ORIGINAL ARTICLE

Value of Central Venous to Arterial CO_2 Difference after Early Goal-directed Therapy in Septic Shock Patients

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Abstract

Background and aims: Venous to arterial difference of carbon dioxide ($Pv–aCO_2$) tracks tissue blood flow. We aimed to evaluate if $Pv–aCO_2$ measured from a superior central vein sample is a prognostic index (ICU length of stay, SOFA score, 28th mortality rate) just after early goal-directed therapy (EGDT)comparing its ICU admission values between patients with normal and abnormal (>6 mm Hg) $Pv–aCO_2$. As secondary objectives, we evaluated the relationship of $Pv–aCO_2$ with other variables of perfusion during the 24 hours that followed EGDT.

Materials and methods: Prospective observational study conducted in an academic ICU adult septic shock patients after a 6-hour complete EGTD. Hemodynamic measurements, arterial/central venous blood gases, and arterial lactate were obtained on ICU admission and after 6, 18 and 24 hours.

Results: Sixty patients were included. Admission $Pv–aCO_2$ values showed no prognostic value. Admission $Pv–aCO_2$ (ROC curve 0.527 [CI 95% 0.394 to 0.658]) values showed low specificity and sensitivity as predictors of mortality. There was a difference observed in the mean $Pv–aCO_2$ between nonsurvivors (NS) and survivors (S) after 6 hours. Central venous oxygen saturation ($ScvO_2$) and $Pv–aCO_2$ showed significant correlation ($R2 = –0.41$, $P < 0.0001$). Patients with normal $ScvO_2$ (>70%) and abnormal $Pv–aCO_2$ (>6 mm Hg) showed higher SOFA scores. Normal $Pv–aCO_2$ group cleared their lactate levels in comparison to the abnormal $Pv–aCO_2$ group.

Conclusion: In septic shock, admission $Pv–aCO_2$ after EGDT is not related to worse outcomes. An abnormal $Pv–aCO_2$ along with a normal $ScvO_2$ is related to organ dysfunction.

Keywords: Central venous saturation, Lactate, Mortality, Septic shock, Venous to arterial difference of CO_2.

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Introduction

Septic shock is a condition in which tissue perfusion is inadequate, leading to multi-organ dysfunction and death.[1] An early optimization of systemic hemodynamic parameters seems to improve outcomes in shock states, reinforcing the idea that is fundamental to reestablish blood flow early in shock.[2] However, maintaining normal systemic hemodynamic parameters does not always guarantee adequate tissue perfusion.[3,4]

As a major determinant of oxygen supply, adequacy of blood flow is a fundamental variable to be evaluated.[5] The venous to arterial difference of partial pressure of carbon dioxide ($Pv–aCO_2$) is an index that has shown to be inversely correlated with the cardiac output (CO) in several shock states.[6-9] Studies using both mixed venous or central venous PCO_2 showed similar inverse curvilinear correlation with CO.[10,11] The enlargement venous to arterial CO_2 difference in animal models is shown during ischemic hypoxia.[12–14] Thus, venous accumulation of CO_2 is secondary either to a reduced blood flow and/or to anaerobic metabolism.[15] Although a few studies demonstrated that the correlation between blood flow and $Pv–aCO_2$ sounds physiological and it was associated with poor outcomes,[16,17] others questioned a clear prognostic implication.[6,18,19]

Several studies showed that oxygen parameters are normalized at ICU admission, showing that early global resuscitation might be partial or completely achieved.[20–23] Recent studies have challenged early goal directed therapy (EGDT) as a strategy to be followed, but all these studies initiated EGDT after significant volume repletion and $ScvO_2$ was close to normal at randomization, suggesting that blood flow was already restored.[21-23] Thus, studies have demonstrated that mixed or venous oxygen saturation normal values may not depict regional or tissues perfusion abnormalities.[4,24] Interestingly, Vallet et al. reported that in adult septic patients with septic shock, having $Pv–aCO_2$ >6 mm Hg after achieving the goal $ScvO_2$ of 70% helped identify patients with ongoing hypoperfusion.[24]

Given that $Pv–aCO_2$ can track blood flow in the tissues, we asked if this index could identify hypoperfusion in septic shock patients admitted to the ICU after adequate EGDT. This investigation may add information to the use of this index to decide if additional increase in blood flow may help septic patients during EGDT. Thus, we aimed to evaluate if $Pv–aCO_2$ measured from a superior central vein sample is related with organ dysfunction and mortality in patients with septic shock after early resuscitation, comparing its ICU admission values between patients with normal and enlarged (>6 mm Hg) $Pv–aCO_2$. As secondary objectives, we evaluated the relationship of $Pv–aCO_2$ with other variables of perfusion (lactate and central venous oxygen saturation) during the 24 hours that followed EGDT.

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Materials and Methods

This prospective observational non-interventional clinical study was conducted in an 18-bedded general ICU of a university hospital. The study population consisted of adult (≥18 years) septic patients admitted to the intensive care unit after EGTD that persisted with shock (need for vasopressors). Our EGDT included a bundle of interventions during 6 hours period that sought to obtain a mean arterial pressure (MAP) ≥65 mm Hg (a fluid challenge of at least 20 mL/kg and need of vasopressors), urine output >0.5 mL/kg/h and a hemoglobin ≥7 g/dL. All patients were required to stay in the unit for at least 24 hours. Patients with liver cirrhosis, pregnancy, absence of a central line for any reason, incomplete EGDT, or considered without therapeutic perspective were excluded.

Measurements on admission had to be obtained in a window not greater than 2 hours after EGDT completion. All patients had to have a superior central venous line and an arterial catheter in place. Hemodynamic measurements and collection of arterial and venous blood gases, and lactate were performed on admission to the ICU and after 6 (T6), 12 (T12), 18 (T18) and 24 (T24) hours. Additional resuscitation (use of crystalloid or colloid and vasopressor) was held at the discretion of the attending physician, according to clinical judgment. Blood gas values were determined using a commercial blood-gas analyzer (Ciba-Corning, San Diego, CA, USA). Blood lactate concentrations were measured by an enzymatic technique (Cobas Mira Plus, Roche, Indianapolis, IN, USA).

This study was approved by the hospital ethics committee. Informed consent was waived because there was no intervention and the collection of blood samples was part of routine assistance protocols.

Outcomes

The primary outcome assessed was 28th mortality. Other outcomes included ICU length of stay and organ dysfunction (sequential organ failure assessment score).

Statistical Analysis

Statistical analyses were performed using SPSS v.18.0. Quantitative variables were expressed as mean ± standard deviation. Qualitative variables were described as frequencies and percentages. The evolution of each variable during 24 hours was analyzed using a repeated-measures analysis of variance. The comparison of means was performed using the Student's *t* test for normally distributed variables and the Mann–Whitney test for variables with non-normal distribution (Kolmogorov–Smirnov test). The frequencies were analyzed using the Chi-squared test (or Fisher's test when appropriate). To evaluate the performance of $Pv–aCO_2$ on admission to predict death at 28th day, receiver operating characteristics (ROC) curve analysis was performed. The Spearman's rho was used to explore the relationship between $Pv–aCO_2$ and $ScvO_2$ on T0. Data are reported as means ± standard deviations unless indicated otherwise. For statistical analysis, SPSS version 18.0 for windows (SPSS, Chicago, IL, USA) was used. The *p* value considered significant was <0.05.

Results

During a 12-month period, 112 patients were screened. After exclusions, a total of 60 patients were analyzed and 271 measures of $Pv–aCO_2$ were obtained, 57% within the normal range (<6 mm Hg). Admission $ScvO_2$ values were normal for 41 patients (68%). The mortality rate at 28 days was 43% (26/60). Survivors showed a significant reduction in SOFA score during 3 days follow-up (Table 1).

Table 1: Demographic, hemodynamic and oxygenation parameters at ICU admission for survivors and nonsurvivors after 28 days

	Survivors (n = 32)	*Nonsurvivors (n = 28)*
AGE (years)	54±15	61±12
APACHE II	24±8	27±6
SOFA Day 1	9,7±3.5	9.9±2.9
SOFA Day 2	7.5±3.7	9.0±3.7
SOFA Day 3 (*s* = 31, *ns* = 27)	5.5±4.4	8.3±4.1*
Mechanical ventilation	27	26
ICU length of stay (days)	15 [9-38]	14[9-20]
$Pv–aCO_2$ (mm Hg)	6.1±4.1	5.6±3.5
MAP (mm Hg)	74±17	67±14
HR (beats/min)	105±19	106±17
CVP (mm Hg)	16±7	14±6
Diuresis (mL/kg/h)	0.4±0.6	0.5±0.9
SaO_2 (%)	96±5	95±8
$ScvO_2$ (%)	72±10	75±9
Arterial lactate (mmol/L)	2.6±2.2	3.3±2.8
Norepinephrine (μg/kg/min)	0.16 [0.08–0.27]	0.16 [0.07–0.26]

APACHE II, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment score; $Pv–aCO_2$, venous to arterial difference of partial pressure of carbon dioxide; MAP, mean arterial pressure; HR, heart rate; CVP, central venous pressure; SaO_2, arterial hemoglobin oxygen saturation; $ScvO_2$, central venous hemoglobin oxygen saturation. *$p < 0.05$.

The admission $Pv–aCO_2$ showed no difference with regard to any possible outcome when categorized in normal and abnormal (Table 2). Admission $Pv–aCO_2$ (ROC curve 0.527 [CI 95% 0.394 to 0.658]), $ScvO_2$ (0.586 [CI 95% 0,452 to 0,712]) and arterial lactate (0589 [CI 95% 0,455 to 0,715]) values showed low specificity and sensitivity to predict mortality. Normal or abnormal $Pv–aCO_2$ values in each time did not show statistical difference for 28th mortality, ICU mortality and SOFA scores.

There was a difference observed in mean $Pv–aCO_2$ between NS and S in T6 (Fig. 1). $SvcO_2$ was similar for both S and NS. Survivors had lower lactate levels at all times and at T12, the difference reached statistical significance (Fig. 1). At admission, patients with normal $Pv–aCO_2$ values did not show any outcome differences when compared to those with normal and low $ScvO_2$ (data not shown). However, patients with normal $ScvO_2$ values but with enlarged $Pv–aCO_2$ showed higher SOFA score values during follow-up (Table 3).

Central venous oxygen saturation and $Pv–aCO_2$ showed a significant but weak correlation (R2 = −0.41, $P < 0.0001$). Central venous oxygen saturation was significantly higher in the first 6 hours in patients with normal $Pv–aCO_2$ (Fig. 2). Patients in the normal $Pv–aCO_2$ group cleared their lactate levels in comparison to the abnormal $Pv–aCO_2$ group (Fig. 2).

Discussion

In our study, $Pv–aCO_2$ after EGDT completion did not correlate with mortality in the ICU or after 28 days, with a longer ICU stay or greater organ dysfunction. Different from others, we did not find

Table 2: Demographic, hemodynamic and oxygenation parameters of patients with normal (≤6 mm Hg) and abnormal (>6 mm Hg) Pv–aCO_2 at ICU admission

	Normal (n = 36)	*Abnormal (n = 24)*
Age (years)	56±13	60±15
APACHE II	26±8	24±7
SOFA day 1	9.6±2.9	10.0±3.7
SOFA day 2	7.9±3.5	8.9±4.1
SOFA day 3	7.3±4.7	6.6±4,4
Mechanical ventilation	32	21
28th day mortality rate (%)	47	46
ICU length of stay (days)	20±14	20±22
Pv–aCO_2 (mm Hg)	3.27±1.71	9.80±2.48*
MAP (mm Hg)	72±17	70±16
HR (beats/min)	107±19	103±17
CVP (mm Hg)	14±6	16±9
Diuresis (mL/kg/h))	0.51±0.77	0.43±0.65
SaO_2 (%)	97±8	96±7
$ScvO_2$ (%)	77±9	68±8*
Arterial lactate (mmol/L)	2.25 [1.17-3.55]	2.3 [1.25-3.90]
Norepinephrine (µg/Kg/min)	0.16 [0.08-0.24]	0.18 [0.08-0.28]

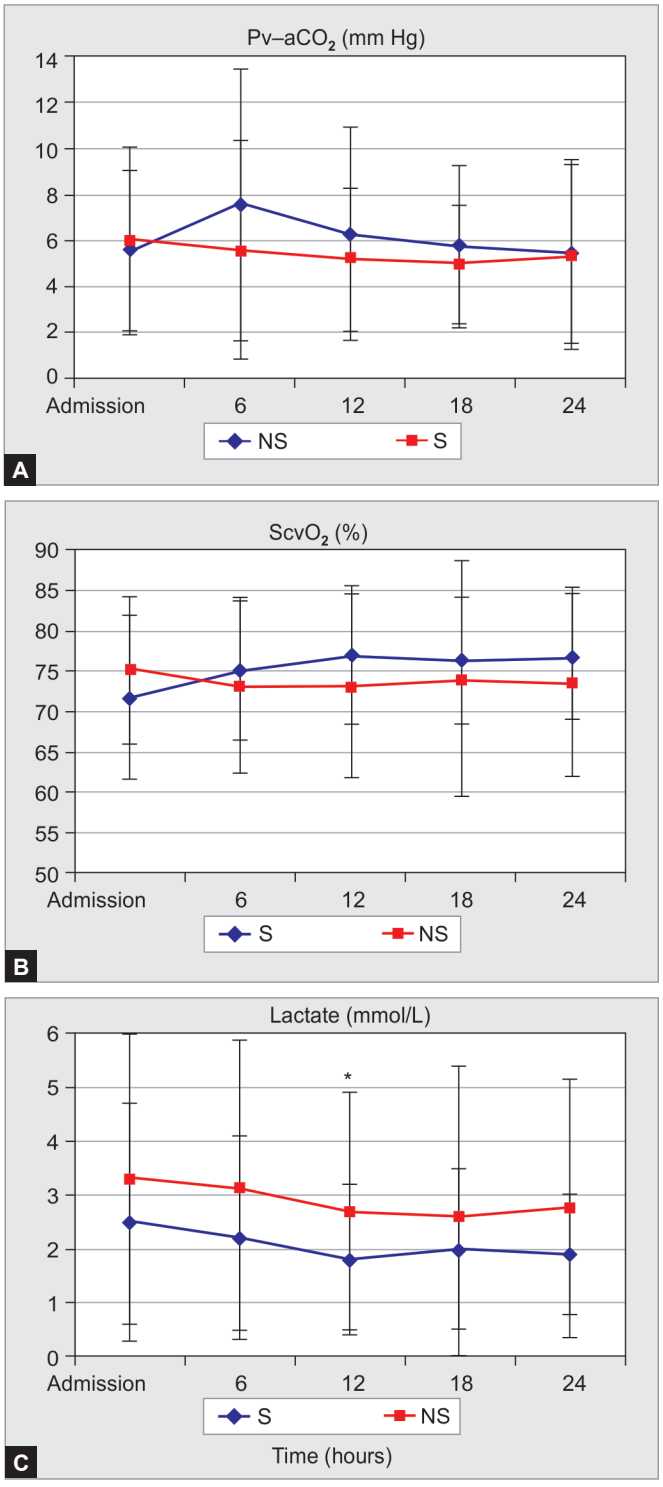
APACHE II, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment score; MAP, mean arterial pressure; HR, heart rate; CVP, central venous pressure; SaO_2, arterial hemoglobin oxygen saturation; $ScvO_2$, central venous hemoglobin oxygen saturation. *$p < 0.001$.

that an abnormal Pv–aCO_2 after apparent global hemodynamic resuscitation identified patients at risk to developed organ dysfunction or to die. The differences between admission normal and abnormal Pv–aCO_2 groups relied on physiological parameters with logical results. Abnormal Pv–aCO_2 was associated with a lower $ScvO_2$ and higher lactate values.

In addition, concerning ICU or 28th Day mortality rates and the degree of organ dysfunction in any of the three assessments by the SOFA score we did not find differences between Pv–aCO_2 groups. Our study evaluated patients after EGDT, which may have led to the inclusion of a high number of patients with high to normal blood flow. It is well known that patients with sepsis, a scenario that is usually associated with a high cardiac output (hyperdynamic state), is a condition in which the Pv–aCO_2 has the worst correlation with cardiac output.[25]

A look at the perfusion parameters also showed small differences between groups and for most patients lactate values were not elevated. Thus, we speculated that global tissue perfusion was restored for majority of the patients. Of 271 measurements obtained in this study, 57 were normal and many values on the abnormal Pv–aCO_2 group were below 8 mm Hg, so that it could be inferred that the majority of patients had enough blood flow just after EGDT completion. KM Ho and colleagues showed that the usefulness of the Pv–aCO_2 appears to be limited to its negative predictive value, to exclude a low cardiac output when it is within its normal range.[26] Here one should also be cautious in interpreting the outcomes findings as the study was underpowered to show the prognostic value of Pv–aCO_2 (small sample size), but that was evidenced in other studies.[16,17]

No differences in lactate levels were found between the two groups of Pv–aCO_2 at the time of admission. Similar findings were



Figs 1A to C: Venous to arterial CO_2 difference (Pv–aCO_2), central venous saturation ($ScvO_2$) and blood lactate values in survivors (S) and non-survivors (NS) during 24 hours. *$p < 0.05$ S vs NS after 12 hours

observed in other studies with septic shock.[6,27,28] This can be explained by the fact that the Pv–aCO_2 is not a marker of tissue hypoxia (such as lactate), but of the adequacy of blood flow to remove tissue CO_2.[12,14,15] However, although with marginal significance ($p = 0.065$), patients with a normal Pv–aCO_2 cleared their blood lactate over 24 hours as shown by others.[16,27] Interestingly,

Table 3: Comparisons of clinical data at admission between patients that normalized $ScvO_2$ values with a normal and abnormal $Pv–aCO_2$ values

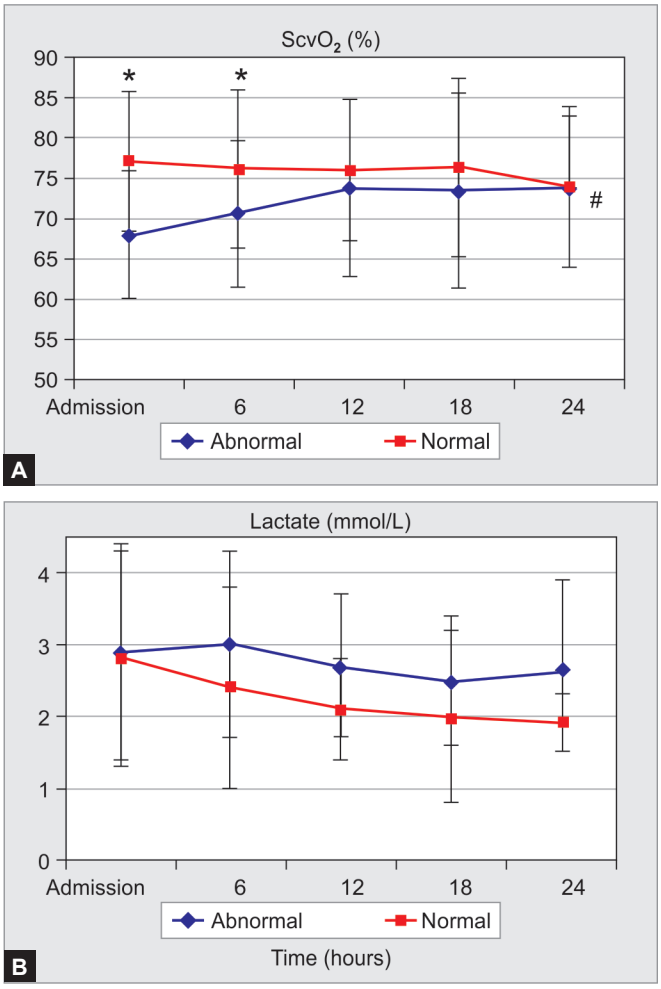
	$ScvO_2$ > 70% and $Pv–aCO_2$ ≤ 6 mm Hg (n = 31)	*$ScvO_2$ > 70% and $Pv–aCO_2$ > 6 mm Hg (n = 10)*
SOFA day 1	9.5±2.8	12±3.9*
SOFA day 2	7.7±3.4	9.8±4.6
SOFA day 3	6.1±4.4	8.4±4.8
$Pv–aCO_2$ (mm Hg)	3.4±1.8	9.9±2.9#
MAP (mm Hg)	71±16	70±17
HR (beats/min)	106±20	101±20
CVP (mm Hg)	13±5	16±12
Diuresis (mL/kg/h))	0.6±0.8	0.5±0.8
$ScvO_2$ (%)	80±6	75±5*
Arterial lactate (mmol/L)	2.2 [1.1–3.2]	3.1 [1.3–4.9]
Norepinephrine (µg/Kg/min)	0.2 [0.1–0.2]	0.2 [0.1–0.3]
28 day mortality *n* (%)	15(48)	5 (50)

APACHE II, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment score; $Pv–aCO_2$, venous to arterial difference of partial pressure of carbon dioxide; MAP, mean arterial pressure; HR, heart rate; CVP, central venous pressure; $ScvO_2$, central venous hemoglobin oxygen saturation. *$p < 0.05$, #$p < 0.001$.

the lactate clearance was accompanied by a lower $ScvO_2$ during the first 6 hours which together may indicate a higher blood flow and less hypoperfusion in several patients. Moreover, hyperlactatemia in septic conditions is complex since lactate accumulation may happen during accelerated aerobic generation and/or slow clearance.[29]

The widening of the arterial venous CO_2 difference was associated with reduced venous saturation, but this correlation, however significant, was poor. The weakness of this association in previously resuscitated patients, such as in this condition, may suggest that even after normalization of venous saturation there is still room to increase the blood flow. In our study, patients with $ScvO_2$ 70% but with an abnormal $Pv–aCO_2$ had more organ dysfunctions since admission. Venous saturation may be falsely normal when oxygen capabilities are compromised and an enlarged $Pv–aCO_2$ may identify a lack of tissue blood flow.[24] In addition, Mahajan et al. showed that a normal $Pv–aCO_2$ together with a normal $ScvO_2$ was even more associated with mortality.[28] A normal $Pv–aCO_2$ in the presence of tissue hypoperfusion or ongoing organ dysfunction may reflect cytophatic dysoxia or microcirculatory abnormalities.[15,30,31] In our study, the weakness of its prognostic value, even in patients considered well resuscitated, may suggest that after global resuscitation the disease process continues. In conjunction with the complex relationship of these variables and cardiac output, this suggests that when oxygen extraction capacity is altered, guiding resuscitation by systemic parameters is a challenge in more advanced stages of septic shock.

Finally, although $Pv–aCO_2$ as an isolated parameter does not serve to guide resuscitation, recently the use of this variable in a resuscitation proposal that integrates several parameters with a physiological view seems to be useful.[32] The Andromeda study, besides suggesting that it is possible to guide resuscitation by capillary refill time, used $Pv–aCO_2$ as one of the targets to be pursued.



Figs 2A and B: Central venous O_2 saturation ($ScvO_2$) and blood lactate values among normal ($Pv–aCO_2$ ≤ 6 mm Hg) and abnormal ($Pv–aCO_2$ >6 mm Hg) venous-arterial carbon dioxide groups patients during 24 hours. *$p < 0.05$ abnormal vs normal. #$p = 0.025$ over 24 hours in abnormal group

The study has limitations beyond the small sample size already highlighted. The venous blood sample is central and not mixed, and although there is reasonable agreement, the differences cannot be neglected. Second, the hemodynamic and perfusion changes that occurred during subsequent hours were not necessarily the result of targeted interventions, but may simply be changes related to the disease process. Third, although $Pv–aCO_2$ enlargement may suggest insufficient blood flow to remove tissue CO_2, venoarterial gradients are the result of interactions between CO_2 production, CO_2 dissociation curve, hemoglobin, blood flow, microcirculatory and cell changes.

Conclusion

This study showed that the admission $Pv–aCO_2$ after EGDT is not associated with worse outcomes. The possible physiologic explanation is that blood flow was restored for most patients. In the future, studies with larger numbers of patients may demonstrate that $Pv–aCO_2$ could be a useful complementary perfusion clinical parameter and help identify patients who remain inadequately managed when the hemodynamic optimization has been reached.

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