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Original Research Article

Difference between Partial Pressure of Venous to Arterial Carbon Dioxide as a Mortality Indicator in Septic Shock Patients After Early Goal Directed Therapy: A Prospective Observational Study

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Abstract

Aim: The aim of the present study was to evaluate if partial pressure of CO_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).

Methods: The present study was conducted at Department of Trauma and Emergency .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). During a 6-month period, a total of 100 patients were analyzed.

Results: Survivors showed a significant reduction in SOFA score during 3 days follow-up. The admission Pv–aCO2 showed no difference with regard to any possible outcome when categorized in normal and abnormal. Admission Pv–aCO2, ScvO2 and arterial lactate values showed low specificity and sensitivity to predict mortality. Normal or abnormal Pv–aCO2 values in each time did not show statistical difference for 28th mortality, ICU mortality and SOFA scores. Patients with normal ScvO2 values but with enlarged Pv–aCO2 showed higher SOFA score values during follow-up.

Conclusion: This study showed that the admission Pv–aCO2 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–aCO2 could be a useful complementary perfusion clinical parameter and help identify patients who remain inadequately managed when the hemodynamic optimization has been reached.

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

Introduction

The evaluation and correction of macrocriculatory and microcirculatory flow play an important role in the resuscitation of circulatory shock. [1] The venous-to-arterial carbon dioxide difference [P(v-a)CO2] has gained great attentions in the resuscitation of sepsis. The P(v-a)CO2 is determined by cardiac output and metabolic status, and it has been taken as an indicator of the adequacy of the venous blood flow to remove the CO2 produced by the peripheral tissues. [2,3]

The P(v-a)CO2 was calculated as the difference between venous PCO2 and arterial PCO2. The venous PCO2 could be obtained from the mixed venous blood through a pulmonary artery catheter or from the central venous blood through a central venous catheter. Researches [4,5] had shown that central venous-arterial PCO2 difference [P(cv-a) CO2] was consistent with mixed venous-arterial PCO2 difference [P(mv-a)CO2] and both of them were inversely related to cardiac index (CI). Nowadays, the central venous PCO2 is commonly used to calculate P(v-a)CO2 in clinical practice. Recent study found that P(mv-a)CO2 might be a

potential indicator to reflect microcirculatory flow in septic shock patients. [6]

The measurement of P[v–a]CO2 needs the insertion of a pulmonary artery catheter, which is seldom used today.

As a central venous catheter is inserted in most patients with septic shock, the use of central venous-arterial carbon dioxide partial pressure difference (DPCO2) is considerably simpler and equally useful. Cuschieri et al [5] have shown that P[v–a]CO2 can be substituted by DPCO2 in critically ill patients. Valle´e et al [7] have shown that, in resuscitated septic shock patients in whom central venous saturation (ScvO2) was already greater than 70%, the subgroup with normal DPCO2 (≤0.8 kPa) had a higher CO with a lower lactate concentration and a greater lactate decrease than those who presented with an initial DPCO2 exceeding 0.8 kPa. In a recent retrospective study, septic shock patients who achieved both normal ScvO2 and DPCO2 after resuscitation had a greater lactate decrease than those who achieved only a normal ScvO2. [8] The mean baseline of ScvO2 in that study was more than 70%. There are no conclusive reports on the relationship between DPCO2 and blood lactate concentrations during the early resuscitation phase of septic shock when normal ScvO2 (≥70%) has not yet been achieved.

The aim of the present study was to evaluate if partial pressure of CO_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) partial pressure of CO_2.

Materials and methods

The present study was conducted at Department of Trauma and Emergency .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). During a 6-month period, a total of 100 patients were analyzed. 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 nonnormal distribution (Kolmogorov–Smirnov test). The frequencies were analyzed using the Chi-squared test (or Fisher's test when appropriate). For statistical analysis, SPSS version 18.0 for windows (SPSS, Chicago, IL, USA) was used. The p value considered significant was <0.05.

Results

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

	Survivors N=60	Non-Survivors N=40
AGE (years)	56±14	62±124
APACHE II	23±7	26±4
SOFA Day 1	9.6±3.4	9.8±2.8
SOFA Day 2	7.4±3.6	9.0±3.5
SOFA Day 3	5.4±4.5	8.2±4.2
Mechanical ventilation	26	25
ICU length of stay (days)	15 [9-38]	14[9-20]
Pv–aCO_2 (mm Hg)	6.3±4.3	5.8±3.7
MAP (mm Hg)	75±15	68±12
HR (beats/min)	104±16	105±15
CVP (mm Hg)	15±6	15±4
Diuresis (mL/kg/h)	0.5±0.7	0.5±0.8
SaO_2 (%)	96±5	95±8
$ScvO_2$ (%)	72±10	75±9
Arterial lactate (mmol/L)	2.7±2.3	3.4±2.7
Norepinephrine (µg/kg/min)	0.16 [0.08–0.27]	0.16 [0.07–0.26]

Survivors showed a significant reduction in SOFA score during 3 days follow-up.

Table 2: Demographic, hemodynamic and oxygenation parameters of patients with normal (≤6 mm Hg) and abnormal (>6 mm Hg) Pv–aCO2 at ICU admission

	Normal	*Abnormal*
	(n = 64)	*(n = 36)*
Age (years)	57±12	61±16
APACHE II	25±7	23±8
SOFA day 1	9.5±2.8	10.0±3.8
SOFA day 2	7.6±3.6	8.8±4.2
SOFA day 3	7.2±4.6	6.5±4.6
Mechanical ventilation	28	16
28th day mortality rate	44	45
ICU length of stay (days)	22±16	21±23
Pv–aCO_2 (mm Hg)	3.28±1.72	9.82±2.46
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]

The admission Pv–aCO2 showed no difference with regard to any possible outcome when categorized in normal and abnormal. Admission Pv–aCO2, ScvO2 and arterial lactate values showed low specificity and sensitivity to predict mortality. Normal or abnormal Pv–aCO2 values in each time did not show statistical difference for 28th mortality, ICU mortality and SOFA scores.

Table 3: Comparisons of clinical data at admission between patients that normalized ScvO2 values with a normal and abnormal Pv–aCO2 values

	$ScvO_2$ > 70% and Pv–aCO_2 ≤6 mm Hg(n = 50)	*$ScvO_2$ > 70% and Pv–aCO_2 > 6 mm Hg(n = 16)*
SOFA day 1	9.4±2.7	11±3.8
SOFA day 2	7.8±3.5	9.6±4.5
SOFA day 3	6.2±4.6	8.5±4.9
Pv–aCO_2 (mm Hg)	3.5±1.7	9.8±2.7
MAP (mm Hg)	72±17	71±16
HR (beats/min)	105±22	102±21
CVP (mm Hg)	14±6	15±11
Diuresis (mL/kg/h))	0.6±0.8	0.5±0.8
$ScvO_2$ (%)	81±7	76±4
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* (%)	12(48)	4 (50)

Patients with normal ScvO2 values but with enlarged Pv–aCO2 showed higher SOFA score values during follow-up.

Discussion

Septic shock is a condition in which tissue perfusion is inadequate, leading to multi- organ dysfunction and death. [8] 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. [9] However, maintaining normal systemic hemodynamic parameters does not always guarantee adequate tissue perfusion. [10,11] As a major determinant of oxygen supply, adequacy of blood flow is a fundamental variable to be evaluated. [12]

Sepsis is the clinical syndrome that results from a dysregulated inflammatory response to an infection. It exists if two or more of the following abnormalities are present, along with either a culture-proven or visually identified infection: temperature >38.3°C or <36°C, heart rate >90 beats/min., respiratory rate >20 breaths/min or partial pressure of arterial carbon dioxide (PaCO2) <32 mmHg, and white blood cell >12,000 cells/mm3, <4000 cells/mm3, or >10% immature (band) forms. [14] Survivors showed a significant reduction in SOFA score during 3 days follow-up. The admission Pv–aCO2 showed no difference with regard to any possible outcome when categorized in normal and abnormal. 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–aCO2 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–aCO2 has the worst correlation with cardiac output. [15] 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–aCO2 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–aCO2 appears to be limited to its negative predictive value, to exclude a low cardiac output when it is within its normal range. [16]

Admission Pv–aCO2, ScvO2 and arterial lactate values showed low specificity and sensitivity to predict mortality. Normal or abnormal Pv–aCO2 values in each time did not show statistical difference for 28th mortality, ICU mortality and SOFA scores. Patients with normal ScvO2 values but with enlarged Pv–aCO2 showed higher SOFA score values during follow-up. The widening of the arterial venous CO2 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 ScvO2 70% but with an abnormal Pv–aCO2 had more organ dysfunctions since admission. Venous saturation may be falsely normal when oxygen capabilities are compromised and an enlarged Pv–aCO2 may identify a lack of tissue blood flow. [17] In addition, Mahajan et al [18] showed that a normal Pv–aCO2 together with a normal ScvO2 was even more associated with mortality. A normal Pv–aCO2 in the presence of tissue hypoperfusion or ongoing organ dysfunction may reflect cytophatic dysoxia or

microcirculatory abnormalities. [19,20] 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–aCO2 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. [21] The Andromeda study, besides suggesting that it is possible to guide resuscitation by capillary refill time, used Pv–aCO2 as one of the targets to be pursued.

Conclusion

This study showed that the admission Pv–aCO2 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–aCO2 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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