Sarcouncil journal of Medical sciences

ISSN(Online): 2945-3526

Volume- 04| Issue- 07| 2025

Research Article

Received: 26-05-2025 | Accepted: 16-06-2025 | Published: 03-07-2025

The Role of Central Venous-Arterial PCO_2 Deference as an Early Predictor of End Organ Dysfunction and Clinical Outcome in ICU Septic Patients

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Abstract: Background: In the treatment of critically ill patients, the detection of tissue hypoxia and hypoperfusion is crucial. Serum lactate and central venous oxygen saturation ($ScvO_2$) are examples of global indicators of tissue perfusion. Despite the fact that the venous-arterial PCO_2 difference (ΔPCO_2) cannot be used as a measure of tissue hypoxia, it is thought to be a sign of adequate venous blood flow (Cardiac output) to remove the total CO_2 produced by the peripheral tissues. **The Aim of the Current Study**: was to assess how the venous-arterial PCO_2 gradient affect the prognosis of septic patients admitted to the intensive care unit. **Patients and Methods:** A prospective observational clinicalp;01 study was accomplished in Iraq from April 2022 to December 2022. In the participation of 51 adult patients who fulfill the criteria of severe sepsis or septic shock, and admitted to the intensive care unit. And were divided on the base of ΔPCO_2 into two groups; The high ΔPCO_2 group($\Delta PCO_2 > 6$ mmHg) including 30 participants and the normal ΔPCO_2 ($\Delta PCO_2 \leq 6$ mmHg) included 21 participants. Scoring systems were recorded. Clinical outcome including organ dysfunction and mortality was recorded in a duration of 10 days. **Results:** The high ΔPCO_2 group showed significant high blood glucose level, Serum lactate, and heart rate ($p = 0.010$, 0.023, and 0.037 respectively) than the normal ΔPCO_2 group. As regarding APACHE II score it shows high significance ($p < 0.001$) in the high ΔPCO_2 group than the normal one. As regard to the clinical outcome, patient mortality was statistically higher and significant ($p = 0.035$) in high ΔPCO_2 group than normal ΔPCO_2 group and the number of organ failure was higher in high ΔPCO_2 group than normal group but not reached a significant level ($p = 0.633$). **Conclusions**: ΔPCO_2 is a reliable indicator for early prediction of clinical outcome including end organ failure and mortality in patients with sepsis and septic shock.

Keywords: sepsis, septic shock, ΔPCO_2, APACHE II score, organ dysfunction.

INTRODUCTION

Sepsis and septic shock are major healthcare problems, impacting millions of people around the world each year and killing as many as one in four (and often more) of those it affects. Early identification and appropriate management in the initial hours after the development of sepsis improve outcomes (Evans, L. *et al*., 2021).

Until recently, septic shock was considered to be composed of three components, including systemic arterial hypotension, tissue hypoperfusion associated with organ dysfunction, and hyperlactatemia (Vincent, J.L. *et al*., 2013).

Identification of tissue hypoxia and hypoperfusion plays an important role in the management of critically ill patients during early resuscitation. Resuscitation may be guided by central venous oxygen saturation ($ScvO_2$) as an indicator of tissue hypoxia. Significant fluctuations in $ScvO_2$ may occur during sepsis (Abdalazeem, E.S. *et al*., 2021).

$ScvO_2$ values are obtained by measuring the oxygen saturation in venous blood returning to the heart. In simple form, it represents the balance between oxygen delivery (DO_2) and oxygen consumption (VO_2). The story is more complex, however, as mechanisms of oxygen supply (microcirculatory flow), distribution (microcirculatory flow), and processing (mitochondrial function) must all function at an adequate level to maintain normal physiology. Thus, a low $ScvO_2$ may indicate a decrease in oxygen delivery, an increase in oxygen extraction, or a combination of the two (Pope, J.V. *et al*., 2010).

When DO_2 is below critical level, OER is no longer capable of upholding O_2 consumption, and global tissue hypoxia ensues, so $ScvO_2$ is a measurement of global tissue oxygenation (Kanzariya, H. *et al*., 2020).

Arterial blood gas (ABG) analysis is used in critical care units to determine the degree of oxygenation, adequacy of ventilation, and the presence and severity of acid-base disturbances in the body.

Central VBG can be used as a useful screening tool for arterial hypercapnia[16]. Under normal conditions of cardiac output and arterial O_2 saturation, arterial PCO_2 = venous PCO_2 - 5.7 mmHg. (Kelly, A.M. *et al*., 2010)

ΔPCO_2 is the difference between the partial pressure of CO_2 in mixed venous blood ($PvCO_2$) and arterial blood (PaCO2). It represents only a fraction of arterial and venous CO_2 content

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DOI-https://doi.org/10.5281/zenodo.15799451

($CaCO_2$ and $CvCO_2$) respectively. However, as the relationship between partial pressure and content of CO_2 is almost linear under normal physiological conditions, PCO_2 can be taken as a measure of CCO_2. At the cellular level, CO_2 is a normal terminal product of oxidative metabolism. Thus, in the absence of a shunt, CCO_2in the efferent venous blood must be higher than in the afferent arterial blood.(Monnet, X. *et al*., 2013)

Global indices of tissue perfusion include lactate and central venous oxygen saturation ($ScvO_2$). Although ΔPCO_2 cannot serve as a marker of tissue hypoxia, it can be considered as a marker of the adequacy of venous blood flow (i.e. Cardiac output) to remove the total CO_2 produced by the peripheral tissues.(Vallet, B. *et al*., 2000)

AIM OF STUDY

To test the hypothesis that ΔPCO2 can predict the outcome in patients with sepsis or septic shock admitted to ICU.

PATIENTS AND METHODS

A cross-sectional study was accomplished in a 17-mixed beds at the Intensive Care Unit (ICU) of AL-Imam Al Hussein medical city, in the governorate of Karbala, Iraq. from April 2022 to December 2022. Adult intensive care unit patients, who were critically ill and admitted after the consultation and approval of our 24\7 working ICU teams, were included in this study.

Approval was obtained from the Scientific Council of Anesthesia and Intensive Care of the Iraqi Board of Medical Specialties. Informed consent was waived because there was no intervention and the collection of blood samples was part of routinely working protocols, except the informed consent that has been taken for the purpose of central line insertion. All the information was kept anonymous, and the collected data were used for scientific purposes only.

Inclusion criteria:

- Age is more than 18 years.
- Admitted to the ICU with a length of stay ≥ 24 hours.
- Matching the criteria of severe sepsis or septic shock.

Arterial blood gases sampling was done by radial artery puncture, central venous line catheter was inserted in subclavian or femoral veins for venous blood gases sampling. The line was flushed by normal saline, and waiting for 10-15 min without any drug administration before taking the venous sample, the first 2ml of blood were discarded, and the next sample was sent for analysis.

Blood samples were analyzed by using (radiometer ABL800 FLEX). Patients were split into two groups and compared based on their ΔPCO_2 measurements taken upon admission into: the High ΔPCO_2 group ($\Delta PCO_2 > 6$ mmHg) and normal ΔPCO_2 group ($\Delta PCO_2 \leq 6$ mmHg).

At admission, patient demographic information's were recorded for both groups. The history, along with a full clinical examination and laboratory testing (Na, K, urea, creatinine, (CBC) complete blood count, (ALT) alanine transaminase, (AST)aspartate transaminase, bilirubin, albumin, serum lactate, INR (International normalized ratio), and random blood sugar were done.

Hemodynamic parameters including (mean arterial blood pressure, heart rate, respiratory rate), clinical scoring systems including Glasgow coma scale (GCS), Acute Physiology and Chronic Health Evaluation (APACHE II), were recorded. Laboratory investigations, hemodynamic parameters, and GCS scoring system were repeated and recorded every other day or when there's need to repeat the test (some patients and in particular situations we may need to repeat the test daily or even every few hours).

The patient follow up is done for ten days duration from the length of ICU stay. The ICU stay, Clinical outcomes including organ dysfunction and 10-days mortality rate were recorded during this period. Delta PCO_2 was correlated to laboratory investigations, GCS, APACHE II scores, and number of organ dysfunction.

The collected data was tabulated and analyzed using SPSS version 26 software (SPSS Inc, Chicago, ILL Company). Categorical data were presented as number and percentages, which were tested and analyzed by Chi square ($\chi 2$) test.

Quantitative data were tested for normality first by using Kolmogorov Smirnov test assuming normality at P- value > 0.05. Normally distributed variables were expressed as mean ± standard deviation and analyzed by Student "t for 2 independent variables. Correlations were assessed by Person's correlation coefficient (r). $P \leq 0.05$ was considered significant.

RESULTS

The total number of cases in the beginning was 59 patients assessed for eligibility, 8 patients were excluded (for lack of lab tests, not accomplishing

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the inclusion criteria, or the lack of central line . The study finally included 51 patients divided according to the ΔPCO2 value into two groups, the normal ΔPCO2 group included 21 patients and the high ΔPCO2 group included 30 patients.

As regard to patient demographic data, there was no significant difference between both groups regarding age (p = 0.183) or sex (p = 0.332). The data are shown in Table 1.

Table 1: Patients demographic data in both groups

	Normal ΔPCo2 group (N=21)	**High ΔPCo2 group (N=30)**	**p-Value**
Age mean ± SD	73 ± 6.782	70.57 ± 8.98	0.183
Sex M/F (%)	9/12 (42.9/57.1%)	17/13 (56.6 /43.4%)	0.332

The heart rate in the high ΔPCO_2 group and the normal group respectively (109.87 ± 9.47 versus 95.86 ± 5.36) beat/min, was significantly statistical (p value = 0.037).

The mean arterial blood pressure was lower in the high ΔPCO_2 group than the normal group (69.17 ± 11.44 versus 88.05 ± 10.15) mmHg with insignificant statistical difference (p = 0.388).

The need for vasopressor drugs was higher in the high ΔPCO_2 group than the normal group (80% versus 76%) with insignificant statistical difference (p value = 0.745), these data demonstrated in figure 1&2.

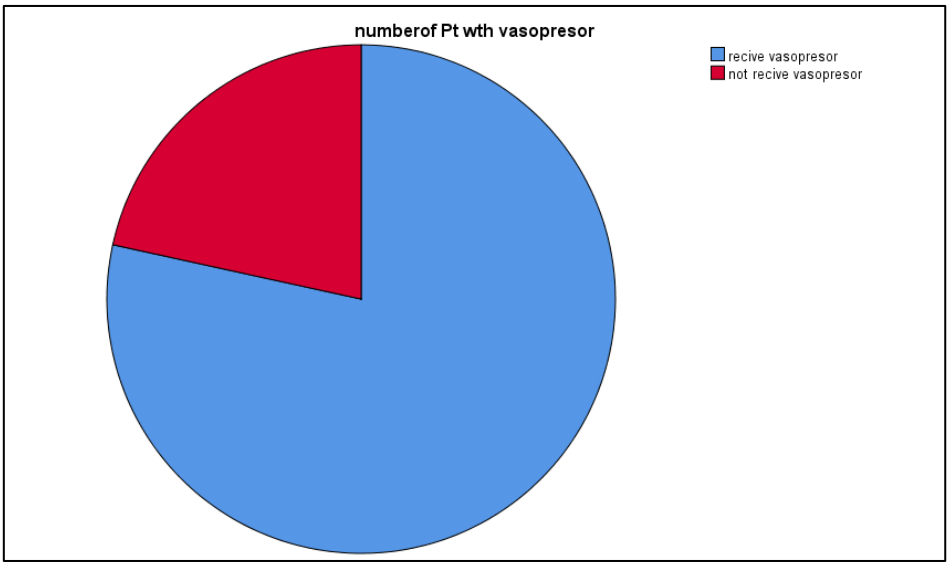

Figure 1: Frequencies of patients who receive vasopressors in the study.

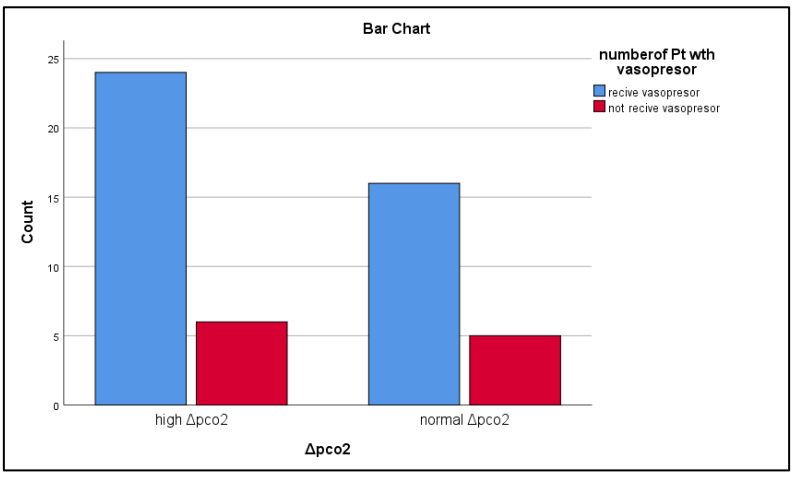

Figure 2: Comparison between the two studied groups about the vasopressors receiving.

As regard laboratory investigations, there was insignificant statistical difference between both groups of ΔPCO_2 in all parameters except for blood glucose, serum lactate level, serum potassium level, serum albumin level, hemoglobin, and white blood cell count.

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Blood glucose was significantly higher (p = 0.010) in the high ΔPCO_2 group than the normal group (213.40 ± 98.30 versus 156.10 ± 58.67) mg/ dl. Serum lactate was significantly higher (p = 0.023) in the high ΔPCO_2 group than the normal group (2.75 ± 0.57 versus 1.92 ± 0.32) mmol/L.

serum potassium was significantly lower (p value < 0.001) in the high ΔPCO_2 group than the normal group (3.85 ± 0.34 versus 4.80 ± 0.32) mmol/L .

serum albumin level was significantly lower (p value = 0.015) in the high ΔPCO2 group than the normal group (2.79 ± 1.12 versus 3.58 ± 1.04) g/dl

hemoglobin was significantly higher (p = 0.013) in the high ΔPCO_2 group than the normal group (11.98 ± 1.79 versus 10.73 ± 1.53) g/dl. total white blood cell count was significantly higher (p = 0.015) in the high group than the normal one (13.19 ± 4.15 versus 10.65 ± 2.32) .

ICU scoring systems including GCS and APACHE II score systems were recorded. There was insignificant statistical difference between both groups except for the APACHE II score that was significantly higher (P value <0.001) in the high ΔPCO_2 group than the normal one (27.73 ± 5.68 versus 16.24 ± 2.84).

The 10- days mortality rate was significantly higher (p = 0.035) in high ΔPCO_2 group than normal ΔPCO_2 group. As shown in figure 3&4.

Table 2: Comparison of the vital signs, some laboratory investigations and ICU scoring systems on the time of ICU admission in both studied groups

	Normal ΔPCO_2 group (N= 21)	**High ΔPCO_2 group (N=30)**	**P value**
Heart rate (beat/min) mean ± SD	95.86 ± 5.36	109.87 ± 9.47	0.037
Mean arterial blood pressure (mmHg) mean ± SD	88.05 ± 10.15	69.17 ± 11.44	0.388
Respiratory rate (breath/min) mean ± SD	18.57 ± 3.24	15.77 ± 4.00	0.294
Number of patients who received vasopressor drugs (%)	16 (76%)	24 (80%)	0.745
glucose levels mg/dl Mean ±SD	156.10 ± 58.67	213.40 ± 98.30	0.010
Lactate level (mmol/L) Mean ±SD	1.92 ± 0.32	2.75 ± 0.57	0.023
Potassium (mmol/L) Mean ±SD	4.80 ± 0.32	3.85 ± 0.34	< 0.001
Creatinine (mg/dl) Mean ±SD	1.81± 0.92	2.36 ± 1.28	0.099
Blood urea (mg/dl) Mean ±SD	75.76 ± 35.61	85.00 ± 26.99	0.297
Albumin (g/dl) Mean ±SD	3.58 ± 1.04	2.79 ± 1.12	0.015
HGB (g/dl) Mean ±SD	10.73 ± 1.53	11.98 ± 1.79	0.013
WBC (10^9/L) Mean ±SD	10.65 ± 2.32	13.19 ± 4.15	0.015
Glasgow coma score mean ± SD	8.07 ± 2.01	7.10 ± 3.08	0.179
APACHE II score. Mean ±SD	16.24 ± 2.84	27.73 ± 5.68	< 0.001
10- days mortality number (%)	5 (23.8%)	18 (60%)	0.035

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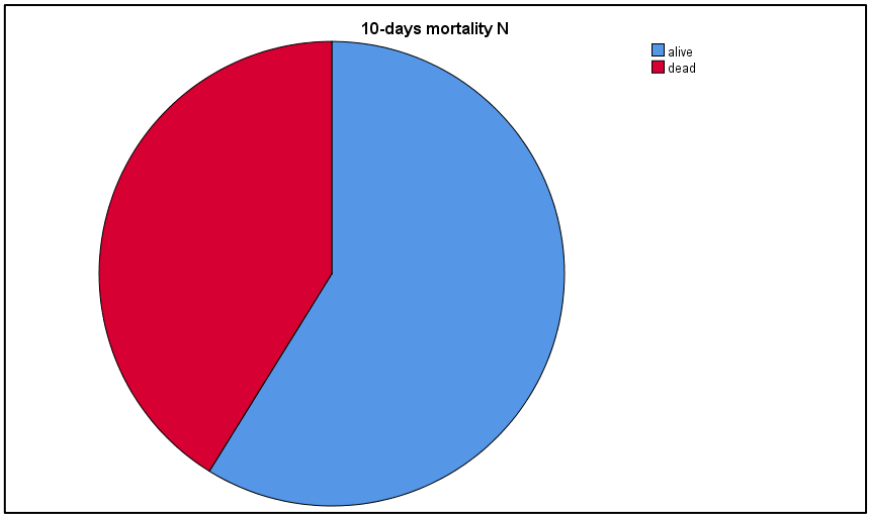

Figure 3: frequency of 10-days mortality among the patients.

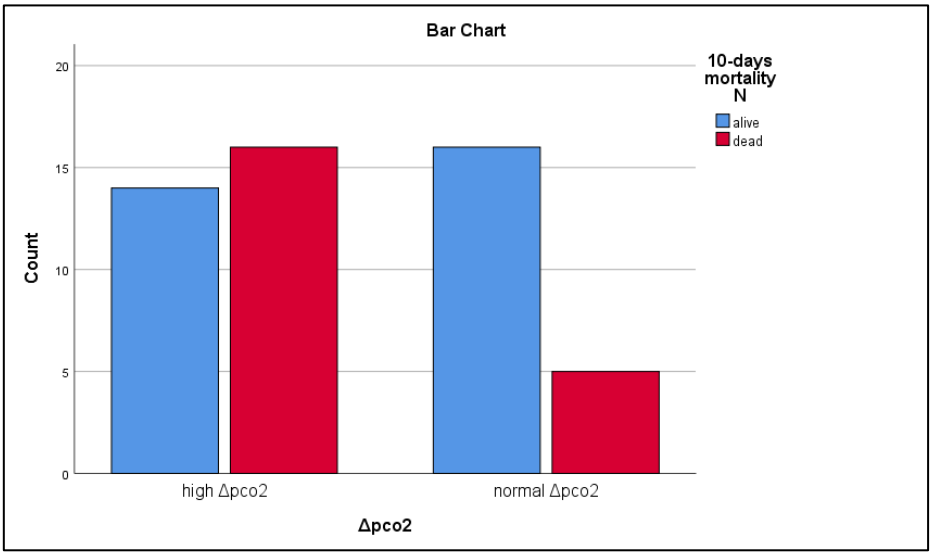

Figure 4: comparison of the 10-days mortality rate between the two studied groups.

As regard to the organ dysfunction in the 10th day in the ICU, it was higher in high ΔPCO_2 group than normal group with insignificant statistical difference (p value = 0.633), as shown in table 3, figure 3&4 helps to illustrate the data.

Table 3: Differences between the ΔPCO_2 groups regarding the number of organ dysfunction in ICU

	Normal Δpco2 N = 21		**High Δpco2 N = 30**		**Total N = 51**		**X2**	**P - value**
	No	%	No	%	No	%		
0	2	9.5	1	3.3	3	5.9	3.440	0.633
1	5	23.8	4	13.4	9	17.6		
2	5	23.8	7	23.3	12	23.5		
3	6	28.5	12	40	18	35.2		
4	3	14.4	4	13.4	7	13.7		
5	0	0	2	6.6	2	4.1		

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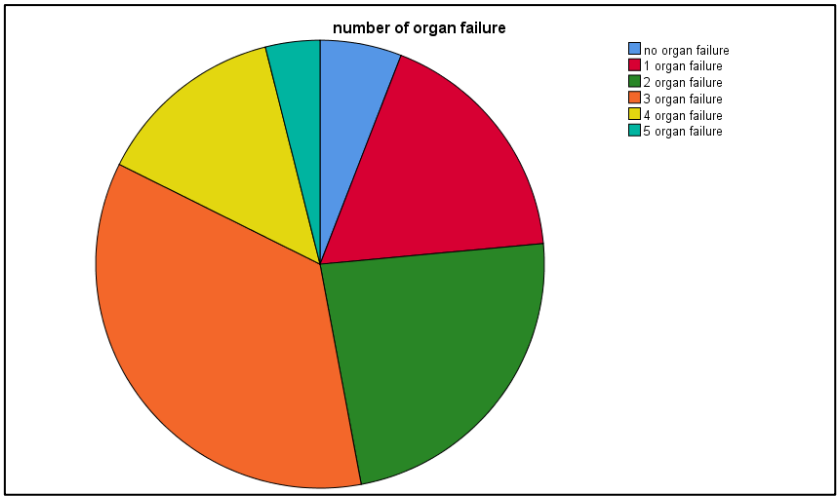

Figure 5: Frequencies of the organ failure among the patients.

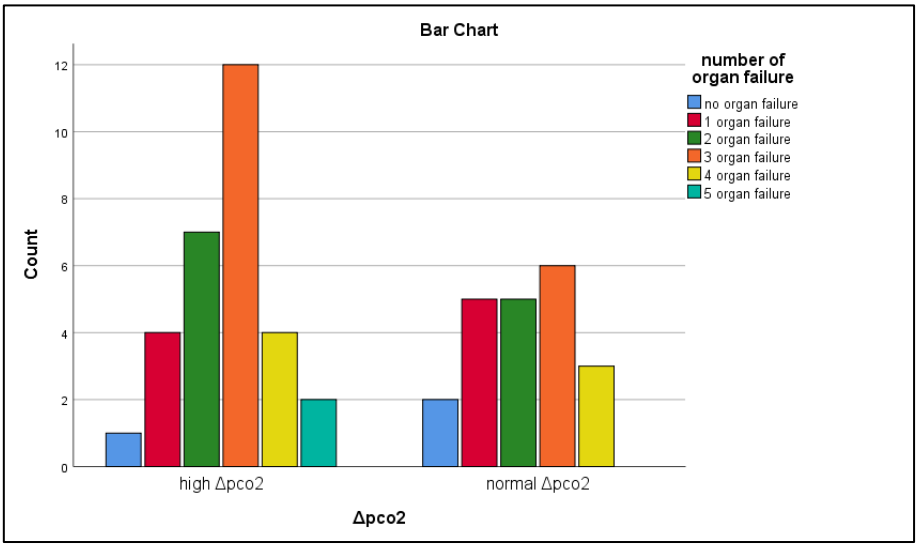

Figure 6: Comparison of the number of organ failure between the two studied groups.

The ΔPCO_2 was tested for correlation with laboratory GCS, APACHE II scores, and organ dysfunction.

The number of organ dysfunction, APACHE II and GCS scores were directly proportional to ΔPCO_2 value. All these correlations were statistically insignificant except APACHE II score as shown in Table 4.

Table 4: Correlation between ΔPCO2 values, number of organ dysfunction and different scoring systems

	R	**P –value**
Number of organ failure	0.082	0.569
GCS	0.107	0.454
APACHE II	0.764	< 0.001

DISCUSSION

Shock is the global tissue hypoxia, which is a result of an imbalance between systemic oxygen delivery and oxygen demand.

Therefore, adequate tissue oxygenation cannot be assured by normal $ScvO_2$ readings, and other circulatory measures are required to assess resuscitation efforts.

The central venous-arterial carbon dioxide differential (pCO_2gap) may serve as a sign that the peripheral tissues' total CO_2 production is sufficiently removed by the venous blood flow.(van Beest, P. A. *et al*., 2013)

This study's objective was to assess how the venous-arterial PCO_2 gradient affected the prognosis of septic patients admitted to the intensive care unit.

Our results were consistent with physiological theory, which proposed a modified Fick equation for a range of CO_2 production that characterized an

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inverse curvilinear relationship between cardiac output and PCO_2 gap.

The delta PCO_2 gap and cardiac index show such a negative correlation with septic circulatory failure, according to several researches.(Bitar, Z. I. *et al*., 2020)

In this study, regarding gender 51% of admitted patients were males and 49% of patients were females, with insignificant statistical difference between the two Δpco2 groups.

The mean age for admitted patients was 70.57 ± 8.98 years for the high ΔPCO_2 group and 73 ± 6.78 years for the normal group with insignificant statistical difference between the two groups.

Regarding the hemodynamics parameters in the analyzed groups, heart rate increased in a significant way ($p = 0.037$) in the high ΔPCO_2 group with a mean of (109.8 ± 9.4) than in the normal one (95.8 ± 10.1).

The explanation is by the compensatory sympathetic stimulation which raises heart rate in the hypoxic and hypoperfused patients to sustain cardiac output and good organ perfusion.

The MAP was lower in the high ΔPCO_2 group (69.1 ± 11.4) and higher in the normal one (88.0 ± 10.1) but without a significant level ($p = 0.388$). Upon admission, 80% of the high group patients required inotropic support versus 76% of the normal group, without a significant statistical difference between both groups.

The mean respiratory rate was lower in the high ΔPCO_2 group (15.7 ± 4.0) than the normal group (18.5 ± 3.2) but with no significant difference ($p = 0.294$).

In agreement with the above-mentioned results, Araujo, *et al*., 2019; detected insignificant difference in the mean arterial blood pressure and the requirement of inotropic support between both ΔPCO_2 groups.

Bitar, *et al*., 2013; detected a significant lower mean arterial blood pressure (p-value, 0.01) in high ΔPCO_2 group. The need for more vasopressors and IV fluid administration were significantly higher in high ΔPCO_2 group than the normal ΔPCO_2 group (p value = 0.01 and 0.009, respectively).

The mean random blood sugar level was significantly higher ($p = 0.010$) in the high ΔPCO_2 group (213.4 ± 98.3) than in the normal group (156.1 ± 58.). This can be explained by Randal, *et al*., 1966; who mentioned that under anaerobic circumstances, accelerated anaerobic glycolysis leads to more lactic acid production (since pyruvate cannot be cleared by the Krebs cycle).

This mechanism explains increased CO_2 production in hypoxic conditions. Another description is the relative adrenal insufficiency that develops in low flow situations and septic shock.

Regarding the clinical scoring systems in the ICU, the APACHE II score was higher and strongly significant ($p < 0.001$) in the high ΔPCO_2 group (mean = 27.7 ± 5.6) than the normal ΔPCO_2 group (mean = 16.2 ± 2.8).

This result was supported by Wang, *et al*., 2021; who mentioned a significant positive correlation between ΔPCO_2 and APACHE II score ($r = 0.377$, $p < 0.001$).

The GCS was lower in the high ΔPCO_2 group than the normal group but without a significant level ($p = 0.179$). This alteration could be explained by brain hypoperfusion and/or patients with cerebral insult.

In this study, serum lactate level was higher with statistically significance ($p = 0.023$) in the high ΔPCO_2 group (2.7 ± 0.5) than the normal group (1.9 ± 0.3). Furthermore, van Beest, *et al*., 2013; reported that ΔPCO_2 was inversely correlated with lactate clearance, which was explained by the noticed significant lower cardiac index in the high ΔPCO_2 group.

The serum potassium level showed a significant negative correlation (p value < 0.01) with ΔPCO_2 value. The lower level of potassium that associated with high ΔPCO_2 could be clarified by the presence of stress associated with infarction, sepsis, or shock that stimulated catecholamine's release.

The catecholamine's in turn activates the Na-K-ATPase enzyme that driving potassium intracellularly. (Gennari, F. J, 2002)

As regarding organ dysfunction in Intensive care unit, high ΔPCO_2 group showed higher number of organ dysfunction than the normal group but not accomplished the significant level (p value = 0.633). Robin, *et al*., 2015; detected similar results. They found that patients with organ dysfunction had a high percentage of individuals with elevated ΔPCO_2.

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In the high ΔPCO_2 group, there was a significant increase (p = 0.035) in the ICU 10- days mortality rate (60% versus 23.68%) than the normal group. Similar results were accomplished by Mallat, *et al*., 2014; with 75% mortality, but within 28-days for the high ΔPCO_2 group versus 42% for the normal group (p = 0.003).

Van beest, *et al*., 2013; reported a higher death rate in the high ΔPCO_2 group but without a significant statistical difference.

CONCLUSION:

In patients with sepsis and septic shock in the intensive care unit:

- ΔPCO_2 can be utilized as a reliable index for the early prediction of organ dysfunction and clinical prognosis.
- Patients with high ΔPCO_2 were more susceptible for organ dysfunction.
- Patients with high ΔPCO_2 had a higher mortality rate.

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Source of support: Nil; **Conflict of interest:** Nil.

Cite this article as:

Hamood, Z.T., Mahdi, F.A. and Albayati, H.Q.M. "The Role of Central Venous-Arterial PCO_2 Deference as an Early Predictor of End Organ Dysfunction and Clinical Outcome in ICU Septic Patients." *Sarcouncil journal of Medical sciences* 4.7 (2025): pp 07-14.

Publisher: SARC Publisher