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Prognostic Value of Venoarterial Carbon Dioxide Gradient in Patients with Severe Sepsis and Septic Shock

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Aim To investigate the changes in the venoarterial carbon-dioxide gradient (V-a Pco_2) and its prognostic value for survival of patients with severe sepsis and septic shock.

Methods The study was conducted in General Hospital Holy Spirit from January 2004 to December 2007 and included 71 conveniently sampled adult patients (25 women and 46 men), who fulfilled the severe sepsis and septic shock criteria and were followed for a median of 8 days (interquartile range, 12 days). The patients were divided in two groups depending on whether or not they had been mechanically ventilated. Both groups of patients underwent interventions with an aim to achieve hemodynamic stability. Mechanical ventilation was applied in respiratory failure. Venoarterial carbon dioxide gradient was calculated from the difference between the partial pressure of arterial CO_2 and the partial pressure of mixed venous CO_2, which was measured with a pulmonary arterial Swan-Ganz catheter. The data were analyzed using Kaplan-Meier survival analysis, along with a calculation of the hazard ratios.

Results There was a significant difference between non-ventilated and ventilated patients, with almost 4-fold greater hazard ratio for lethal outcome in ventilated patients (3.85; 95% confidence interval, 1.64-9.03). Furthermore, the pattern of changes of many other variables was also different in these two groups (carbon dioxide-related variables, variables related to acid-base status, mean arterial pressure, systemic vascular resistance, lactate, body mass index, Acute Physiology and Chronic Health Evaluation II, Simplified Acute Physiology II Score, and Sepsis-related Organ Failure Assessment score). Pco_2 values (with a cut-off of 0.8 kPa) were a significant predictor of lethal outcome in non-ventilated patients ($P=0.015$) but not in ventilated ones ($P=0.270$).

Conclusion V-a Pco_2 was a significant predictor of fatal outcome only in the non-ventilated group of patients. Ventilated patients are more likely to be admitted with a less favorable clinical status, and other variables seem to have a more important role in their outcome.

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Although oxygen delivery (Do_2) in septic shock can be elevated, oxygen consumption (VO_2) is impaired (1). This could be a consequence of mitochondrial dysfunction in sepsis (2,3). Blood circulation is slow and consequently the elimination of CO_2 from the tissue is slower, making the tissue CO_2 concentration high. Venoarterial carbon dioxide gradient (V-a Pco_2) was calculated from the difference between the partial pressure of arterial CO_2 ($Paco_2$) and the partial pressure of mixed venous CO_2 ($PvCO_2$), which was measured with a pulmonary arterial Swan-Ganz catheter.

The venoarterial CO_2 gradient (V-a Pco_2) is influenced by two other factors: the dissociative curve of CO_2 and tissue blood flow. The curve of CO_2 dissociation from hemoglobin follows the so-called Haldane's effect, in which oxygen and its bonding with hemoglobin allows easier release of carbon dioxide in lungs (4). Experimental models have shown that in toximia, venous hypercapnia is a more significant contributor to the increase in the venoarterial CO_2 gradient than arterial CO_2 values (4-7). Elevated V-a Pco_2 has also been described in patients with sepsis, cardiogenic shock, acute myocardial infarction, and congestive heart failure, as well as cardiac arrest following cardiopulmonary resuscitation and heart surgery (8-13).

In septic patients, the significance of the connection between an elevation of V-a Pco_2 and the course and outcome of the illness is not sufficiently known. It has been established that V-a Pco_2 shows a negative exponential relationship with the cardiac index (CI) (14,15). The negative association with CI has been observed not only in septic shock patients but also in postoperative patients without sepsis. In patients with a lethal outcome, CI was reduced, but V-a Pco_2 was not an independent predictor of outcome (14,16).

The aim of this study was to investigate the changes in V-a Pco_2 to better understand the possibilities of using it as a predictor of clinical outcomes in patients with severe sepsis and septic shock.

PATIENTS AND METHODS

This was a prospective observational study that included all patients admitted to the 8-bed intensive care unit of Holy Spirit Hospital, Zagreb, Croatia, in the period from January 2004 to December 2007. The study protocol was approved by the Local Ethics Committee of the Holy Spirit Hospital. Standards of Good Clinical Practice (17) and the Declaration of Helsinki (18) were followed. There were 189 admitted patients with the initial diagnosis of sepsis, but only 114 patients satisfied the inclusion criteria of having severe sepsis and septic shock according to the American College of Chest Physicians and the Society of Critical Care Medicine criteria for severe sepsis and septic shock (19,20). Four patients were excluded because they had acute pancreatitis, which is initially presented as systemic inflammatory response syndrome. Thus, the final study population consisted of 71 patients. All patients, or their legal representatives, reviewed and signed the informed consent form approved by the local Ethics Committee.

Conventional hemodynamic monitoring was carried out using a pulmonary arterial Swan-Ganz catheter (PAC). We carried out PAC measurements an average of 6-8 times per month on critically ill patients. At the time of this study, severe sepsis and septic shock were the indications for PAC and it was the part of "the standard of hospital care" at our institution. Cardiac output was determined by thermodilution using a PAC; 10 mL of 5% glucose was administered at room temperature 3 times over two-minute intervals to calculate the mean values. Oxygen delivery (Do_2) was determined using an in-vitro analysis of arterial blood, according to the standard formula (21). Oxygen consumption (VO_2) was measured according to direct and indirect Fick's principles (21). The venoarterial difference in CO_2 partial pressure (V-a Pco_2) was calculated from the difference between the partial pressure of arterial CO_2 ($Paco_2$) and the partial pressure of mixed venous CO_2 ($PvCO_2$). The limiting value of V-a Pco_2 was set at 0.8 kPa (22). This information was used as a binary variable in all subsequent analyses. V-a Pco_2 values >0.8 kPa were defined as pathological and V-a Pco_2 values <0.8 kPa as normal.

To measure the hemodynamic variables, the oxygen and carbon dioxide variables and the variables related to acid-base status, blood samples were taken simultaneously from a peripheral artery and the pulmonary artery at the following time points: (i) upon admission to the intensive care unit; (ii) immediately after administration of the specific therapy (plasma expanders, vasoactive medications, and mechanical ventilation); and (iii) 6 hours after the beginning of monitoring. The patients were divided in two groups depending on whether or not they had been mechanically ventilated before the measurements were conducted: non-ventilated group (n = 31) and ventilated group (n = 40).

For the patients suffering from sepsis, there is still no standardized recommended scoring system. Therefore, we

used the APACHE II scoring system to evaluate high mortality risks (23,24). Furthermore, organ failure is a main mortality risk factor in critically ill patients, and it may have a significant impact on CO_2 production. Thus we also assessed our patients using the SOFA scoring system (25).

The analyses were performed to make comparisons between non-ventilated and ventilated patients and also between the survivors and non-survivors.

Statistical methods

Due to the small sample size, the median and interquartile range (IQR) were used in the descriptive statistical analysis. The analytical methods included the χ^2 test, Mann-Whitney test, and Friedman test. The Kaplan-Meier method was used for survival analysis, along with the Breslow test, where the duration of hospitalization was used as time variable and lethal outcome was considered to be an outcome variable. Correlation was investigated using Spearman rank test. Cox regression analysis was used as the multivariate method for survival analysis. All analyses were performed using SPSS 13.0 (SPSS Inc., Chicago, IL, USA). Significance level was set at $P < 0.05$.

RESULTS

The study included 71 patients (25 women and 46 men), with median age of 67.0 years (IQR, 14.0 years). The origin of sepsis was most frequently lungs (pneumonia) in 34 (48%) cases and the abdominal cavity in 16 (23%) cases, including inflamed gallbladder in 6 patients (8.5%), cholangitis in 8 patients (11.3%), infected pancreatic necrosis in 2 patients (2.8%), and urinary tract in 9 (11.7%) cases. Other non-abdominal sites were the cause in 8 patients (11.3%). In 4 patients (5.6%), the source was not established.

Using cultures from blood, urine, sputum, and wound aspiration, we determined the cause of sepsis in 50 patients (70%). We obtained a total of 85 positive isolates with 3 or more positive samples belonging to one patient. In 51 positive isolates (60%), Gram-negative bacteria were identified and the most frequent species were *Escherichia coli, Proteus mirabilis,* and *Klebsiella pneumoniae.* In 26 isolates (31%), Gram-positive bacteria were isolated and identified; the most common species were *Staphylococcus aureus, Enterococcus faecalis,* and *Streptococcus pneumoniae.*

Before Swan-Ganz catheterization and the collection of the first measurements, 31 of our patients (44%) did not require mechanical ventilation, while the remaining 40 (56%) had already been ventilated. Subsequent to pulmonary catheterization, another 4 patients were placed on ventilation due to respiratory insufficiency.

TABLE 1. Comparison of clinical, hemodynamic, and blood gas variables in non-ventilated and ventilated patients with severe sepsis and septic shock

Parameter*	Non-ventilated patients (n = 31)†	Ventilated patients (n = 40)	*P*‡
CaO_2 (mL/dL)	15.5 (4.6)	15.3 (4.6)	0.842
CvO_2 (mL/dL)	9.8 (4.3)	9.6 (3.3)	0.956
A-V Do_2 (mL/dL)	5.7 (2.1)	5.6 (3.8)	0.877
SaO_2 (%)	94.5 (6.8)	94.0 (12.8)	0.807
SvO_2 (%)	61.0 (10.8)	60.5 (19.0)	0.681
PaO_2 (kPa)	8.9 (2.6)	9.1 (7.5)	0.352
PvO_2 (kPa)	4.3 (0.8)	5.0 (1.7)	0.061
$Paco_2$ (kPa)	4.3 (1.2)	5.1 (2.1)	0.044
$PvCO_2$ (kPa)	4.9 (1.3)	6.7 (4.3)	0.001
V-a Pco_2 (kPa)	0.6 (0.6)	1.2 (1.9)	0.009
A pH	7.4 (0.1)	7.3 (0.3)	0.040
V pH	7.4 (0.1)	7.2 (0.3)	0.006
BMI (kg/m^2)	26.5 (5.9)	27.4 (4.0)	<0.001
APACHE II score	18.0 (10.0)	35.0 (11.0)	<0.001
SAPS II score	45.0 (21.0)	67.0 (23.0)	<0.001
SOFA score 1st day (23)	10.0 (5.0)	13.0 (3.0)	<0.001
SOFA score 3rd day (23)	10.5 (5.0)	14.0 (4.0)	<0.001
DO_2 (mL/min/m^2)	805.1 (410.0)	848.0 (334.0)	0.293
VO_2 (mL/min/m^2)	237.0 (131.0)	284.0 (227.0)	0.268
O_2 ER (%)	36.0 (18.5)	34.8 (22.3)	0.315
Lactate (mmol/L)	5.7 (2.0)	6.3 (7.1)	0.016
MAP (mmHg)	81.0 (23.8)	70.5 (37.8)	0.021
HR (beat/min)	107.0 (29.3)	118.5 (28.5)	0.119
CI (L/min/m^2)	2.4 (1.32)	3.0 (1.11)	0.281
CVP (cmH_2O)	10.0 (5.0)	7.0 (7.0)	0.304
MPAP (mmHg)	30.5 (14.3)	25.0 (13.0)	0.955
PCWP (mmHg)	9.0 (16.0)	12.0 (9.0)	0.611
SVR (dynes.sec/m^5)	1468.0 (662.8)	1275.0 (469.0)	0.030
PVR (dynes.sec/m^5)	202.0 (167.5)	157.0 (106.8)	0.449

*Abbreviations: CaO_2 – arterial oxygen content; CvO_2 – venous oxygen content, A-V Do_2 – arterial-venous oxygen content difference; Sao_2 – arterial oxygen saturation; SvO_2 – mixed venous saturation; Pao_2 – partial pressure of arterial oxygen; PvO_2 – partial pressure of mixed venous oxygen; $Paco_2$ – partial pressure of arterial carbon dioxide; $PvCO_2$ – partial pressure of mixed venous carbon dioxide; V-a Pco_2 – venoarterial carbon dioxide gradient; a pH – arterial pH; V pH – venous pH; BMI – body mass index; Do_2 – oxygen delivery; VO_2 – oxygen consumption; O_2 ER – oxygen extraction ration; MAP – mean arterial pressure; HR: heart rate; CI – cardiac index; CVP – central venous pressure; MPAP – mean pulmonary artery pressure; PCWP – pulmonary capillary wedge pressure; SVR – systemic vascular resistance; PVR – pulmonary vascular resistance.
†Values are median (IQR).
‡Mann-Whitney test.

Overall, the mortality rate among the included patients was 65%, and there was no sex difference (71.8% of men and 50.0% of women; $\chi^2 = 23.77$; $P = 0.096$); however, there was a significant difference in the overall mortality between the ventilated (92.3%) and non-ventilated patients (35.0%; $\chi^2 = 16.89$; $P < 0.001$). The median age of the surviving group was 61 years (IQR, 22) and of the group with fatal outcomes 67 years (IQR, 9). The difference between them was not significant ($P = 0.453$).

In all our patients, the median for V-a Pco_2 was 0.9 kPa (IQR, 1.0): 0.6 kPa (IQR, 0.6) in non-ventilated patients and 1.2 kPa (IQR 1.9) in ventilated patients ($P = 0.009$). In addition to V-a Pco_2 values, we observed a number of significant differences between non-ventilated and ventilated patients, especially in the variables related to CO_2 pressures ($Paco_2$, $PvCO_2$), pH values (a pH, v pH), clinical variables (body mass index, Acute Physiology and Chronic Health Evaluation II score (23), Simplified Acute Physiology II Score (26), and Sepsis-related Organ Failure Assessment score 1st day and 3rd day) and lactate and hemodynamic variables (mean arterial pressure and systemic vascular resistance) (Table 1).

Age and sex did not significantly affect survival: however, a significant difference was found between patients who

TABLE 2. Survival in relation to age, sex, and use of mechanical ventilation in patients with severe sepsis and septic shock (n = 71).

Parameter	*P*	Hazard ratio (95% confidence interval)*
Age	0.577	1.01 (0.97-1.05)
Sex:		
men (ref.)		1.00
women	0.519	0.76 (0.33-1.76)
Use of mechanical ventilation:		
yes (ref.)		1.00
no	0.002	3.85 (1.64-9.03)

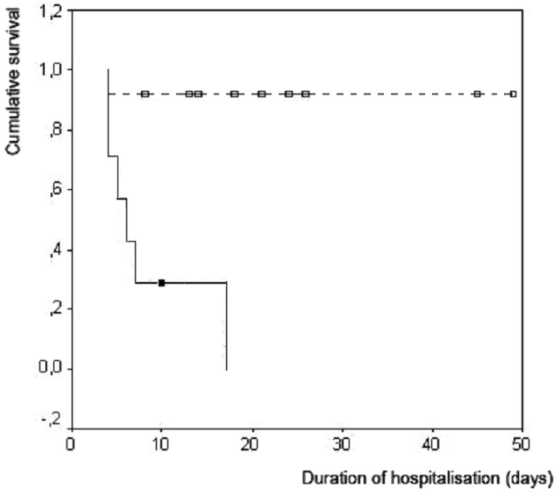
*Cox regression.

TABLE 3. Prediction of fatal outcome in non-ventilated and ventilated patients with severe sepsis and septic shock*

	Non-ventilated patients (n = 31)		Ventilated patients (n = 40)	
Parameter	*P*	HR (95% CI)*	*P*	HR (95% CI)†
Age	0.439	1.04 (0.95-1.13)	0.858	1.00 (0.94-1.05)
Sex:				
men (ref.)		1.00		1.00
women	0.617	0.58 (0.07-4.99)	0.904	0.93 (0.29-3.02)
V-a Pco_2	0.015	4.33 (1.33-14.11)	0.270	1.25 (0.84-1.86)
$PvCO_2$	0.146	0.60 (0.30-1.19)	0.946	0.99 (0.81-1.22)

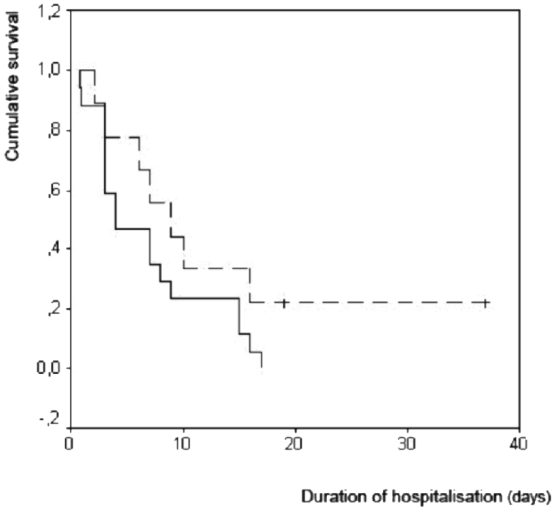
*Abbreviations: V-a Pco_2 – venoarterial carbon dioxide gradient, $PvCO_2$ – partial pressure of mixed venous carbon dioxide; CI –confidence interval; HR – hazard ratio.
†Cox regression.

Figure 1.



Values of venoarterial carbon dioxide gradient (V-a Pco_2) in relation to survival in the group of non-ventilated patients. Dash line <0.8 kPa; solid line 0.8≥kPa; square – censored. Breslow $P = 0.002$.

Figure 2.



Venoarterial carbon dioxide gradient (V-a Pco_2) levels in relation to survival in the group of ventilated patients. Dash line <0.8 kPa; solid line 0.8≥kPa; square – censored. Breslow $P = 0.002$.

had required mechanical ventilation and those who had not, with hazard ratios of survival being almost 4 times greater in those who had not been ventilated (Table 2).

Because of the limited sample size, the variables of age and sex were included in the Cox regression analysis, as well as the two variables with the strongest bivariate correlation with fatal outcome: V-a Pco_2 and $PvCO_2$. The analysis was applied separately to the ventilated group and separately to the non-ventilated group. V-a Pco_2 was determined to be the best outcome predictor, but only in the non-ventilated group (Table 3). We analyzed the data for a possible correlation between V-a Pco_2 and CI, but the association was not significant ($r=-0.21$; $P=0.162$).

The next step was to determine the influence of the selected predictive variables on V-a Pco_2. In both non-ventilated and ventilated patients, 0.8 kPa was taken as the cut-off point of V-a Pco_2. Difference in survival between non-ventilated and ventilated patients was significantly affected by the values of V-a Pco_2. In the non-ventilated group, survival was significantly higher among the patients with V-a Pco_2 values lower than 0.8 kPa (Figure 1). In the ventilated group, V-a Pco_2 had no significant effect on survival (Figure 2). These results indicate that V-a Pco_2 does not have a predictive role in ventilated patients, while in the non-ventilated group, it is a significant predictor of fatal outcome.

DISCUSSION

This study showed the strong clinical importance of V-a Pco_2 for prediction of fatal outcomes in non-ventilated patients but not in ventilated patients. This parameter indicates the difference between partial pressure of mixed venous and arterial blood CO_2 and does not exceed 0.8 kPa (6 mm Hg) under normal conditions (22). An increase in the gradient above normal values can be caused by either an increase in partial pressure of mixed venous blood CO_2, a reduction in the partial pressure of CO_2 in arterial blood, or a simultaneous change in both. The venoarterial gradient of CO_2 is also influenced by two other factors: the dissociative curve of CO_2 (Haldane's effect) and tissue blood flow (4). The relationship between V-a Pco_2 and CI was inverse, but it was not significant. In normoxic conditions, the association between V-a Pco_2 and CI is nonlinear. The association between V-a Pco_2 and cardiac output is also nonlinear: changes in cardiac output values led to increases in V-a Pco_2 that are greater at lower values of cardiac output than at higher values of cardiac output (27). Earlier research on patients with septic shock and postoperative patients without sepsis has indicated that an increase in V-a Pco_2 above 6 mm Hg (0.8 kPa) precipitated a decrease in the CI and that the association was exponential (14-16). Other studies conducted on experimental models of severe sepsis and septic shock (4,5,28,29) have mostly indicated that an increase in V-a Pco_2 is associated with a reduction in cardiac output. However, during sepsis, tissue hypercapnia may develop despite a normal or even high CI (29). However, in patients with reduced CI, the index can generally be improved by supplementing the blood volume with colloid or crystalloid solution, plasma expanders, operative procedures (30,31), or vasoactive medication (32).

The difference in survival between non-ventilated and ventilated patients is likely to be explained by a confounding effect due to indication, because patients with more severe initial clinical presentation are more likely to be attached to a ventilator. Indeed, this study indicates a number of changes in ventilated patients; they presented higher values for variables related to CO_2 ($PvCO_2$, $Paco_2$, V-a Pco_2, lactate) and for clinical variables (body mas index, APACHE II score, Simplified Acute Physiology Score, SOFA 1st and 3rd day score), lower values for variables related to acid-base status (pH, v pH) and hemodynamic variables (mean arterial pressure and systemic vascular resistance). These numerous differences further support the assertion that these two groups of patients experience vastly different clinical courses. Ventilated patients had significantly higher values of APACHE II score and SOFA 1st and 3rd day score.

We found a significantly greater survival rate among the patients in the non-ventilated group with V-a Pco_2 lower than 0.8 kPa. It has been shown that V-a Pco_2 exceeding 0.8 kPa is associated with numerous hemodynamic changes and with overall survival but that its predictive value is mediocre and that it is not an independent predictor of outcome (14,16,28). The difference from previously published studies could partly be explained by the differences in the inclusion criteria, as the patients who participated in previous studies were not divided according to ventilation (16), thus preventing a more detailed analysis and understanding of clinically important metabolic changes (29).

Several oxygen-based clinical parameters have been proposed as possible predictors of sepsis outcome. An additional process that can exacerbate sepsis is general adrenergic stimulation brought on by a reduction in blood flow. This process increases oxygen consump-

tion, which worsens the situation on the periphery. However, the accumulating CO_2 inhibits the alpha-adrenergic receptors; this effect conserves oxygen but can also negatively impact flow. As a result of the redistribution of flow that begins to appear at this stage of sepsis, the splanchnic circulation is seriously affected, potentially leading to multiple organ dysfunctions and fatal outcome (33). Compromised pulmonary function could be an additional source of lactates in patients with acute lung damage (34), which further contributes to the dysfunction of multiple organs and increases the chances of a fatal outcome (33,35,36). Furthermore, during mechanical ventilation, fraction of inspired oxygen affects the alveolar-arterial oxygen tension difference. This effect is explained by a decrease in hypoxic pulmonary vasoconstriction, which normally acts to redirect blood flow away from poorly ventilated lung regions. Breathing that does not participate in gas exchange is characterized by a disproportion of ventilation perfusion (mismatch) ratio, V/Q ratio >1. An increase of dead space is produced by reduction of the Pa_{O_2} and Pa_{CO_2} elevation. Retention of CO_2 in the blood occurs when VD/VT rises above 50% (37).

None of the oxygen variables was a good indicator of the outcome in our population of patients with severe sepsis or septic shock. Earlier studies have also failed to determine whether oxygen-related variables were useful in outcome prediction in patients with sepsis (38-42). Accordingly, a significant improvement in outcome in severe sepsis and septic shock is associated with achieving a target of ≥70% central venous oxygen saturation during the first 6 hours after admission (43). Despite its effects on systemic circulation and elevated supply and consumption of oxygen, sepsis is often accompanied by circulatory failure and multiple organ dysfunctions (39,41). Some recent studies support the use of monitoring-driven treatment protocols and argue against the concept of normal and supernormal cardiac output values, instead classifying the values into adequate or inadequate to meet the metabolic demands (44). Ultimately, one of the major changes in sepsis is a loss of microcirculatory autoregulation – vasoplegia (45). Our results suggest that cardiac output may not be the most reliable predictor of sepsis outcome.

The main limitation of this study was the small sample size. The study was based on a pre-defined set of study parameters, which might not have reflected the true nature of general changes observed in sepsis. In addition, a PAC, which is quite an invasive method, was used to monitor hemodynamics and V-a P_{CO_2}.

Despite the limitations of the study, our data suggest that venoarterial gradient P_{CO_2} might be used as a fatal outcome predictor in non-ventilated patients with severe sepsis and septic shock but not in the group of ventilated patients. Further studies on a larger number of patients are needed to confirm the reliability of this predictor.

Note

M. Z. is the Multimedia Editor of the *Croatian Medical Journal*. To ensure that any possible conflict of interest has been addressed, this article was reviewed according to best practice guidelines of international editorial organizations.

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