Hypoxia-related parameters during septic shock resuscitation: Pathophysiological determinants and potential clinical implications

Nicolás Pavez[1], Eduardo Kattan[2], Magdalena Vera[2], Giorgio Ferri[3], Emilio Daniel Valenzuela[2], Leyla Alegría[2], Sebastian Bravo[1], Ronald Pairumani[3], César Santis[3], Vanessa Oviedo[2], Dagoberto Soto[2], Gustavo Ospina-Tascón[4], Jan Bakker[2,5,6,7], Glenn Hernández[2], Ricardo Castro[2]

[1]Departamento de Medicina Interna, Facultad de Medicina, Universidad de Concepción, Concepción, Chile; [2]Departamento de Medicina Intensiva, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile; [3]Unidad de Cuidados Intensivos, Hospital Barros Luco-Trudeau, Santiago, Chile; [4]Department of Intensive Care Medicine, Fundación Valle del Lili, Universidad ICES, Cali, Colombia; [5]Division of Pulmonary, Allergy, and Critical Care Medicine, Columbia University Medical Center, New York, NY, USA; [6]Erasmus MC University Medical Center, Department Intensive Care Adults, Rotterdam, CA, The Netherlands; [7]Division of Pulmonary, and Critical Care Medicine, New York University-Langone, New York, NY, USA

Contributions: (I) Conception and design: N Pavez, R Castro, G Ferri, E Kattan, G Ospina-Tascón, J Bakker, G Hernández; (II) Administrative support: G Ferri, E Kattan, L Alegría, V Oviedo, R Pairumani, D Soto; (III) Provision of study materials or patients: C Santis, L Alegría, V Oviedo, R Pairumani, G Ferri, S Bravo, M Vera, ED Valenzuela; (IV) Collection and assembly of data: D Soto, C Santis, BA, L Alegría, V Oviedo, R Pairumani, G Ferri, S Bravo, M Vera, ED Valenzuela; (V) Data analysis and interpretation: E Kattan, R Castro, G Hernández, N Pavez, ED Valenzuela; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Dr. Ricardo Castro, MD, MPH. Unidad de Paciente Crítico, Hospital Clinico UC-CHRISTUS, Departamento de Medicina Intensiva, Pontificia Universidad Católica de Chile, Diagonal Paraguay 362, Santiago Centro, Chile. Email: rcastro.med@gmail.com.

Background: Assessment of tissue hypoxia at the bedside has yet to be translated into daily clinical practice in septic shock patients. Perfusion markers are surrogates of deeper physiological phenomena. Lactate-to-pyruvate ratio (LPR) and the ratio between veno-arterial PCO_2 difference and $Ca–vO_2$ ($\Delta PCO_2/Ca–vO_2$) have been proposed as markers of tissue hypoxia, but they have not been compared in the clinical scenario. We studied acute septic shock patients under resuscitation. We wanted to evaluate the relationship of these hypoxia markers with clinical and biochemical markers of hypoperfusion during septic shock resuscitation.

Methods: Secondary analysis of a randomized controlled trial. Septic shock patients were randomized to fluid resuscitation directed to normalization of capillary refill time (CRT) versus normalization or significant lowering of lactate. Multimodal assessment of perfusion was performed at 0, 2, 6 and 24 hours, and included macrohemodynamic and metabolic perfusion variables, CRT, regional flow and hypoxia markers. Patients who attained their pre-specified endpoint at 2-hours were compared to those who did not.

Results: Forty-two patients were recruited, median APACHE-II score was 23 [15–31] and 28-day mortality 23%. LPR and $\Delta PCO_2/Ca–vO_2$ ratio did not correlate during early resuscitation (0–2 h) and the whole study period (24-hours). $\Delta PCO_2/Ca–vO_2$ ratio derangements were more prevalent than LPR ones, either in the whole cohort (52% *vs.* 23%), and in association with other perfusion abnormalities. In patients who reached their resuscitation endpoints, the proportion of patients with altered $\Delta PCO_2/Ca-vO_2$ ratio decreased significantly (66% to 33%, P=0.045), while LPR did not (14% *vs.* 25%, P=0.34).

Conclusions: Hypoxia markers did not exhibit correlation during resuscitation in septic shock patients. They probably interrogate different pathophysiological processes and mechanisms of dysoxia during early septic shock. Future studies should better elucidate the interaction and clinical role of hypoxia markers during septic shock resuscitation.

Keywords: Hypoxia; septic shock; capillary refill time; lactate

Introduction

Despite recent advances in septic shock biochemical and clinical understanding, mortality remains around 40% (1). Sepsis-induced hypoperfusion leads to tissue hypoxia, cell and mitochondrial dysfunction, finally leading to multiorgan failure (2). Timely resolution of hypoperfusion through the judicious administration of fluids and vasoactive drugs, among other therapies, may deactivate this vicious cycle and lead to an adequate cellular oxygen delivery and recovery of organ function (3).

Available markers of hypoperfusion in the clinical practice are mere surrogates of deeper physiological phenomena occurring at the tissue and cellular level. Some markers, like central venous oxygen saturation ($SvcO_2$) or the veno-arterial $PCO2$ difference reflect global DO_2/VO_2 and flow balances (4-6). Other parameters, like lactate, represent complex interactions between non-aerobic metabolism, hyperadrenergia, and liver lactate clearance (7). On the other side, regional perfusion assessment, like sublingual microcirculation (8) or near infrared spectroscopy (9), can assess specific tissue-derived parameters, which may not reflect other territories of the economy. Recently, capillary refill time (CRT) has emerged as an interesting perfusion monitor, that has a fast kinetics (10,11), and correlates with other perfusion parameters such as hepatosplanchnic indices (12). Furthermore, its behavior also has correlation with severity and mortality (13,14).

The possibility to assess tissue hypoxia at the bedside has been pursued by clinicians and investigators along the years (15,16), but experimental methods have yet to be successfully translated into clinical practice. One proposed alternative is the lactate/pyruvate ratio (LPR). If the electron transport chain of the mitochondria fails due to tissue hypoxia, the cell uses a non-aerobic pathway to synthesize ATP leading to an increase of the LPR. This ratio has been utilized to differentiate hypoxia-related from other causes of hyperlactatemia, such as increased glycolysis without hypoxic stress (17,18). On the other hand, according to the Fick equation (19), the ratio between veno-arterial PCO_2 difference and $Ca–vO_2$ ($\Delta PCO_2/Ca–vO_2$) represents a clinical surrogate for the respiratory quotient and its increase could signal anaerobic metabolism (20,21). To the best of our knowledge, both parameters have not been yet compared in the clinical scenario.

Recently, the ANDROMEDA-SHOCK trial compared CRT- versus lactate-guided early resuscitation during septic shock, demonstrating benefits in mortality, treatment intensity and organ dysfunction for the CRT arm (13,14,22,23). In a subsequent randomized controlled trial, we assessed both resuscitation strategies in 42 patients, in order to assess the impact of resuscitation strategy on fluid administration, perfusion and deep hypoxia markers during the study protocol, focusing on LPR and $\Delta PCO_2/Ca–vO_2$ (24).

The objective of this study is to perform an assessment of the relationship between LPR and $\Delta PCO_2/Ca–vO_2$, and the relationship between deep hypoxia markers with clinical markers of hypoperfusion during the initial resuscitation of this cohort of septic shock patients. We present the following article/case in accordance with the CONSORT reporting checklist (available at http://dx.doi.org/10.21037/atm-20-2048).

Methods

Patient selection and study protocol

We performed a prospective randomized controlled clinical trial. The design, main outcome and protocolization is detailed in clinicaltrials.gov (NCT03762005). Major outcomes have been previously reported (24). Data for this analysis was obtained from the final study's database.

This study was conducted during an 18-months period at two intensive care units of teaching hospitals in Santiago de Chile (Hospital Clínico de la Pontificia Universidad Catolica de Chile and Hospital Barros Luco Trudeau). Respective IRBs and Ethics committees approved the study. A signed informed consent was obtained from patients or next of kin before study inclusion.

During the study period, patients equal or older than 18 years old, who fulfilled the following inclusion criteria were considered for randomization:

(I) Septic shock, defined according to SEPSIS-3 criteria (serum lactate >2 mmol/L, with vasopressor requirements after initial fluid loading of 20–

30 mL/kg) (3).

(II) Positive fluid responsiveness state (25,26).

Exclusion criteria considered the following: >24 hours of septic shock onset, anticipated surgical or dialytic procedure during study period, pregnancy, active bleeding, liver cirrhosis, do-not-resuscitate status or severe ARDS. Randomization was performed through a computerized software, with a permuted block of eight and an allocation of 1:1 into each study arm. Concealment was maintained through centralization of the randomization process. Patients were allocated either into CRT-targeted or Lactate-targeted study arms.

The study protocol lasted 6 hours, and a full set of measurements were performed until hour 24 (see more detailed information in supplementary material 1). Due to the difference in target dynamics, CRT arm was tested every 30 minutes, while lactate arm every 2 hours. If the perfusion target was not met, additional interventions could be initiated at discretion by attending physicians. Other therapies were performed according to current guidelines of septic shock management (3).

Measurements and data collection

Demographic and clinical data were registered at baseline and throughout hospitalization until discharge. Relevant clinical variables, multimodal perfusion assessment, and deep hypoxia makers were registered at baseline (T0), 2 hours (T2), 6 hours (T6) and 24 hours (T24).

Hemodynamic and perfusion variables (see more detailed information in supplementary material 1)

(I)   Macrohemodynamic variables;
(II)   Cardiac output (CO) and derived indices;
(III) Metabolic-related perfusion variables (11);
(IV)   Capillary refill time (13);
(V)   Regional flow:
    (i)   Sublingual microcirculation (27);
    (ii) Near infrared spectroscopy (NIRS) (8,9,27);
    (iii) Liver blood flow by Indocyanine green plasma disappearance rate (PDR-ICG) (27).

Deep hypoxia variables (see more detailed information in supplementary material 1)

To evaluate the presence of tissue hypoxia, we measured the LPR and the $\Delta PCO_2/Ca–vO_2$ ratio. Pyruvate was determined by using pyruvate assay kit Cayman N°700470. $\Delta PCO_2/Ca–vO_2$ ratio was calculated using a validated equation (20,28). In order to ease the interpretation of both markers, data analysis was performed with the percentage of abnormality of each variable, a more intuitive approach for clinicians. For LPR a value of 15 or more was considered abnormal (17). For $\Delta PCO_2/Ca–vO_2$ ratio, a value of 1.4 or more was considered abnormal (29).

In order to assess if derangements in clinical perfusion markers associated with deep hypoxia markers, we assessed the incidence of abnormal hypoxia markers when each clinical parameter presented abnormal values, at any timepoint.

"Target reachers" analysis

Patients of both study arms who attained their prespecified perfusion target at T2 were considered target reachers, while those who did not were considered target non-reachers. We chose this timepoint as it was the first moment at which new measurements were made in both arms after randomization. Both groups were compared according to baseline characteristics and perfusion state. Evolution of deep hypoxia variables represented as percentage of patients with abnormal values, were compared through time in both groups.

Statistical analysis

After discarding normal distribution, non-parametric tests were used. Descriptive statistics are shown as median [interquartile range] or percentage (%) accordingly. Mann-Whitney U, chi-square and Fisher's exact, were used when appropriate. Data were analyzed with Minitab v17 (Minitab Inc, State College, PA) and GraphPad Prism (GraphPad Softwares, La Joya, CA) softwares. Two-tailed P value <0.05 was considered statistically significant.

Results

Forty-two patients were included in this analysis. Demographic, hemodynamic, and other parameters are shown in *Table 1*. Main septic foci were abdominal (57%), respiratory (19%) and urinary (12%). Among rescue therapies implemented, 18% used steroids, 18% used epinephrine, and 13% used high-volume hemofiltration.

One hundred and twenty-five measurements of LPR and 121 measurements of $\Delta PCO_2/Ca–vO_2$ ratio were available

Page 4 of 9

Pavez et al. Hypoxia-related parameters during septic shock resuscitation

Table 1 General characteristics of the included population

Parameter	Value
Age (years)	63 [47–75]
Female (%)	55
APACHE-II	23 [15–31]
SOFA	10 [7–13]
Charlson index	1 [0–4]
Septic foci (%)	
Abdominal	57
Respiratory	19
Urinary	12
Other	12
Surgical (%)	60
Pre ICU fluids (mL)	2,250 [1,000–3,025]
MAP (mmHg)	71 [63–76]
HR (bpm)	104 [93–130]
CVP (mmHg)	8 [5–11]
Cardiac index (L/min/m^2)	2.9 [2–3.6]
Norepinephrine dose (mcg/kg/min)	0.29 [0.17–0.48]
CRT (s)	6 [3–6]
Lactate (mmol/L)	3.6 [2.9–6.4]
ScvO$_2$ (%)	70 [62–78]
Delta pCO$_2$(v-a) (mmHg)	8 [4.8–11]
ΔPCO_2/Ca–vO$_2$	1.9 [1.1–2.8]
LPR	8.7 [4.2–13.8]
MV days	5 [2–10]
ICU LOS (days)	8 [4–15]
Hospital LOS (days)	25 [9–56]
28-day mortality (%)	23

APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment score; MAP, mean arterial pressure; DBP, diastolic blood pressure; CVP, central venous pressure; CRT, capillary refill time; ScvO$_2$, central venous oxygen saturation Delta pCO$_2$(v-a), difference between central venous carbon dioxide pressure and arterial carbon dioxide pressure; ΔPCO_2/Ca–vO$_2$, ratio between veno–arterial PCO$_2$ difference and Ca–vO$_2$; LPR, lactate/pyruvate ratio; MV, mechanical ventilation; LOS, length of stay.
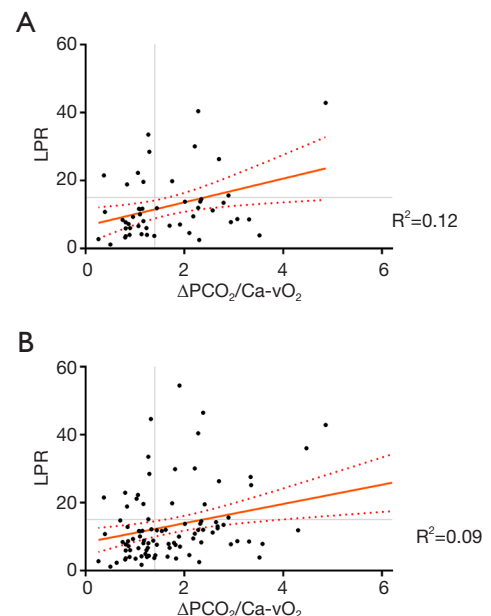
Figure 1 Concordance between LPR and ΔPCO_2/Ca–vO$_2$ at initial septic shock resuscitation (0–2 h) and the whole study period (24 h). LPR, lactate/pyruvate ratio; ΔPCO_2/Ca–vO$_2$: ratio between veno–arterial PCO$_2$ difference and Ca–vO$_2$.

during the study period. In 94 occasions both indices were measured simultaneously at specific time-points, and 51 of these measurements corresponded to the first 2 hours. Of these, 22% of LPR and 52% of ΔPCO_2/Ca–vO$_2$ ratio exhibited abnormal values. *Figure 1* shows the lack of correlation between both hypoxia markers, both at early resuscitation (0-2 h, panel A) and the whole study period (0–24 h, panel B).

Patients with abnormal LPR at baseline (6), compared to those with normal LPR (27) had higher CRT {7 [5–14] *vs.* 4 [3–6], P=0.02}, but similar APACHE score, lactate levels, NE dose, and 28-day mortality. Patients with abnormal ΔPCO_2/Ca–vO$_2$ ratio at baseline (19), compared to those with normal ratio (14), presented higher baseline lactate levels {6.1 [3–8.4] *vs.* 3.4 [2.7–4.1], P=0.049}, but similar severity scores and mortality.

The incidence of abnormal hypoxia markers when different perfusion-related parameters were abnormal at any time point is shown in *Table 2*. As seen, abnormal values

Table 2 Presence of abnormal hypoxia markers in patients with abnormal perfusion markers

Abnormal parameter	Abnormal $\Delta PCO_2/Ca–vO_2$	Abnormal LPR	P
Lactate >2 mmol/L	69% (58/84)	15% (13/87)	0.0001
ScvO$_2$ <70%	55% (33/60)	5% (3/56)	0.0001
CRT >3 s	64% (35/55)	22% (12/53)	0.0001
Delta pCO$_2$(v-a) >6 mmHg	85% (41/48)	16% (7/45)	0.0001
StO$_2$ <70%	62% (13/21)	0% (0/24)	0.0001
PDR <18%	78% (35/45)	12% (6/51)	0.0001
MFI <2.5	85% (6/7)	42% (3/7)	0.26

$\Delta PCO_2/Ca–vO_2$, ratio between veno–arterial PCO_2 difference and $Ca–vO_2$; LPR, Lactate/pyruvate ratio; CRT, Capillary refill time; ScvO$_2$, central venous oxygen saturation Delta pCO$_2$(v-a), difference between central venous carbon dioxide pressure and arterial carbon dioxide pressure; StO$_2$, Tissue oxygen saturation; PDR-ICG, liver blood flow by Indocyanine green plasma disappearance rate; MFI, mean flow index.

of $\Delta PCO_2/Ca–vO_2$ ratio were significantly more prevalent than LPR alterations in the context of any abnormal perfusion-related parameter.

In 50% of patients cardiac output increased with fluid loading between T0 and T2, while the others it remained constant or decreased. LPR and $\Delta PCO_2/Ca–vO_2$ tended to improve in patients who increased cardiac output [delta LPR: 0.89 (0.15–4) *vs.* –0.12 (–2–2.2), P=0.12; delta $\Delta PCO_2/Ca–vO_2$ ratio: 0.48 (0.04–1) *vs.* –0.01 (–0.42–0.3), P=0.11].

Eighteen patients were considered target reachers at 2 hours, while 24 patients were not. *Table 3* shows the main clinical, demographic, severity and perfusion characteristics of both subgroups. As shown in *Figure 2*, target reachers significantly decreased the proportion of abnormal $\Delta PCO_2/Ca–vO_2$ ratio between 0 and 2 hours, while this did not occur in LPR. On the other hand, target non-reachers maintained similar proportions of abnormal deep hypoxia markers.

Discussion

Our study showed that in a population of fluid responsive patients with septic shock according to SEPSIS-3 (septic patients with hyperlactatemia and vasopressors for arterial hypotension), the presence of concurrent abnormal values of deep tissue hypoxia markers is erratic during early resuscitation. In addition, measured hypoxia markers do not exhibit concordance between them. However, further analysis of our results suggests that both LPR and $\Delta PCO_2/Ca–vO_2$ ratio interrogate different pathways on the hypoxia/

hypoperfusion processes of septic shock.

Lactate prognostic value and response to therapy is well established in the literature (30,31), and is still the main resuscitation target recommended by the Surviving Sepsis Campaign for septic shock (3). Its use was primarily advocated under the hypothesis that decreases in tissue blood flow cause tissue hypoxia that increases non-aerobic lactate production due to low mitochondrial oxygen availability (30,32). This latter condition results in tissue injury that leads to organ failure and subsequent morbidity and mortality.

Nevertheless, though by shock definition each patient in our series had hyperlactatemia, only few of them presented a high LPR. We believe that the explanation for these findings can be drawn after reviewing previous reports on the topic:

Levy studied 60 patients with septic shock, lactic acidosis and vasopressor requirements (33). In them, higher lactate levels were closely related with elevated LPRs with a notable direct progression between severity of the septic shock according to norepinephrine requirements, hyperlactatemia levels and LPR. In the subgroup these authors called 'intractable septic shock', the APACHE II score was 32 and the norepinephrine dose 2.3 µg/kg/min. The authors concluded their study stating that hyperlactatemia with an elevated LPR is associated with the development of multiple organ failure and death (33).

In the same line, Rimachi studied 17 hyperlactatemic septic patients, and 13 of them (75%) presented high LPR (17). Their APACHE II score was 21±8 and mortality was 58%. Norepinephrine doses were not provided, but

Table 3 Comparison between demographic, severity scoring, and baseline perfusion variables in target reachers and non-reachers

Variable	Reacher	Non-reacher	P
N	18	24	
Age (years)	63 [47–74]	64 [43–75]	0.9
Female (%)	10	14	0.8
Surgical foci (%)	44	71	0.08
SOFA	9 [6–12]	11 [7–14]	0.19
APACHE-II	24 [15–30]	23 [15–32]	0.7
Charlson	1 [0–3]	1 [0–5]	0.5
Pre protocol fluid (mL)	2,375 [1,000–3,138]	2,025 [1,050–3,000]	0.8
Time to antibiotics (min)	60 [30–98]	60 [30–60]	0.3
CRT (seconds)	4 [3–5]	6 [3.1–8.7]	0.07
Lactate (mol/L)	3 [2.5–4.3]	4.6 [3–8.7]	0.01
Norepinephrine dose (mcg/kg/min)	0.27 [0.11–0.42]	0.3 [0.2–0.5]	0.9
$ScvO_2$ (%)	68 [64–74]	75 [61–82]	0.3
Delta pCO_2(v-a) (mmHg)	8 [6–12]	7 [3–11]	0.3
Ca–vO_2 (ΔPCO_2/Ca–vO_2)	2.3 [1.1–2.8]	1.3 [0.9–2.5]	0.3
LPR	7.4 [4–13.8]	9.5 [5.3–14]	0.4
NIRS (%)	79 [73–83]	75 [66–82]	0.3
PDR-ICG (%)	12 [9–20]	15 [11–19]	0.6
MFI	2.4 [1.9–3]	2.5 [1–2.6]	0.6

APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment score; MAP, mean arterial pressure; DBP, diastolic blood pressure; CVP, central venous pressure; CRT, Capillary refill time; $ScvO_2$, central venous oxygen saturation delta pCO_2(v-a), difference between central venous carbon dioxide pressure and arterial carbon dioxide pressure; ΔPCO_2/Ca–vO_2, ratio between veno–arterial PCO_2 difference and Ca–vO_2; LPR, lactate/pyruvate ratio; NIRS, near-infrared spectophotoscopy; PDR-ICG, liver blood flow by Indocyanine green plasma disappearance rate MFI, Mean flow index

the data indicate that these patients were sicker and, consequently, a higher proportion of them presented an elevated LPR as well.

In contrast, Suistomaa studied LPR in 98 patients admitted to the ICU, and 32% of them presented hyperlactatemia (34). Although there were few septic patients (8/98) in this series and data on norepinephrine dose and mortality was not provided, it is specifically mentioned that hyperlactatemia was not associated with LPR elevation. Moreover, their APACHE II score was around 16, indicating that those patients were less severely ill. The no elevation in LPR is concordant with our data.

Considering the previously published evidence, we can speculate that the low prevalence of an elevated LPR may be explained by inclusion of less severe cases of septic shock

in our study, which is consistent with the mortality of only 23%.

Regarding ΔPCO_2/Ca–vO_2 ratio, a retrospective study reported a close correlation between blood lactate concentration and the ΔPCO_2/Ca–vO_2 ratio in a cohort of critically ill patients (29). Monnet demonstrated that ΔPCO_2/Ca–vO_2 ratio was able to predict an increase in VO2 in fluid responsive septic shock patients subjected to volume expansion (35), a fact confirmed later by Mallat *et al.* (36).

Even though we didn't assess VO_2 systematically, our results are in line with these previous reports. As hypoperfusion resolution is the ultimate goal of VO_2 increase, we expanded the findings to a clinical scenario where hypoperfusion resolution was assessed at the bedside.
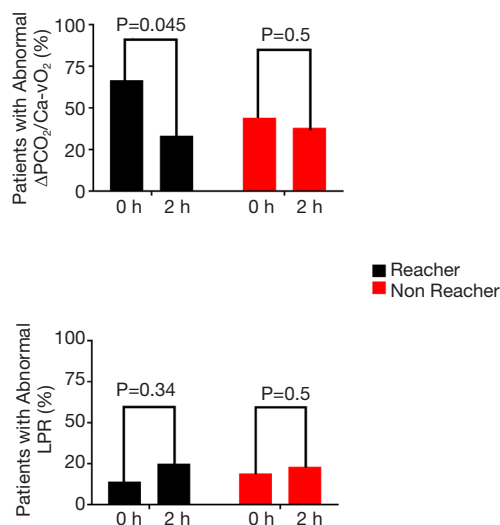
Figure 2 Evolution of patients with abnormal hypoxia related parameters between 0–2 hours in target reachers and non-reachers. LPR, lactate/pyruvate ratio; $\Delta PCO_2/Ca–vO_2$, ratio between veno–arterial PCO_2 difference and $Ca–vO_2$.

In practical terms, a $\Delta PCO_2/Ca–vO_2$ ratio normalization could work as a surrogate for an effective rise on DO_2 with a concurrent correction of the oxygen debt, or an effective flow rectification. In other words, in this scenario, fluid responsiveness with $\Delta PCO_2/Ca–vO_2$ ratio improvement after fluid loading could be an indirect marker of VO_2 improvement as evidence of flow responsiveness. This can ultimately explain the reason why LPR and $\Delta PCO_2/Ca–vO_2$ ratio are not concordant as they interrogate different mechanisms and subcellular processes of the pathophysiology of septic shock. Of course, another possibility is that the lack of correlation simply is due to the slower kinetics of recovery of lactate as compared to the rapid changes in O_2 and CO_2 metabolism/production.

Despite the fact that LPR clinical use has been abandoned due to technical complexities and that $\Delta PCO_2/Ca–vO_2$ ratio has not found its place as a functional marker for hypoxia in septic shock, in light of our results, we think that these markers may have a relevant place in the clinical understanding and management of the septic shock patient.

Limitations

This study has several limitations. First, this is a post hoc analysis of a randomized controlled trial. Second, there were some missing values of perfusion variables, mainly

due to problems in the preanalytical phase. Third, some technical issues around pyruvate measurements were present. However, our lab personnel have a long-time experience with biologic samples handling and processing. Finally, there is no universal acceptance on the best method to clinically assess the respiratory quotient (i.e., the ratio between VCO_2 and VO_2), including the use of central venous gases over mixed venous gases and the use of CO_2 and O_2 pressures over arterial and venous content (21,37,38). Despite this, recent evidence has provided support for this practical approach (28), which is the one we used in our study.

Conclusions

To our knowledge, this is the first time that the LPR and $\Delta PCO_2/Ca–vO_2$ ratios were compared as hypoxia markers. Despite the huge experimental and theoretical backgrounds, at first, we found no evident correlation between their kinetics. Nevertheless, exploring the contexts for these markers we believe that LPR may help on the assessment of the depth of the dysoxia state and eventually as a prognostic marker, and that the $\Delta PCO_2/Ca–vO_2$ ratio may serve as a more precise signal for flow rectification in previously hypoperfused fluid responsive patients subjected to fluid resuscitation. Undoubtedly, further information on the best scenarios where LPR and $\Delta PCO_2/Ca–vO_2$ ratios may exhibit their full usefulness is still to be gathered.

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Footnote

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Page 8 of 9

Pavez et al. Hypoxia-related parameters during septic shock resuscitation

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Study protocol

Each study arm had a specific perfusion target (normalization or 20% decrease of serum lactate levels, or normalization of CRT). When there was an abnormal perfusion target, fluid challenges were performed (500 of crystalloids in 30 minutes) until normalization of target, negativization of fluid responsiveness or pre-defined safety limits were met (i.e., raise in central venous pressure of 5 cmH$_2$O or more).

Hemodynamic and perfusion variables

Macrohemodynamic variables, including, mean arterial pressure, CV, heart rate, norepinephrine dose (NE dose); fluid responsiveness state; fluid boluses, fluid balance, and outputs.

Cardiac output (CO) and derived indices, measured either with a pulse-contour CO technique (PiCCO device) or a pulmonary artery catheter.

Metabolic-related perfusion variables, such as arterial lactate, central venous-arterial (pCO$_2$) gradient [P(cv-a) CO$_2$] (6), and central venous oxygen saturation (ScvO$_2$) (5).

Capillary refill time measured with a standardized technique (13).

Regional flow

Sublingual microcirculation

Assessed through side dark field (SDF) device. At least five 10–20 second videos were recorded by an expert user and analyzed manually according to recent recommendations. Then, we calculated the microcirculatory flow index (MFI). A value ≤2.5 was considered microcirculatory hypoperfusion (27).

Near infrared spectroscopy (NIRS)

A NIRS probe was placed in the skin of the thenar eminence, in order to assess muscle oxygen saturation (StO$_2$), with a tissue spectrometer (InSpectra Model 325; Hutchinson Tc, Mn, USA). Values of StO$_2$ <70% was considered abnormal (8,9,27).

Liver blood flow

Indocyanine green plasma disappearance rate (PDR-ICG) was measured with a transcutaneous assessment if ICG clearance, measured through a finger clip and connected to a liver function monitor (LiMON-Pulsion Medical Systems, Munich, Germany) 0.25 mg/kg of ICG was injected through a central line. Normal ranges described for PDR-ICG is 18% to 25% per minute, and we considered a value <15%/min as categorically abnormal, thus suggesting liver hypoperfusion assuming stable liver function (27).

Deep hypoxia variables

Briefly, plasma from venous blood (using EDTA as an anticoagulant) was obtained by centrifugation of the sample and then deproteinate followed by centrifugation and posterior neutralization with potassium carbonate. The pyruvate level was fluorescently determined by enzymatic reaction coupled to resorufin production. The relationship was then calculated as lactate divided to pyruvate, and a value of 15 or more was considered abnormal (17).

$PaCO_2 - PvCO_2/[(SaO_2 - SvO_2) \times Hb \times 1.36]$; whereas $PaCO_2$ and $PvCO_2$ are arterial and central venous carbon dioxide, respectively, SaO_2 is arterial saturation of oxygen and Hb is hemoglobin. A value of 1.4 or more was considered abnormal (20,28,29).