

# Prognostic Value of Venous to Arterial Carbon Dioxide Difference during Early Resuscitation in Critically Ill Patients with Septic Shock

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## Abstract

**Context:** The partial pressure of venous to arterial carbon dioxide gradient (PCO<sub>2</sub> gap) is considered as an alternative marker of tissue hypoperfusion and has been used to guide treatment for shock. **Aims:** The aim of this study was to investigate the prognostic value of venous-to-arterial carbon dioxide difference during early resuscitation of patients with septic shock and compared it with that of lactate clearance and Acute Physiology and Chronic Health Evaluation II (APACHE-II) score. **Settings and Design:** Forty patients admitted to one Intensive Care Unit were enrolled. **Subjects and Methods:** APACHE-II score was calculated on admission. An arterial blood gas, central venous, and lactate samples were obtained on admission and after 6 h, and lactate clearance was calculated. Patients were classified retrospectively into Group I (survivors) and Group II (nonsurvivors). Pv-aCO<sub>2</sub> difference in the two groups was evaluated. **Statistical Analysis Used:** Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. **Results:** At T0, Group II showed high PCO<sub>2</sub> gap (8.37 ± 1.36 mmHg) than Group I (7.55 ± 0.95 mmHg) with statistically significant difference ( $P = 0.030$ ). While at T6, Group II showed higher PCO<sub>2</sub> gap (9.48 ± 1.47 mmHg) with statistically significant difference ( $P < 0.001$ ) and higher mean lactate values (62.71 ± 23.66 mg/dl) with statistically significant difference ( $P < 0.001$ ) than Group I where PCO<sub>2</sub> gap and mean lactate values became much lower, 5.91 ± 1.12 mmHg and 33.61 ± 5.80 mg mg/dl, respectively. Group I showed higher lactate clearance (25.42 ± 6.79%) with statistically significant difference ( $P < 0.001$ ) than Group II (-69.40–15.46%). **Conclusions:** High PCO<sub>2</sub> gap >7.8 mmHg after 6 h from resuscitation of septic shock patients is associated with high mortality.

**Keywords:** Acute Physiology and Chronic Health Evaluation II score, lactate, partial pressure carbon dioxide gap

## INTRODUCTION

### Background

Sepsis, severe sepsis, and septic shock are major healthcare problems, affecting millions of people worldwide each year, killing one in four (and often more), and increasing in incidence.<sup>[1]</sup>

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 (PaCO<sub>2</sub>) <32 mmHg, and white blood cell >12,000 cells/mm<sup>3</sup>, <4000 cells/mm<sup>3</sup>, or >10% immature (band) forms.<sup>[2]</sup>

Septic shock exists if there is severe sepsis plus one or both of the following: systemic mean blood pressure is <60 mmHg (or <80 mmHg if the patient has baseline hypertension) despite adequate fluid resuscitation.

Maintaining the systemic mean blood pressure >60 mmHg (or >80 mmHg if the patient has baseline hypertension) requires dopamine >5 µg/kg/min, norepinephrine <0.25 µg/kg/min, or epinephrine <0.25 µg/kg/min despite adequate fluid resuscitation.<sup>[3]</sup>

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**How to cite this article:** Helmy TA, El-reweny EM, Ghazy FG. Prognostic value of venous to arterial carbon dioxide difference during early resuscitation in critically ill patients with septic shock. *Indian J Crit Care Med* 2017;21:589-93.

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10.4103/ijccm.IJCCM\_64\_16

## Partial pressure carbon dioxide gap in sepsis

The partial pressure of venous to arterial CO<sub>2</sub> difference (V-a PCO<sub>2</sub>) or PCO<sub>2</sub> gap was calculated as the difference between the PaCO<sub>2</sub> and the partial pressure of mixed venous CO<sub>2</sub> (PvCO<sub>2</sub>), which was measured with a pulmonary arterial Swan-Ganz catheter.<sup>[4]</sup> Central venous CO<sub>2</sub> tension measurement, obtained in a less risky and costly manner from a central venous catheter, may be an interesting alternative to mixed venous CO<sub>2</sub> tension measurement.<sup>[5]</sup> Under normal conditions, the PCO<sub>2</sub> gap ranges from 4 to 6 mmHg.<sup>[6]</sup> Previous studies considered that Pv-aCO<sub>2</sub> >6 mmHg is abnormal.<sup>[7]</sup>

The PCO<sub>2</sub> gap depends on the global CO<sub>2</sub> production, on cardiac output and on the complex relation between CO<sub>2</sub> tension and CO<sub>2</sub> content.<sup>[8]</sup> It is also influenced by two other factors: the dissociative curve of CO<sub>2</sub> and tissue blood flow. The curve of CO<sub>2</sub> dissociation from hemoglobin follows the so-called Haldane's effect, in which oxygen and its bonding with hemoglobin allows easier release of CO<sub>2</sub> in lungs.<sup>[6]</sup>

## Partial pressure of carbon dioxide gap or (central partial pressure of carbon dioxide gap) as a therapeutic endpoint

Several clinical studies have demonstrated that persistent impairment of perfusion-related physiological variables is associated with increased mortality in septic shock patients.<sup>[9-11]</sup> Therefore, current guidelines for hemodynamic management of severe sepsis and septic shock recommend the use of global markers of tissue hypoxia as resuscitation endpoints.<sup>[12,13]</sup>

In the initial resuscitation period, targeting either central venous oxygen saturation (ScvO<sub>2</sub>) normalization or lactate clearance, or the combination of both, basically through oxygen transport optimization,<sup>[12,14]</sup> is accepted with proven reduction in mortality.<sup>[12,15,16]</sup> Recently, the central venous-to-arterial CO<sub>2</sub> difference (Pcv-aCO<sub>2</sub>) or central PCO<sub>2</sub> gap has been proposed as an alternative marker of tissue hypoperfusion<sup>[17,18]</sup> and have been used to guide treatment for shock.<sup>[19]</sup> In fact, persistently, high Pcv-aCO<sub>2</sub> predicts adverse clinical outcomes independently of oxygen-derived parameters and it could anticipate lactate variations.<sup>[20]</sup>

## SUBJECTS AND METHODS

This prospective study enrolled 40 adult patients after fulfilling the diagnostic criteria of septic shock on arrival to the Intensive Care Unit (ICU) according to latest sepsis definitions.<sup>[2]</sup>

Patients with a history of chronic obstructive pulmonary disease or bronchial asthma were excluded from the study.

All patients were followed for 6 h from admission.

The following data were obtained for each patient: complete history taking; detailed physical examination; Acute Physiology and Chronic Health Evaluation II (APACHE II) score was calculated on admission; routine laboratory investigations were done for every patient; an arterial

blood gas sample was done; and another central venous sample was obtained on admission and after 6 h. The hemodynamic and respiratory variables were registered at each measurement.

PCO<sub>2</sub> gap was calculated as the difference between the central venous CO<sub>2</sub> partial pressure and the arterial CO<sub>2</sub> partial pressure. The patients were retrospectively classified into two groups: Survivors and nonsurvivors group. Pva-CO<sub>2</sub> difference was evaluated in the two groups. Lactate level was measured on admission and after 6 h, and lactate clearance was calculated. Two blood cultures from different sites were collected from each patient on admission. Chest X-ray was done for every patient. Patients were managed according to the latest surviving sepsis campaign guidelines. Patients were followed till death or discharge from ICU, and the following parameters were recorded: need for mechanical ventilation and its duration, days of vasopressor need, application of renal replacement therapy, and days of ICU stay.

## RESULTS

Group I included 24 (60%) patients while Group II included 16 (40%) patients as shown in Table 1.

There were no significance between the two groups regarding age and sex.

On admission, the two groups had high APACHE-II score with significant difference as it was higher in Group II ( $P < 0.001$ ) as shown in Table 2.

### Initial data

At T0, patient of Group I had a significantly lower P (v-a) CO<sub>2</sub> than patients of Group II ( $7.55 \pm 0.95$  versus  $8.37 \pm 1.36$  mmHg,  $P 0.030$ ) as shown in Figure 1. There was no significant statistical difference between the 2 groups according to serum lactate as shown in Figure 2.

**Table 1: Classification of the studied patients according to mortality (n=40)**

	n (%)
Group I survivors	24 (60.0)
Group II nonsurvivors	16 (40.0)

**Table 2: Comparison between the two studied groups according to Acute Physiology and Chronic Health Evaluation II score on admission with statistical difference (P<0.001)**

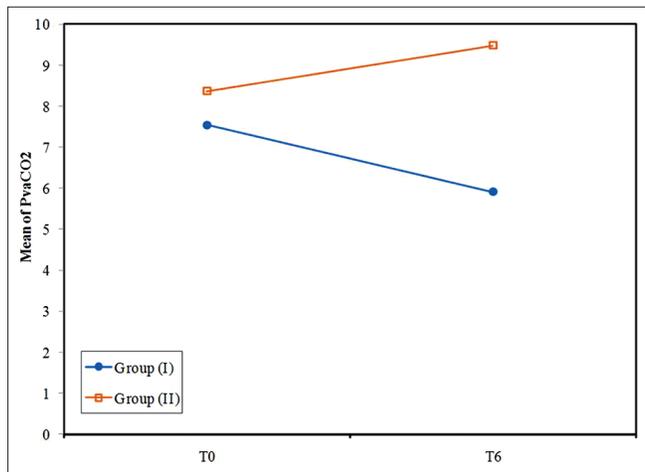
	Group I (n=24)	Group II (n=16)	t	P
APACHE II				
Minimum-maximum	21.0-26.0	23.0-29.0	4.695*	<0.001*
Mean±SD	23.92±1.25	26.0±1.55		
Median	24.0	26.0		

t: Student t-test; SD: Standard deviation; APACHE: Acute Physiology and Chronic Health Evaluation

### Evolution between T0 and T6

At T6, there was a significant statistical difference between the two groups for P (v-a) CO<sub>2</sub> values ( $P < 0.001$ ) where it became higher in group II ( $9.48 \pm 1.47$ ) while became lower in Group I ( $5.91 \pm 1.12$ ) as shown in Figure 1. There was statistically significant difference between the 2 groups according to serum lactate ( $P < 0.001$ ) where it became higher in Group II ( $62.71 \pm 23.66$  mg/dl) and decreased in Group I ( $33.61 \pm 5.8$  mg/dl) as shown in Figure 2.

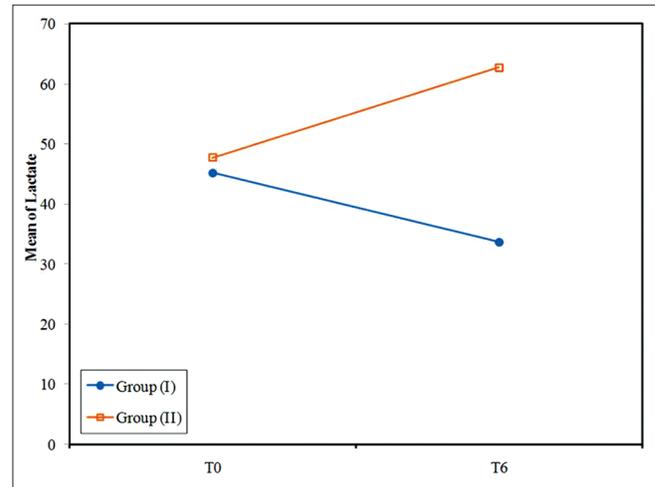
Furthermore, lactate clearance was higher in Group I ( $25.42 \pm 6.79\%$ ) than Group II ( $-69.40--15.46\%$ ) with



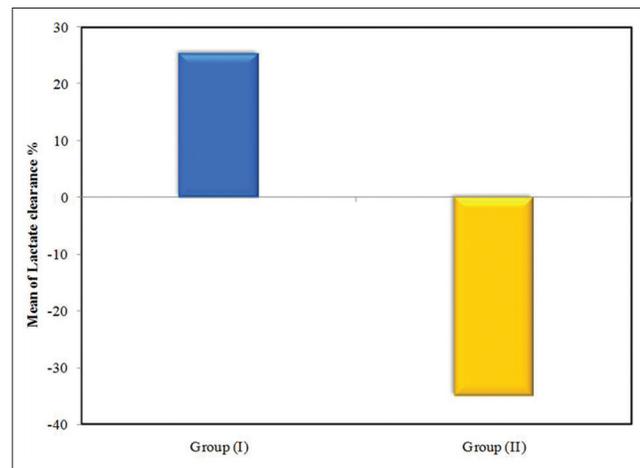
**Figure 1:** Comparison between the two studied groups according to Pv-aCO<sub>2</sub>

statistically significant difference ( $P < 0.001$ ) as shown in Figure 3.

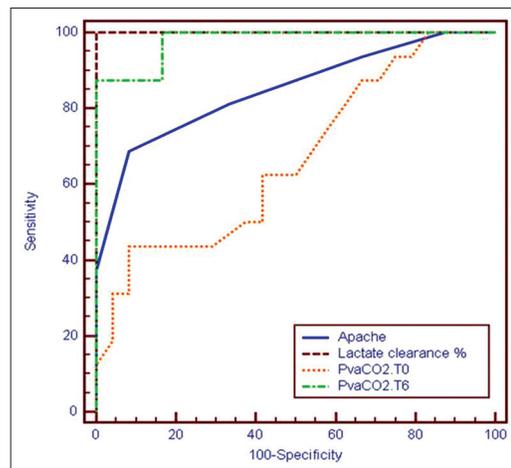
As shown in Table 3 and Figure 4, Pv-aCO<sub>2</sub> at T6 showed more specificity (100%), sensitivity (87.50%), PPV (100%) as well as NPP (92.3%) than APACHE II score which had specificity, sensitivity, PPV, and NPP of 91.67%, 68.75%, 84.6%, and 81.5%, respectively. The cutoff values that predicted the mortality in septic shock patients according to the current study were Pv-aCO<sub>2</sub> T6 >7.8 and APACHE II score on admission >25 while



**Figure 2:** Comparison between the two studied groups according to serum lactate level



**Figure 3:** Comparison between the two studied groups according to lactate clearance



**Figure 4:** Receiver operating characteristic curve for different parameters to predict mortality

	Cut-off	AUC	P	Sensitivity	Specificity	PPV	NPV
Lactate clearance (%)	11	1.000*	<0.001*	100.0	100.0	100.0	100.0
APACHE II score	>25	0.850*	<0.001*	68.75	91.67	84.6	81.5
Pv-aCO <sub>2</sub> T0	>8.4	0.668	0.075	43.75	91.67	77.8	71.0
Pv-aCO <sub>2</sub> T6	>7.8	0.979*	<0.001*	87.50	100.0	100.0	92.3

APACHE: Acute Physiology and Chronic Health Evaluation; NPV: Negative predictive value; PPV: Positive predictive value; AUC: Area under the curve

that of lactate clearance was 11% with 100% sensitivity, specificity, PPP, and NPP.

According to ICU LOS, Group I showed higher ICU length of stay ( $9.08 \pm 2.64$  days) than Group II ( $5.75 \pm 3.04$  days) with statistically significant difference ( $P = 0.001$ ). Furthermore, 100% of patients were mechanically ventilated in Group II while 20 (83.3%) patients were mechanically ventilated in Group I with no statistically significant difference. Duration of mechanical ventilation was not statistically significant between the two groups. All patients in this study were put on vasopressor therapy without statistical difference according to duration of vasopressors.

## DISCUSSION

Given the importance of the high mortality rate associated with sepsis, it is of great benefit to study factors that could predict outcome in septic patients.

In the current study, there was statistically significant difference between the 2 groups according to APACHE-II score on admission ( $P < 0.001$ ), where Group II showed higher APACHE-II score than group I.

This was inconsistent with a prospective observational study done by Vallée *et al.*<sup>[21]</sup> on 50 consecutive patients with septic shock admitted to ICU in a university hospital where they discussed PCO<sub>2</sub> gap in septic shock patients and their results showed that there was no significant difference between the two tested groups for APACHE II score on admission.

In the current study, there was statistically significant difference between the 2 groups according to PCO<sub>2</sub> gap ( $P = 0.030$ ) where it was higher in Group II on admission (T0).

In 2013, van Beest *et al.*<sup>[18]</sup> published a prospective observational study to investigate the interchangeability of mixed PCO<sub>2</sub> gap and central PCO<sub>2</sub> gap and the relation between the central PCO<sub>2</sub> gap and CI. They performed a *post hoc* analysis of a well-defined population of 53 patients with severe sepsis or septic shock. The population was divided into two groups based on PCO<sub>2</sub> gap (cut off value 0.8 kPa or 6 mmHg). Results at T0 showed that patients in the low gap group had a significantly lower PCO<sub>2</sub> gap than patients of the high gap group ( $0.38 \pm 0.42$  kPa vs.  $1.10 \pm 0.33$  kPa;  $P = 0.001$ ).

This also was in line with a prospective observational study done by Vallée *et al.*<sup>[21]</sup> on 50 consecutive patients with septic shock admitted to the ICU in a university hospital where they discussed how PCO<sub>2</sub> gap could be a tool to detect persistent inadequate resuscitation despite attaining the SvO<sub>2</sub> and ScvO<sub>2</sub> targets during septic shock. Patients were separated into low PCO<sub>2</sub> gap group and high PCO<sub>2</sub> gap group according to a threshold of 6 mmHg on admission. Results showed that at T0, low gap group patients had a significantly lower P (cv-a) CO<sub>2</sub> than patients of the high gap group:  $3.2 \pm 1.3$  versus  $8.9 \pm 2.6$  mmHg, ( $P < 0.0001$ ).

In the current study, there was statistically significant difference between the 2 groups according to PCO<sub>2</sub> gap ( $P < 0.001$ ) where

the gap narrowed toward normal in Group I while it became higher in group II at T6.

This was agreeing with aforementioned study done by van Beest *et al.*<sup>[18]</sup> whose results showed that at ICU admission, 24 patients had a PCO<sub>2</sub> gap  $>0.8$  kPa (or 6 mmHg). Persistence of such a large PCO<sub>2</sub> gap after 24 h of treatment was predictive of higher mortality.

This was also in parallel with a previous study done by Vallée *et al.*<sup>[21]</sup> whose results showed that at T6 and T12, there was a significant difference between the two groups for P (cv-a) CO<sub>2</sub> values where the low PCO<sub>2</sub> gap group showed much lower P (cv-a) CO<sub>2</sub> gradient values in comparison to the high PCO<sub>2</sub> gap group who showed more increase of the gap values.

In the current study, there was statistically significant difference between the 2 groups according to ICU length of stay ( $P = 0.001$ ) where the duration was longer in Group I.

This was explained by the aggressive course of sepsis due to poor prognosis confirmed by the higher significant APACHEII score observed in Group II which leads to early mortality.

In the current study, there was statistically significant difference between the 2 groups according to serum lactate ( $P < 0.001$ ) where it was persistently higher in Group II and while it was decreasing in group I at T6.

Moreover, as regard lactate clearance, there was statistically significant difference between the 2 groups according to lactate clearance ( $P < 0.001$ ) where Group I showed higher rate of lactate clearance while a lower rate of clearance was observed in Group II during the study.

Results of the current study were closely similar to a prospective observational study that done by Philippe Marty *et al.*<sup>[22]</sup> that enrolled 94 patients hospitalized in the ICU for severe sepsis or septic shock. That study was designed to investigate the prognostic value for death at day-28 of lactate course and lactate clearance during the first 24 h in ICU after initial resuscitation. Results of their study showed that there was a significant difference between H0 lactate value and H6, H12, or H24 lactate value in survivor group ( $P < 0.05$  for each studied period). Mean blood lactate concentrations were lower in survivors than in nonsurvivors patients at H0 ( $5 \pm 3.1$  mmol/L vs.  $6.9 \pm 4.3$  mmol;  $P = 0.049$ ). Afterward, blood lactate concentrations were lower in survivors than in nonsurvivors at each studied time ( $4.1 \pm 3.2$  vs.  $6.9 \pm 4.3$  at H6;  $3.6 \pm 2.9$  vs.  $6.7 \pm 4$  at H12 and  $3 \pm 3$  vs.  $6.4 \pm 4.5$  at H24.  $P < 0.05$  for each studied period). Lactate clearance was  $13 \pm 38\%$  in survivors and  $-13\% \pm 67\%$  in nonsurvivors patients for the H0-H6 period ( $P = 0.021$ ) and remained higher in survivors than in nonsurvivors for each studied period ( $42 \pm 33\%$  vs.  $-17 \pm 76\%$ ;  $P < 0.001$  for the H0-H24 period).

In the current study, the cutoff values that predict mortality were Pv-aCO<sub>2</sub> difference at T6 of  $>7.8$ , APACHE II score  $>25$ , and lactate clearance of 11%. Furthermore, the current study showed that PCO<sub>2</sub> gap (Pv-aCO<sub>2</sub>) at T6 showed higher

sensitivity and specificity in predicting mortality in patients with septic shock than APACHE-II score and that sensitivity and specificity was close to those of lactate clearance.

Furthermore, these results were closely parallel to aforementioned prospective observational study done by van Beest *et al.*<sup>[18]</sup> where patients were divided into two groups based on PCO<sub>2</sub> gap (cut off value 0.8 kPa or 6 mmHg). Results showed that patients with a central PCO<sub>2</sub> difference larger than 0.8 kPa (>6 mmHg) at  $T = 4$ , which was already present at  $T = 1$ , had a higher mortality change ( $n = 8$ ; in hospital mortality 38%) compared to patients with a central PCO<sub>2</sub> difference smaller than 0.8 kPa (<6 mmHg) at  $T = 4$ .

Furthermore, the results were agree with that of Robin *et al.*<sup>[23]</sup> in which they found that mean P (cv-a) CO<sub>2</sub> was larger in patients who developed postoperative complications than in those who did not ( $7.8 \pm 2$  vs.  $5.6 \pm 2$  mmHg,  $P < 10$ -6). The area under the receiver operating characteristic curve for P (cv-a) CO<sub>2</sub> was 0.751 (95% CI: 0.71–0.79). The best cutoff P (cv-a) CO<sub>2</sub> value was 6 mmHg (sensitivity 79%, specificity 66%, positive predictive value 56%, negative predictive value 85%) for discrimination of patients who did and did not develop postoperative complications in high-risk surgical patients.

The importance of identifying patients at high risk of dying of septic injury, through the determination of PCO<sub>2</sub> gap, would recognize patients who may require monitoring or more complex interventions to reduce mortality. In other words, the potential outcomes of this research can be an element to optimize the care of critically ill patients with septic shock. PCO<sub>2</sub> gap >7.8 mmHg then just seems to be a marker of severity of septic injury, in the clinical context of a patient with septic shock, that measuring early associate a worse prognosis for the patient which is considered the most useful tool to implement interventions to reduce mortality.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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