

Temporal Evolution of the PcvCO₂–PaCO₂/CaO₂–CcvO₂ Ratio vs Serum Lactate during Resuscitation in Septic Shock

Shyam Madabhushi¹, Anjan Trikha², Rahul K Anand³, Rashmi Ramachandran⁴, Preet M Singh⁵, Vimi Rewari⁶

ABSTRACT

Background: Lactate as a target for resuscitation in patients with septic shock has important limitations. The PcvCO₂–PaCO₂/CaO₂–CcvO₂ ratio may be used as an alternative for the same. The primary outcome of the study is to evaluate the correlation between serum lactate and PcvCO₂–PaCO₂/CaO₂–CcvO₂ ratio measured at various time points to a maximum of 24 hours in patients with septic shock [mean arterial pressure (MAP) <65 mm Hg]. The secondary outcomes were to study the (1) relationship between the PcvCO₂–PaCO₂/CaO₂–CcvO₂ ratio and lactate clearance at 6, 12, and 24 hours as compared to the initial serum lactate, (2) to ascertain whether the PcvCO₂–PaCO₂/CaO₂–CcvO₂ ratio and the arterial lactate levels in the first 24 hours are able to predict mortality at day 28 of enrollment, and (3) to determine whether the PcvCO₂–PaCO₂/CaO₂–CcvO₂ ratio and arterial lactate are useful in discriminating survivors from nonsurvivors.

Materials and methods: Thirty patients with sepsis-induced hypotension who were being actively resuscitated were enrolled. Paired arterial and central venous blood samples were obtained 0.5 hourly till stabilization of MAP and 6 hourly thereafter for the first 24 hours. Patients were followed up to day 28 of enrollment for mortality and organ system failure.

Results: A positive correlation was observed between arterial lactate and PcvCO₂–PaCO₂/CaO₂–CcvO₂ ratio at 0, 6, 12, and 18 hours ($R = 0.413$, $p = 0.02$; $R = 0.567$, $p = 0.001$; $R = 0.408$, $p = 0.025$; $R = 0.521$, $p = 0.003$, respectively). No correlation was seen between PcvCO₂–PaCO₂/CaO₂–CcvO₂ ratio and lactate clearance. The subgroup analysis showed that PcvCO₂–PaCO₂/CaO₂–CcvO₂ ratio >1.696 at 24 hours of resuscitation predicted 28-day mortality (sensitivity: 80%, specificity 69.2%, area under the receiver operating characteristic curve 0.82).

Conclusion: The PcvCO₂–PaCO₂/CaO₂–CcvO₂ ratio and lactate are positively correlated during the first 24 hours of active resuscitation from sepsis-induced hypotension, and a threshold of 1.696 mm Hg/mL/dL at 24 hours significantly differentiates survivors from nonsurvivors (CTRI/2017/11/010342).

Keywords: PcvCO₂–PaCO₂/CaO₂–CcvO₂ ratio, Resuscitation, Septic shock, Serum lactate.

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INTRODUCTION

Sepsis has been defined as a dysregulated host response to infection.¹ Patients with sepsis are frequently admitted to the intensive care unit (ICU) for managing hypotension and are resuscitated with vasopressors and intravenous crystalloids. The Surviving Sepsis Campaign² recommends resuscitation end points, which may be classified as macro- or microcirculatory.³ Arterial lactate, a commonly used end point, is considered an imperfect marker of anaerobic metabolism in sepsis.⁴ As an alternative, the PcvCO₂–PaCO₂/CaO₂–CcvO₂ ratio has been proposed. The shock causes a decrease in tissue perfusion and oxygen availability, which shifts energy production to anaerobic pathways, leading to a decrease in the ratio of aerobic to anaerobic metabolism. To detect this shift, the ratio of CO₂ production and O₂ utilization is measured. In a perfectly aerobic system, all CO₂ production is derived from aerobic glucose oxidation, which leads to a CO₂ production: O₂ utilization ratio of 1.0. If anaerobic metabolism increases, the O₂ utilization reduces but the anaerobic production of CO₂ continues, thereby resulting in an increase in the CO₂ production: O₂ utilization ratio. Since the measurement of the actual CO₂ production and O₂ utilization is not practical in the clinical setting, the PcvCO₂–PaCO₂/CaO₂–CcvO₂ ratio is used as a surrogate of the same. The numerator reflects CO₂ production, whereas the denominator reflects O₂ utilization. In shock, the ratio is expected to increase, implying worsening tissue hypoxia. Resuscitation would improve O₂ utilization, which would result in a reduction of the ratio. This ratio may be alternatively called the “calculated respiratory quotient.”

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Previous studies that have investigated the utility of the PcvCO₂–PaCO₂/CaO₂–CcvO₂ ratio have important limitations. Some were retrospective in nature⁵ or included patients after attaining resuscitation end points as defined by the Surviving Sepsis Campaign guidelines.⁶ Our study, therefore, is aimed at delineating the evolution of the PcvCO₂–PaCO₂/CaO₂–CcvO₂ ratio during the first 24 hours of resuscitation in patients with sepsis-induced hypotension and contrast it with the evolution of arterial lactate.

AIMS AND OBJECTIVES

The primary objective of the study is to examine the correlation between the PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio and the arterial lactate during the first 24 hours of resuscitation from septic shock. The secondary objectives of the study are: (1) to examine the correlation between the PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio and the lactate clearance within the same time period, (2) to ascertain whether the PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio and the arterial lactate levels in the first 24 hours are able to predict mortality at day 28 of enrollment, and (3) to determine whether the PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio and arterial lactate are useful in discriminating survivors from nonsurvivors. A subgroup analysis (survivors and nonsurvivors at day 28 of enrollment) of the PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio and the arterial lactate was also planned.

MATERIALS AND METHODS

Patients

A prospective observational study was designed and conducted in two ICUs of a tertiary care hospital in North India. One is a 10-bedded mixed medical-surgical ICU and the other is a 12-bedded level-3 trauma ICU. Patients were recruited from September 2016 to June 2018. All adult patients admitted to the ICU with sepsis-induced hypotension [defined as mean arterial pressure (MAP) <65 mm Hg] and with an arterial and central venous catheter were considered for inclusion into the study. Pregnancy, patients less than 18 years of age, those who did not have a central or arterial line inserted, those in whom resuscitation was aimed at supraphysiological targets, and those in whom consent was not available were excluded from the study. [Flowchart 1](#) depicts the procedure of enrollment of patients in the study. The trial was approved by the institutional ethics committee and was registered with the Clinical Trials Registry of India (CTRI/2017/11/010342).

Measurements

Paired arterial and central venous samples were drawn from enrolled patients to measure lactate and calculate the PcvCO₂-

PaCO₂/CaO₂-CcvO₂ ratio. Two sampling intervals were followed. To capture the early phase of resuscitation, initially, these paired samples were drawn and analyzed at half-hourly intervals till stable MAP targets were achieved. Stability was defined as MAP >65 mm Hg for more than 15 minutes without escalating the doses of vasopressors. A maximum of four such samples was permitted (accounting for the first 2 hours). For the remainder of the first 24 hours, sampling and measurement were done six hourly. Data were entered into a standard format. Clinical decision-making and interventions were as per the intensivist in charge of the case. Hemoglobin levels were obtained from the central laboratory. The following were calculated according to standard formulae:

- Arterial oxygen content (CaO₂): $CaO_2 \text{ (mL O}_2\text{/dL)} = (1.34 \times \text{hemoglobin concentration} \times SaO_2) + (0.0031 \times PaO_2)$
- Central venous oxygen content (CcvO₂): $CcvO_2 \text{ (mL O}_2\text{/dL)} = (1.34 \times \text{hemoglobin concentration} \times ScvO_2) + (0.0031 \times PaO_2)$
- Lactate clearance at 6, 12, 18, and 24 hours using arterial lactate at enrollment as baseline (lactate T₀). Lactate clearance (using 6 hours as an example): $(\text{arterial lactate at T}_0 - \text{arterial lactate at 6 hours}) / \text{arterial lactate at T}_0 \times 100\%$

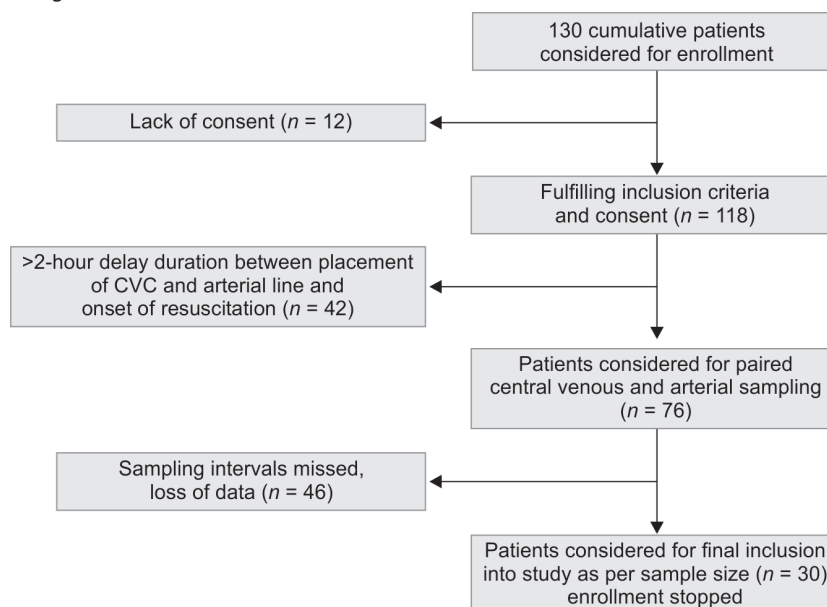
All patients were followed up for 28 days after enrollment or death or hospital discharge (whichever was earlier).

To calculate the sample size, data from a study by Mekontso-Dessap et al.⁵ were used. The correlation between the PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio and the lactate was 0.57. Using a two-tailed type-I error of 0.05 and a type-II error of 0.2, a sample size of 22 was obtained. We enrolled 30 patients in our study.

Statistical Analysis

Patient characteristics and demographic data were described in terms of mean and standard deviation (SD) or median and range, as applicable. Correlation between the PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio and lactate and PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio and lactate clearance were calculated using the Spearman's coefficient (*p*).

Flowchart 1: Study flow diagram



Subgroup analysis of these variables between survivors and nonsurvivors was done using the Wilcoxon-Mann-Whitney test. Sensitivity and specificity of the PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio and lactate for predicting mortality were calculated, and receiver operating characteristic (ROC) curves were constructed. To analyze whether the proportion of patients with calculated thresholds for lactate and the PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio were different between survivors and nonsurvivors, the Fisher's exact test was used. A *p* value of <0.05 was considered statistically significant. All statistical analyses were performed using Stata (Ver 15.1; StataCorp LLC, Texas, USA).

RESULTS

Data from all 30 patients were analyzed which included a total of 186 samples. Two patients died in the 18–24 hours' period. Their data till the 18-hour mark were collected and analyzed. Eight patients were sampled half-hourly beyond the first half hour. The rest of the patients had a stable MAP at the end of the first half hour and did not need additional half-hourly sampling.

The mean age of the patients was 38 years (SD 17.54; range 18–77 years). The median time between hospital admission and the development of septic shock was 97 hours (range: 2–1116 hours). The median time between the identification of hypotension and the first paired arterial and central venous sample was 0.5 hours (SD 0.298, range 0–1 hours) (Table 1). The main source (suspected or proven) of sepsis was respiratory (*n* = 15; 50%), followed by the abdomen (*n* = 8; 26.67%). The source of sepsis remained unknown in two patients. The median length of ICU stay was 15.5 days.

Thirteen patients survived to day 28 of enrollment (28-day mortality was 56.6%).

The primary outcome of the study was the correlation between the PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio and the arterial lactate at each of the sampling time points. The correlation between the PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio and the arterial lactate was positive and was statistically significant at time points 0, 6, 12, and 18 hours. The correlation was strongest at the 18-hour time point (Table 2). The correlation between the PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio and the lactate clearance was negative but reached significance only at one time point (*T* = 18 hours; *p* = -0.4448, *p* = 0.0138) (Table 3).

The study population was divided into survivors and nonsurvivors, and data were analyzed to discern differences, if any, in the parameters assessed. There was no difference in the mean values of hemoglobin and ScvO₂ between the survivors and nonsurvivors (*p* > 0.05). The PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio was higher in nonsurvivors than in survivors at all time points except at 1 hour. However, the difference reached a statistical significance only at 24 hours (*z* = -2.879; *p* = 0.0040) (Table 4). Assuming that the PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio remained constant between two measurements, the time duration for which it remained abnormal (>1) was calculated for differences between survivors and nonsurvivors. No such difference was found (Student's *t* test, *p* > 0.05). Similar calculations were made for the arterial lactate between survivors and nonsurvivors (Table 5). The median lactate was greater in nonsurvivors than in survivors, but the difference reached significance only at 18 and 24 hours. There was no difference between the time duration for

Table 1: Demographic and disease characteristics

Variable	Mean	Median	SD	Maximum	Minimum
Age (in years)	38.4		17.54	77	18
Height (in cm)	165.8 cm		6.664	178	155
Weight (in kg)	64.9		10.24	85	40
Time between clinical event and hospital arrival (in hours)		38		720	0
Time between hospital admission and development of septic shock (in hours)		97		1116	2
Time between identification of hypotension and first paired sample (in hours)		0.5	0.298	1	0
APACHE II score		20.5		42	7
SOFA at enrollment		10		19	4
Hemoglobin (g/dL)	9.0		1.663	14.3	6.5
ScvO ₂ (%)	73.1		10.26	89.1	51

Table 2: Correlation between PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio and lactate

Time point	Spearman's rho (<i>ρ</i>)	Probability (<i>p</i>) value
0 hour (enrollment)	0.4137	0.0231
0.5 hour	0.1908	0.3126
1 hour	0.4072	0.3167
6 hours	0.5671	0.0011
12 hours	0.4085	0.0250
18 hours	0.5216	0.0031
24 hours	0.3392	0.0774

Table 3: Correlation between the PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio and the lactate clearance

Time point	Spearman's rho (ρ)	Probability value (<i>p</i>)
0.5 hour	0.0980	0.6065
1 hour	-0.4286	0.2894
6 hours	-0.2511	0.1889
12 hours	-0.1427	0.4520
18 hours	-0.4448	0.0138
24 hours	-0.2370	0.2246

Table 4: PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio in survivors and nonsurvivors

Time point	Wilcoxon rank sum	Probability value (<i>p</i>)
0	-0.984	0.3253
0.5 hour	-1.611	0.1071
1 hour	0.745	0.4561
6 hours	0.314	0.7536
12 hours	-1.235	0.2170
18 hours	-1.569	0.1165
24 hours	-2.879	0.0040

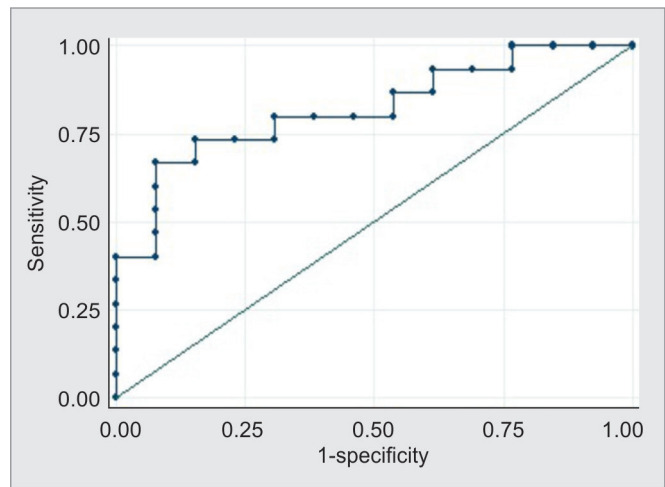
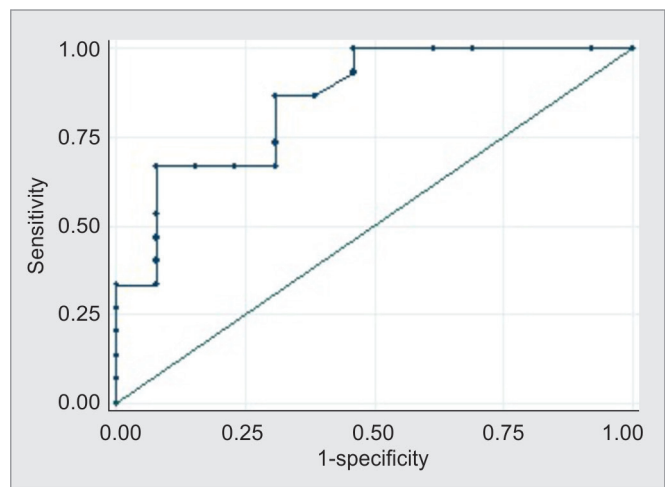
Table 5: Arterial lactate in survivors and nonsurvivors

Time point	Wilcoxon rank sum	Probability value (<i>p</i>)
0	-1.027	0.3043
0.5 hour	-1.027	0.3044
1 hour	-1.050	0.2938
6 hours	-1.634	0.1022
12 hours	-1.848	0.0646
18 hours	-2.556	0.0106
24 hours	-3.182	0.0015

which lactate was elevated (>2 mmol/L) among survivors and nonsurvivors ($p > 0.05$).

ROCs were constructed after calculating the thresholds for variables predictive of 28-day mortality. The variables considered were arterial lactate, venoarterial PCO₂ gap, PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio, ScvO₂, and arteriovenous O₂ content difference. Of these variables, only the arterial lactate and the PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio had a significant area under the ROC curve (AU-ROC). The PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio at 24 hours with a value greater than 1.696 mm Hg/mL/dL was predictive of mortality with a sensitivity of 80% and a specificity of 69.2%. The AU-ROC was 0.8205 (95% confidence interval [CI] 0.661-0.979) (Fig. 1). For arterial lactate at 24 hours, a value >1.6 mmol/L was predictive of mortality at 28 days with a sensitivity of 73.33% and a specificity of 69.23%. The AU-ROC was 0.853 (95% CI 0.712-0.915) (Fig. 2).

Using the log-rank test, survival differences were estimated for threshold values of both the arterial lactate and PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio. At time 0, the thresholds chosen were the normal values of the variables [1 for PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio and 2 mmol/L for arterial lactate]. At the 24-hour time point, the thresholds chosen were those that were estimated to have the best sensitivity and specificity for mortality prediction from the ROC curves. Accordingly, these values were 1.696 for the PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio and 1.6 mmol/L for the arterial lactate. For the thresholds chosen at enrollment, there were no differences in the

**Fig. 1:** Receiver operating characteristic curve for PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio at 24 hours for predicting 28-day mortality**Fig. 2:** Receiver operating characteristic curve for arterial lactate at 24 hours for predicting 28-day mortality

Kaplan-Meier survival estimates [$\chi^2 = 0.70$, $p = 0.4016$ for lactate 2 mmol/L; $\chi^2 = 0.69$, $p = 0.4076$ for PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio]. For the thresholds chosen at time point 24 hours, there were significant differences in the Kaplan-Meier survival estimates. For a lactate of 1.6 mmol/L, the probability of 28-day survival was 26.6 and 69.2% above and below this threshold, respectively ($\chi^2 = 5.62$, $p = 0.0177$) (Fig. 3). For the PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio of 1.696, the probability of 28-day survival was 25 and 75% above and below this ratio, respectively ($\chi^2 = 6.00$, $p = 0.0143$) (Fig. 4).

DISCUSSION

Our results demonstrated a significant positive correlation between lactate and the (PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio at 0, 6, 12, and 18 hours during the first 24 hours of resuscitation after sepsis-induced hypotension. Resuscitation attempts to increase DO₂, which then increases VO₂ causing lactate levels to fall. Simultaneously, the anaerobic production of CO₂ decreases, and the PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio falls. This physiology explains the positive correlation between these two variables. To the best of our knowledge, this is probably the only prospective study that has

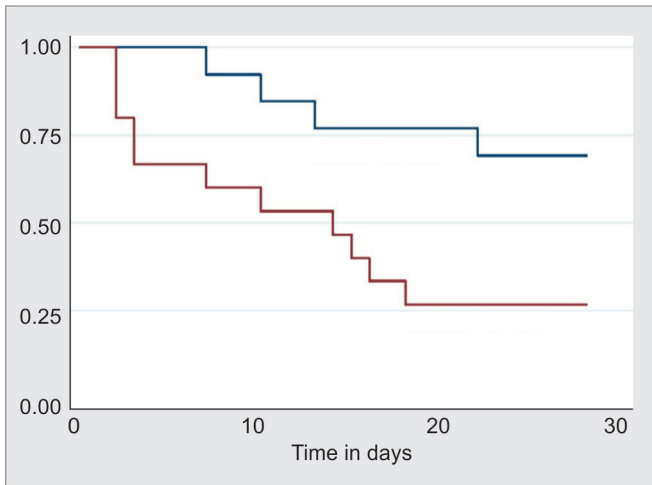


Fig. 3: Kaplan-Meier survival estimate for lactate >1.6 mmol/L at 24 hours

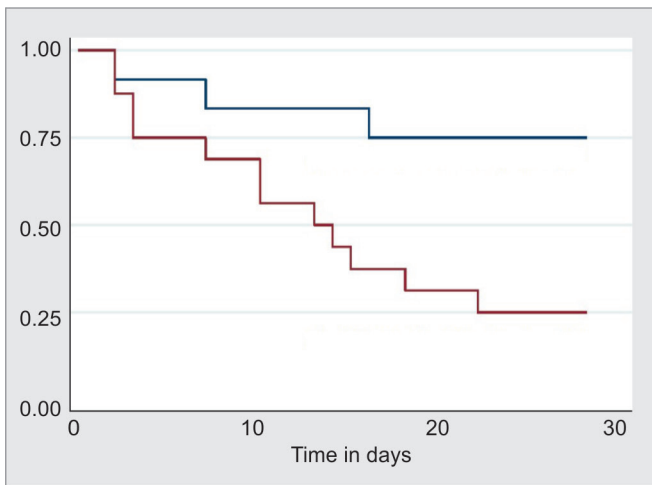


Fig. 4: Kaplan-Meier survival estimate for PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio >1.696 mm Hg/mL at 24 hours

looked at stepwise lactate and the PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio kinetics and studied correlation at each time point with predefined sampling intervals.

There was a significant negative correlation between the lactate clearance and the PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio at only one time point (18 hours; $p = -0.4448$, $p = 0.0138$). This is probably because patients were resuscitated early during sepsis-induced hypotension, and therefore, the lactate levels were not severely elevated. The median lactate at enrollment was 1.8 mmol/L, and the median lactate at the end of 24 hours was 1.65 mmol/L. Only 14 of the 30 patients (47%) had a serum lactate >2.0 mmol/L at enrollment. Therefore, the overall scope for lactate reduction in the study population was rather low.

Mekontso-Dessap et al.⁵ in their retrospective study on ICU patients divided them into those with a high (>2.0 mmol/L) and low lactate (<2.0 mmol/L). They too found good correlation between the PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio and the lactate ($R = 0.57$, $p < 0.0001$). However, the time intervals of these measurements were not clearly defined. Mesquida et al.⁶ in their retrospective analysis of 35 patients explored the ability of the PcvCO₂-PaCO₂ gap and

PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio to predict the evolution of lactate. Their patient population included those that had normalized their ScvO₂ and MAP. Their study showed correlation between the initial lactate and the PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio ($R = 0.73$, $p < 0.001$). Although this correlation is higher than the correlation obtained in our study, this could be due to the fact that samples were obtained only after normalization of ScvO₂ and MAP.

In terms of secondary outcomes, both the PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio and the arterial lactate are predictive of mortality. For this, Kaplan-Meier curves were calculated at two points: at enrollment and at 24 hours. The enrollment curves were constructed to determine if there was any survival difference at day 28 for lactate >2 mmol/L and <2 mmol/L. Similarly, the threshold chosen for the PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio was >1 mm Hg/mL/dL and <1 mm Hg/mL/dL. Both these thresholds were chosen as the upper limit of normal values for the lactate and the PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio. There was no difference in the survival probability at enrollment for both the variables chosen. This is physiologically explicable again from the observation that the median lactate at enrollment in the study was below this threshold (1.8 mmol/L). The median PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio at enrollment was 1.759. Although this value was higher than 1.0, in the analysis between survivors and nonsurvivors, the median value of the PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio at enrollment was not different between the two subgroups. The Kaplan-Meier survival curves at 24 hours were constructed using the thresholds with the best combination of sensitivity and specificity obtained from the ROC tables. It is also notable that the largest differences between survivors and nonsurvivors in terms of the PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio and the arterial lactate were at the 24-hour time point. The threshold for the PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio was 1.696, and that for lactate was 1.6 mmol/L. The Kaplan-Meier curves at 24 hours for these thresholds show a significant difference in the survival probability. This reinforces the general theme that in patients with sepsis-induced hypotension if resuscitation targets [lactate and the PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio in this case] are not attained even after 24 hours of resuscitation, the outcome is poor. Therefore, these thresholds may be used as resuscitation targets.

The study performed by Ospina-Tascon et al.⁷ demonstrated that the prognostic value afforded by lactate was enhanced by the PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio. The values of AU-ROC for the lactate and the PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio in our study are similar, including the sensitivity and specificity. This implies that the PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio can be reasonably used to estimate the presence of anaerobic metabolism and predict the outcome in lieu of the lactate. However, it is noticeable that these indicators become statistically significant predictors of mortality only by 24 hours of the onset of hypotension. One can therefore conclude that hypotension is a relatively early clinical event in sepsis, while derangements in lactate are a late event.

Although not designed for evaluation of this difference, it is notable that 73% of patients had an abnormal PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio, while only 46.67% of patients had abnormal lactate. At the 24-hour time point, the PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio remained deranged in 78% of patients, while only 61% of patients had abnormal lactate (>2.0 mmol/L). If one were to look at lactate alone at the time of enrollment, more than 50% of patients in our study would not be classified as being in shock. We feel that it could be further explored whether the PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio is a more sensitive indicator of tissue hypoxia than the arterial lactate.

The patient population in our study was relatively young (mean age 38.4 years). This is partly because of many patients with polytrauma being enrolled, which primarily affects the younger population. The median time between the onset of symptoms and hospitalization in our study was more than 36 hours. The median time between hospitalization and recruitment was 97 hours. These numbers have important implications. A longer time between symptom/event onset and hospital arrival signifies the possibility of physiological derangement that has progressed untreated. The time from hospitalization to recruitment is also long. This meant that most of the infections that these patients were hospital-acquired, which have a much higher mortality than community-acquired infections. It also implies that these episodes of sepsis are potentially not the first that the patients had. Repeated episodes of sepsis and septic shock have higher mortality than the first episode. This is an important distinction between our study and other studies that enrolled only patients with the first episode of sepsis.

In the present study, the key parameter for enrollment was the occurrence of hypotension due to sepsis (suspected or proven). We did not choose any other parameter because hypotension is the usual clinical marker for intervention, and resuscitation begins only after the recognition of the clinical marker. Making the entry criterion clinical would allow more ICUs and centers to test our hypothesis using the current methodology. We did not exclude patients based on the first episode of sepsis or the time since hospitalization. The sole criterion was direct observation of hypotension and initiation of resuscitation. If a marker of anaerobic metabolism must perform in clinical practice [the PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio in this case], it must be validated across patient categories and severity with minimal exceptions. We feel this reflects clinical reality, where unselected patients in the ICU develop hypotension and are resuscitated accordingly. The quantity of fluids administered in our patients in the first 3 hours of resuscitation is not in accordance with the surviving sepsis guidelines (30 mL/kg). The standard protocol in our institution is not to administer such a large quantity of fluids as a matter of routine. Our patients spent a considerable amount of time in the hospital on the general wards/ED before being transferred to the ICU. This has been alluded to before in this discussion. Consequently, they invariably receive intravenous crystalloids and are usually volume replete. This is different from other studies. In the study by Gustavo-Ospina et al.,⁸ patients received 1977 mL (1200–2800 mL) of fluids before the first sampling, which was 3 hours after the first episode of hypotension. In our study, the interval between the onset of hypotension and the first sample was a maximum of 1 hour. This is because most of these patients already had a central venous catheter/intra-arterial catheter *in situ* or had these devices inserted almost immediately at the onset of hypotension. Our approach to hypotension in sepsis is the simultaneous use of fluids and vasopressors, without waiting for the completion of fluid boluses. Norepinephrine was the most common vasopressor used. Dobutamine was used at the discretion of the treating physician, either aimed at optimizing ScvO₂ or in response to evidence of reduced cardiac contractility on bedside point-of-care ultrasound (POCUS). This strategy is to minimize the hypotensive period. The importance of minimizing the hypotensive duration was shown in a retrospective review of a large medical database by Maheshwari et al.⁹ In this study, hypotension exposure was defined by the time-weighted average MAP (TW-MAP) and cumulative time below 55, 65, 75,

and 85 mm Hg thresholds. For every one-unit increase in the TW-MAP <65 mm Hg, the odds of inhospital mortality increased by 11.4%, the odds of acute kidney injury increased by 7.0%, and the odds of myocardial injury increased by 4.5%. Sampling intervals were initially half-hourly till stabilization of the MAP, for a maximum of 2 hours. This was done to capture the early changes in PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio and see if these changes were reflected by the lactate concentrations. The results demonstrate that such a correlation does exist. However, there was no correlation with lactate clearance. We did not use a pulmonary artery catheter or other direct carbon monoxide monitoring devices. This is in line with our institutional practice. The study demonstrates the correlation between two important markers of tissue hypoxia without measuring CI. In resource-constrained settings like ours, keeping costs low is also important.

This study did have a few limitations. We used the definition of sepsis as per the Surviving Sepsis Campaign guidelines, 2012. The Surviving Sepsis Campaign guidelines 2016 were published after the finalization of the study design. The use of CO₂ partial pressures instead of contents, as illustrated by Ospina-Tacson et al.,⁸ is a potential shortcoming. However, considering the linearity of the CO₂ dissociation curve and the simplicity of using values from a direct readout of the analyzer, it was felt that the use of pressures was an acceptable substitute. In an ideal setting, the cardiac output should have been measured and VO₂ calculated. A correlation between the VO₂ and the PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio would be attractive. This is because the ultimate objective of any resuscitation protocol is to increase the VO₂ and reduce anaerobic metabolism. Bedside POC US and echocardiography, although freely in use in our ICU, is not part of the written protocol. Key decisions in the study population (fluid administration and limitation, determination of the condition of the lung parenchyma, etc.) were taken using ultrasound. However, since these were done at the discretion of the treating clinician and performed in an unselected manner, we could not integrate them into the study protocol. The details of fluids received in the preceding 24 hours and cumulative fluid balance were not known to the treating team. This, unfortunately, reflects the reality of practice in a large public hospital with no electronic monitoring records and inadequate staffing at the ward/ER level. Such records would have been invaluable both for the management of the patient and for the purposes of this study.

In conclusion, the PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio and the lactate are positively correlated during the first 24 hours following active resuscitation from sepsis-induced hypotension. The PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio at 24 hours is significantly higher in nonsurvivors, and a threshold of 1.696 mm Hg/mL/dL for PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio at 24 hours significantly differentiates survivors from nonsurvivors. The PcvCO₂-PaCO₂/CaO₂-CcvO₂ ratio may be used as an end point of hemodynamic resuscitation from septic shock.

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