times Hb) + (0.003 \times P_{cv}O_2)$.
- $C_{av}O_2 = C_aO_2 - C_{cv}O_2$.
- $P_{cva}CO_2 = P_{cv}CO_2 - P_aCO_2$.

Global oxygen delivery (DO_2), consumption (VO_2), and extraction (O_2ER) were calculated according to the following formulas:

- DO_2 = cardiac output x $C_aO_2 \times 10$.
- VO_2 = cardiac output x $C_{av}O_2 \times 10$.
- $O_2ER = C_{av}O_2/C_aO_2$.

Patient demographics, sepsis origin, and the trigger for the hemodynamic intervention were recorded at inclusion.

Outcomes

The primary outcome was the increase in VO_2 following the fluid challenge. Secondary outcomes encompassed the evaluation of the responses in CO, and in the different metabolic variables.

Statistical analysis

Statistical analysis was conducted using IBM SPSS statistics 28.0 software (IBM Corporation). The normal distribution of the studied variables was confirmed via 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. A two-step cluster analysis was used to group patients according to baseline metabolic variables, including lactate, O_2ER, $ScvO_2$, $PcvaCO_2$ and $PcvaCO_2/CavO_2$. Clustering analysis is an exploratory method for detecting non-apparent similarities within a population [18]. In order to detect these hidden similarities or patterns, several variables are included in the model. Since we aimed at unmasking different metabolic patterns, we decided to include baseline metabolic variables in the analysis. Of note, all the included variables have a distinctive physiological meaning, and our hypothesis was that their combination might be of value when trying to detect different metabolic patterns. Several models, using different metabolic variables were built, and the best model was finally processed. Comparisons between clusters were made using the Student's t-test and Chi-squared test for continuous and categorical variables, respectively. Correlations between hemodynamic and metabolic variables, and their changes after the FC, were explored using the Pearson correlation test. A two-tailed p value of less than 0.05 was taken to indicate statistical significance.

Results

A total of seventy-seven fluid expansions from fifty-five patients were analysed. The mean age of the patients was 62 ± 16 years, with 34 (62%) being males. Nearly all patients were receiving norepinephrine infusion (96%) and were mechanically ventilated (91%). The primary triggers for performing the fluid challenge were persistence of elevated lactate values (lactate > 2.2 mMol/L) (81%), and/or low $ScvO_2$ values ($ScvO_2$ < 70%) (42%).

Clustering analysis

Baseline metabolic status was explored by means of two-step cluster analysis. The best model identified two distinct metabolic clusters, based on the distribution of baseline $ScvO_2$, $PcvaCO_2$ and $PcvaCO_2/CavO_2$ (Fig. 1). The main determinants of this model were $ScvO_2$ and $PcvaCO_2$. The addition of lactate values diminished the performance of the model. Cluster A exhibited significantly lower $ScvO_2$ values (66 ± 8 vs. 79 ± 5%, p < 0.001), higher $PcvaCO_2$ (8.1 ± 1.8 vs. 5.0 ± 1.4 mmHg, p < 0.001), and lower $PcvaCO_2/CavO_2$ (1.7 ± 0.5 vs. 2.3 ± 0.9 mmHg/mL, p < 0.001), with no differences in lactate levels (44 ± 35 vs. 54 ± 46 mg/dL, p = 0.3). Baseline metabolic and hemodynamic characteristics are detailed in Table 1. Globally, cluster A showed lower DO_2 values, but higher VO_2 than cluster B, reflecting greater oxygen extraction (higher O_2ER).

Response to fluid administration

The fluid challenge was associated to increases in cardiac output in 65% of the cases (in 71% of cluster A, and 56%

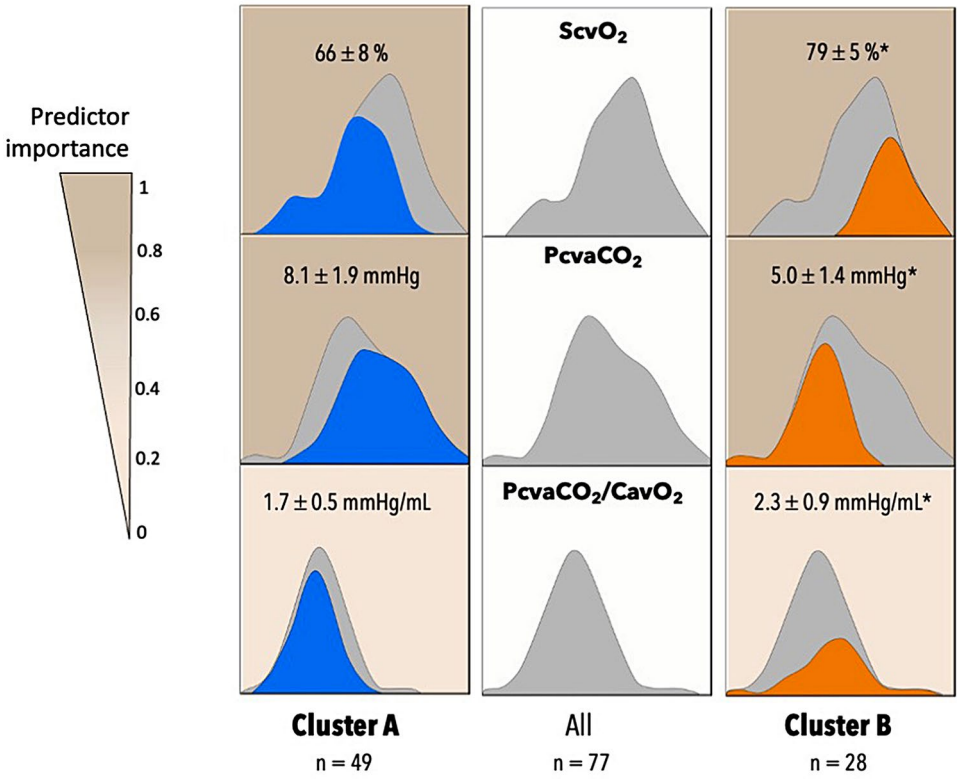

Fig. 1 Metabolic clusters model. The best model was obtained combining $ScvO_2$, $PcvaCO_2$ and PcvaCO2/$CavO_2$, where $ScvO_2$ and $PcvaCO_2$ showed higher weight. The figure shows the distribution of the three metabolic parameters at baseline in all the measurements (central panel), in cluster A (left panel) and in cluster B (right panel). The distribution was significantly different between the two final clusters: * $p < 0.001$ as compared to cluster A

of cluster B, *p* ns), with increases > 10% (CO-R) observed only in 35% (38% of cluster A, and 30% of cluster B, *p* ns). Changes in CO positively correlated with changes in DO_2 ($r=0.8$, $p<0.001$), as expected. A positive relationship between cardiac output changes (%) and VO_2 increase (%) was observed only in cluster A patients (*r* 0.33, *p* 0.03 in cluster A vs. *r* -0.01, *p* 0.1 in cluster B; Fig. 2). Accordingly, while in cluster A patients, a significant increase in CO during the fluid challenge (CO-R) was associated to higher probability of increase in VO_2 (OR 4.6, 95% CI 1.2–18.1, *p* 0.02), in cluster B, CO-R did not show any association with the probability of VO_2 increase (OR 0.9, 95% CI 0.15–4.8, *p* 0.9).

Metabolic markers as surrogates of VO_2 increase

At baseline, no single metabolic or hemodynamic variable was associated with VO_2 evolution after the fluid bolus. Figure 3 depicts the evolution of the different variables according to VO_2 response and to the baseline metabolic cluster. Significant differences in the evolutive changes in $ScvO_2$ and $PcvaCO_2$ were observed in cluster A patients according to their response in VO_2. Neither baseline lactate nor its evolution was associated to VO_2 response, irrespectively of the metabolic cluster. Cluster A patients showed a significant decrease in O_2ER (from 0.32 ± 0.08 to 0.30 ± 0.09, $p=0.04$), whereas it did not change in cluster B patients (from 0.17 ± 0.05 to 0.17 ± 0.05, $p=0.8$) (Fig. 4).

Discussion

In this study, we show that the metabolic profile of septic shock patients with high lactate values can be categorised into two distinct situations, indicative of either hypoxia or dysoxia. This differentiation may be crucial for making the right clinical decisions, such as determining whether a patient may benefit from further hemodynamic interventions aimed at increasing CO, such as fluid administration. In our study, tissue hypoxia was suspected when VO_2 increased as results of a fluid challenge, unmasking a situation of VO_2/DO_2 dependency [2, 3]. This metabolic profile can be defined integrating $ScvO_2$, $PcvaCO_2$ and $PcvaCO_2/CavO_2$, as the combination of oxygenation, perfusion, and anaerobic metabolism, and where $ScvO_2$ and $PcvaCO_2$ emerge as the major determinants. Our findings underscore the importance of a physiology-based evaluation at the bedside, suggesting that the integration of different metabolic variables provides a more comprehensive understanding of a patient's status. Not surprisingly, our model identified a significant pattern of patients with lower $ScvO_2$ and higher $PcvaCO_2$, as compared to a

Table 1 Main baseline hemodynamic and metabolic characteristics before fluid expansion according to the observed metabolic clusters. HR, heart rate; MAP, mean arterial pressure; NE, norepinephrine; CO, cardiac output; DO_2, global oxygen delivery; VO_2, global oxygen consumption; O_2ER, oxygen extraction ratio; hb, hemoglobin; HCO^{3-}, plasma bicarbonate; $ScvO_2$, central venous oxygen saturation; $PcvaCO_2$, central venous-to-arterial carbon dioxide difference; $PcvaCO_2/CavO_2$, $PcvaCO_2$ corrected by the difference in arterial-to-venous oxygen content. *P* value corresponds to Student's t-test comparisons between clusters

	All (*n* = 77)	Cluster A (*n* = 49)	Cluster B (*n* = 28)	*p*
HR (bpm)	106 ± 23	106 ± 24	106 ± 21	1
MAP (mmHg)	77 ± 11	79 ± 9	74 ± 13	0.1
NE dose (mcg/kg/min)	0.96 ± 0.72	0.94 ± 0.76	1.01 ± 0.65	0.7
CO (L/min/m^2)	5.3 ± 2.2	4.4 ± 1.5	6.7 ± 2.6	< 0.001
DO_2 (mL/min/m^2)	769 ± 323	688 ± 274	929 ± 373	0.01
VO_2 (mL/min/m^2)	192 ± 66	213 ± 62	152 ± 55	< 0.001
O_2ER	0.26 ± 0.09	0.32 ± 0.08	0.17 ± 0.05	< 0.001
Hb (g/dL)	11.6 ± 2.4	11.9 ± 2.3	10.9 ± 2.4	0.09
pH	7.3 ± 0.1	7.32 ± 0.1	7.26 ± 0.1	0.02
HCO^{3-} (mmol/L)	18 ± 4	18 ± 4	17 ± 5	0.4
Lactate (mMol/L)	5.3 ± 4.3	4.9 ± 3.8	6.0 ± 5.1	0.3
$ScvO_2$ (%)	71 ± 10	66 ± 8	79 ± 5	< 0.001
$PcvaCO_2$ (mmHg)	6.9 ± 2.3	8.1 ± 1.9	5.0 ± 1.4	< 0.001
$PcvaCO_2/CavCO_2$ (mmHg/mL)	1.9 ± 0.7	1.7 ± 0.5	2.3 ± 0.9	0.006

group of patients with higher $ScvO_2$ and lower $PcvaCO_2$. Of note, $PcvaCO_2/CavO_2$ values were abnormal in both groups, but the dysoxic cluster displayed significantly higher values. According to our results, an integrative approach to assessing the metabolic status enhances our ability to detect situations of VO_2/DO_2-dependency and, therefore, this approach would be of help to decide which patients might benefit from further increasing DO_2.

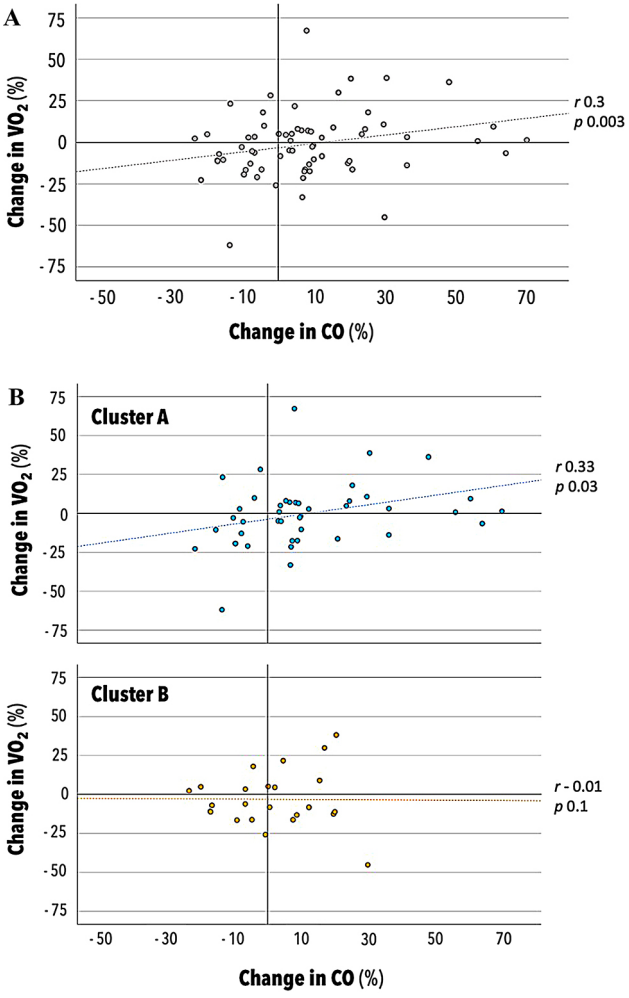

Fig. 2 Changes in CO and VO_2 as results of the fluid expansion. Relationship between change in cardiac output (CO), and global oxygen consumption (VO_2), expressed as % change from baseline (2**A**). When separately analyzing the metabolic clusters, the correlation was only significant for cluster A patients (2**B**)

Metabolic targets in resuscitation

Current international guidelines recommend guiding the resuscitation process of septic shock patients based on lactate dynamics [2]. However, lactate levels might not only reflect the persistence of tissue hypoxia, but a dysoxic state, where oxygen utilization by the tissues is impaired [5]. On that behalf, the combination of lactate with other metabolic variables, such as $ScvO_2$, seemed highly useful to help detecting these dysoxic situations [4]. However, and after nearly two decades of resuscitation strategies including $ScvO_2$ as a metabolic endpoint, the recently published Surviving Sepsis Campaign guidelines no longer endorse its use [2]. This disappearance occurs as results of the lack of benefit of $ScvO_2$-guided algorithms in three large multicenter trials [19–21]. These three studies faced numerous criticisms but, probably, the most remarkable was that, in all of them, $ScvO_2$ values at inclusion were already above the predefined target in almost 80% of the patients. No additional analyses were performed on those patients who showed low $ScvO_2$ values at inclusion. Despite the negative results of these trials, our findings reaffirm that $ScvO_2$ is a valuable global oxygenation marker, with strong physiological meaning and clinical relevance. While the interpretation of isolated $ScvO_2$ values may have its limitations, in the context of acute illness with high lactate values, combining this variable with other biomarkers provides a deeper insight on the real metabolic status of the patient, and may be crucial for overcoming the limitations of using lactate as a sole metabolic endpoint [4].

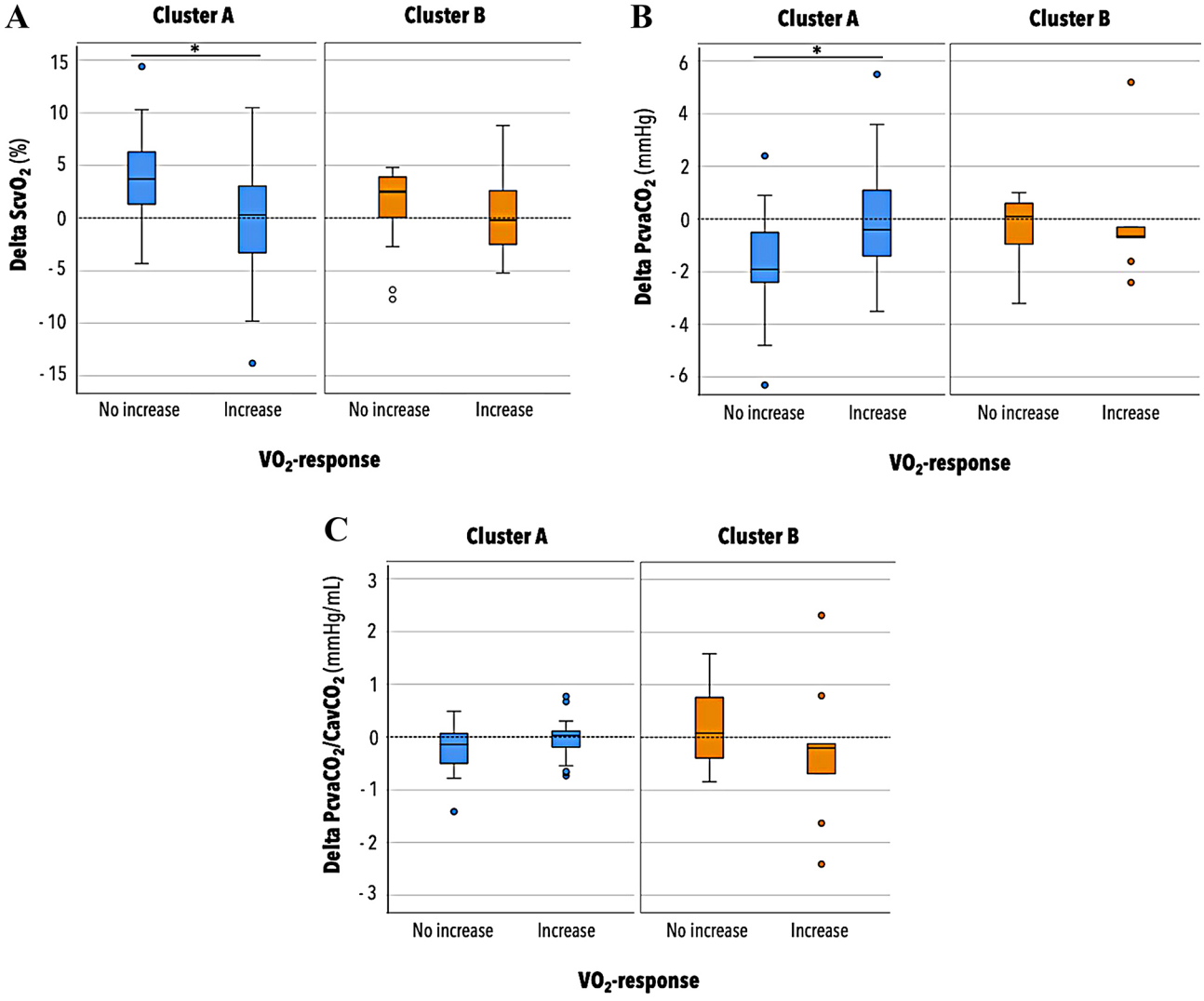

Fig. 3 Changes in metabolic parameters according to baseline cluster and VO_2 response. Absolute change in $ScvO_2$ (3**A**), $PcvaCO_2$ (3**B**), and $PcvaCO_2/CavO_2$ (3**C**), according to the increase of VO_2 after the fluid challenge. The final value was obtained as (post-intervention - baseline) value. * $p < 0.05$ for comparisons within the same cluster

Carbon dioxide (CO_2) derived variables

In addition to lactate and $ScvO_2$, two different variables combining CO_2 measurements at the central venous and arterial territories have gained relevance in the past years. While $PcvaCO_2$ seems more related to perfusion than to metabolism [8, 22], its combination with $CavO_2$, as an estimate of the respiratory quotient, has shown better performance for detecting ongoing anaerobic metabolism [10]. Despite both variables seem physiologically robust and have been associated with patients' outcome [23–25], their integration into daily practice has not been thoroughly explored. Over the past decade, several authors have investigated the ability of $PcvaCO_2$ and/or $PcvaCO_2/CavO_2$ to predict either lactate evolution or VO_2 response to a fluid challenge [9, 10, 26]. To summarize current evidence, $PcvaCO_2$ has shown poor performance, and while low $PcvaCO_2/CavO_2$ seems to predict lactate decrease [10], moderate or elevated values have shown limited capability for differentiating whether the suspected anaerobic metabolism is DO_2-dependent [26]. Our data suggests that both variables may play an important role in defining VO_2/DO_2 dependence, not as isolated variables, but in their combination with $ScvO_2$.

Estimating VO_2-response to hemodynamic interventions

Although the current resuscitation paradigm is based in the intention to minimise oxygen demand and increase DO_2 to rescue the patient from VO_2/DO_2 dependency, monitoring VO_2 is not recommended in international guidelines. Instead, using metabolic variables as indirect markers of VO_2/DO_2 relationship and evolution has become the standard of care [1, 2]. According to

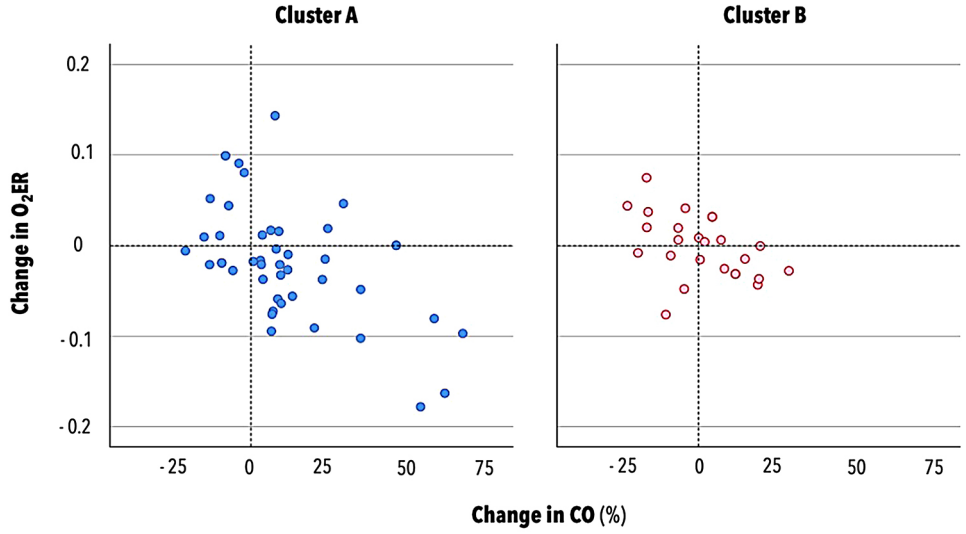

Fig. 4 Changes in CO and O_2ER as results of the fluid expansion. Change in O_2ER was computed from (O_2ER after the FC) - (O_2ER at baseline). A negative value indicates a decrease in O_2ER as results of the FC

our results, although no single variable would predict a positive VO_2 response to increasing CO, their combination significantly increases the odds of detecting a VO_2/DO_2 dependent state. Moreover, when trying to infer VO_2 evolution, the performance of the different metabolic markers is also poor. Interestingly, while in cluster B the evolutive pattern of the three variables did not differ according to VO_2 response, in Cluster A the increase in VO_2 was associated to smaller increases in $ScvO_2$ and to smaller decreases in $PcvaCO_2$. These findings are relevant and highlight the limitation of interpreting increases in $ScvO_2$ as results of fluid administration to a positive metabolic response. From a physiological perspective, it would be genuine to infer that greater increases in $ScvO_2$ might reflect increased shunting effect.

Study limitations

Several limitations should be considered when evaluating our results. Firstly, the sample size may be limited to accurately categorise the patients in the different situations. Of note, we performed several clustering analyses, including different metabolic variables, and the best model was finally selected. Increasing the sample size might help in generating more robust models, where other metabolic variables might gain significance. Secondly, the design of the study, with the need for a cardiac output monitor in place, might be responsible for a selection bias, since initial resuscitation phases, or those patients exhibiting a positive response to hemodynamic interventions upon ICU admission have not been properly explored. As results of the nature of our study, where reliable CO values were needed, some degree of invasiveness was unavoidable. Of note, it has been repeatedly demonstrated that non-invasive technologies lack accuracy for tracking CO changes in critically ill patients, especially those receiving amine or inotropic agents [27–29]. Thirdly, since the VO_2 was calculated from the Fick principle, and hence, VO_2 and DO_2 were calculated from the same variables, it might result in some degree of mathematical coupling of data [30]. The inclusion of O_2ER evolution, which does not include the CO in its calculation, may help to mitigate this risk. Moreover, we assessed O_2 and CO_2-derived variables using central venous blood, not mixed venous blood, what might miss changes in oxygenation of the splanchnic territory. This approach has been used by other authors [9, 26], and since we evaluated evolutive changes in VO_2 within the same patient, the impact of not measuring mixed venous blood might be minimal. Finally, the value of lactate evolution to reflect VO_2 improvement might be limited due to the fact that changes in blood lactate are very slow [31, 32]. Since we did not design a follow-up protocol for adequately measuring lactate clearance [33], the short period of time between measurements might be responsible, at least in part, for a lack of lactate clearance.

Conclusions

In a population of early septic shock patients, two differentiated metabolic profiles were detected, suggesting either tissue hypoxia or dysoxia. The association between cardiac output increase and increase in VO_2 was limited to the hypoxic profile. Integration of metabolic variables enhances the ability to detect those patients whose VO_2 might increase as results of fluid administration Using lactate levels as the only metabolic marker for guiding resuscitation may be insufficient, and even erroneous, in the decision-making process in the hemodynamic approach to septic shock patients.

Abbreviations

C_aO_2	Arterial Oxygen content
$C_{av}O_2$	Arterial-to-venous Oxygen content difference
DO_2	Global Oxygen delivery
Hb	Hemoglobin
MAP	Mean arterial pressure
O_2ER	Oxygen Extraction Ratio
P_aCO_2	Arterial Carbon dioxide tensión
$P_{cv}CO_2$	Central venous Carbon dioxide tensión
$P_{cva}CO_2$	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
S_aO_2	Arterial Oxygen saturation
$S_{cv}O_2$	Central venous oxygen saturation
VO_2	Global oxygen consumption

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Author contributions
C.E. and J.M. conceived, designed, and coordinated the study. C.E., P.S., A.P.M., A.G., A.C., S.N., E.C., G.G. and J.M. performed data extraction. C.E. and J.M. analyzed the data and drafted the manuscript. All authors read and approved the final version of the manuscript. All authors reviewed the manuscript.

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Data availability
The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request. Data are located in controlled access data storage at Parc Taulí Hospital Universitari.

Declarations

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). Informed consent to participate was obtained from each patient's next of kin.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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