THE CORRELATION BETWEEN CENTRAL VENOUS AND ARTERIAL CARBON DIOXIDE DIFFERENCE (PCO2 GAP) WITH CARDIAC OUTPUT IN EARLY SEPSIS A PROSPECTIVE OBSERVATIONAL STUDY

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Abstract

Background: Sepsis, a life-threatening organ dysfunction caused by a dysregulated host response to infection, occurs when chemicals cause a cascade of changes that damage multiple organ systems, leading to failure and sometimes even death.This study aimed to evaluate the prognostic significance of the PCO2 gap on cardiac output during early sepsis.

Methods: This prospective observational study was conducted on 224 patients admitted with a diagnosis of sepsis according to the international guidelines of the Department of Anesthesiology, SRM Medical College Hospital and Research Centre, between 2022 and May 2023.The PCO2 gap was measured from the arterial blood gas (ABG) and the difference between PaCO2 in the ABG and PVCO2 in the venous sample.

Results: Cardiac output was significantly higher in the high PCO2 gap group (p =0.0367 and p = 0.0315, respectively).The cardiac index was significantly higher in the low PCO2 gap group at 0 h (p=0.0067) and 6 h (p=0.0082).There was no significant difference between the PCO2 gap and the serum lactate and vasopressor requirements.There was a significant relationship between IV fluid requirement and the PCO2 gap at 0 h (p=0.0039) but not at 6 h (p=0.5773).There was a positive correlation between MAP and PCO2 gap at baseline and at 6 h.There was a negative correlation between the PCO2 gap and serum lactate, intravenous fluids, and vasopressor requirements.

Conclusion: The PCO2 gap can be used as an index to assess the severity of sepsis and its progression since it directly correlates with cardiac index and cardiac output.

Keywords: PCO2,Pv-aCO2, PVCO2, Sepsis, Cardiac output.

INTRODUCTION

Sepsis, also known as septicaemia, is a life-threatening organ dysfunction caused by dysregulated host response to infection.It occurs when a chemical released into the bloodstream to fight an infection triggers inflammation, leading to damage to multiple organ systems and potentially causing death.The sepsis pathophysiologyinvolves immune stimulation, suppression, hypercoagulation, and hypofibrinolysis.[1] Cardiovascular management is crucial in treating sepsis and septic shock, as hypotension occurs due to failure of vasoconstriction by vascular smooth muscle.[2]Cardiovascular resuscitation is a crucial

determinant of survival in patients with septic shock.Appropriate initial antimicrobial treatment is crucial for patient outcomes. Using crystalloids, red blood cell transfusions, vasopressors, and inotropes within 6 hours of presentation to the emergency department resulted in a 16% decrease in absolute 28-day mortality.[3] The main differences between the intervention and control groups were in the volume of intravenous fluids received, the number of patients transfused packed red blood cells, the use of dobutamine, and the presence of a dedicated study team for the first 6 hours of care.[4]

Specific complications and patterns of organ dysfunction vary among patients.Many patients require renal support, and some may develop prolonged GI tract failure, and a large proportion develop ARDS or coagulopathy.Some patients develop multiple organ dysfunction and failure. Specific supportive measures for each system are required (see relevant sections). Overall, mortality from severe sepsis with shock remains high, ranging from 30 to 70% in various studies.Early recognition, effective resuscitation, timely source control, and attention to detail will likely obtain the best results.[5]

Treatment pathways such as those used in previous studies have been implemented in clinical settings.This approach focused on intravenous fluid administration and initial antimicrobial therapy for sepsis and septic shock. Patients managed this way are more likely to receive fluids above 20 mL/kg before vasopressor administration, reducing the need for vasopressor administration at the intensive care unit transfer. This aggressive management leads to shorter hospital stays and lower 28-day mortality rates, as reported in a multicentre study and meta-analysis.[6]Recent international consensus guidelines on sepsis management in critical care have been widely adopted, focusing on early effective resuscitation, antibiotic therapy, source control, and biological response modifiers. Activated protein C (drotrecoginalfa) is the only available agent despite low-level evidence based on expert opinion.[7]

Sepsis is a high-risk condition with high mortality rates, making the early detection of tissue hypoperfusion crucial.The effectiveness of oxygen-derived parameters as resuscitation goals has been questioned, and recent data have not shown any clinical advantages.Venous oxygen saturation (SvO2) is less than 70% in early sepsis patients, and the venous-to-arterial carbon dioxide difference (Pv-aCO2) indicates microvascular blood flow adequacy.[8] Other resuscitation goals, such as the PCO2 gap, are suggested because of their ability to predict adverse outcomes and simplicity in achieving normal oxygen-derived parameters.Theoptimisation of MAP during early resuscitation of patients with sepsis is crucial for managing the condition. Pv-aCO2 typically doesn't exceed 0.8 kPa (6 mmHg), indicating adequate venous blood flow and cardiac output.In critically ill patients with early sepsis, an inverse relationship exists between the PCO2 gap and CO.[9] Combining ScvO2 values with the PCO2 gap may be practical for resuscitation. However, despite adequate CI, microcirculatory level distributive changes may be independent of CI in sepsis patients, allowing for carbon dioxide (CO2) accumulation.[10]We studied the relationship between the Pv-aCO2 and CI and tackled whether the Pv-aCO2 can add value to the outcome prediction.

AIM

This study aimed to evaluate the prognostic significance of the PCO2 gap on cardiac output during early sepsis.

MATERIALS AND METHODS

This prospective observational study was conducted on 224 patients admitted with a diagnosis of sepsis according to the international guidelines of the Department of Anesthesiology, SRM Medical College Hospital and Research Centre, between 2022 and May 2023.The institutional ethics committee approved the study before initiation, and informed consent was obtained from all patients.

Inclusion criteria

Patients aged > 18 years who were admitted to the ICUs with early sepsis were included.

Exclusion criteria

Patients admitted to the ICUs without sepsis were excluded from the study.

Central and arterial lines were inserted, and the patient was admitted to the ICU.Haemodynamic data were collected at admission and every 6 h until the first 24 h.In addition, serum lactate levels, vasopressors, intravenous fluids, urine output, and length of ICU stay were also measured.

The duty cardiologist measured the cardiac output and index using an ECHO cardiogram.The PCO2 gap was measured from the arterial blood gas (ABG) and the difference between the PaCO2 in the ABG and PVCO2 in the venous sample.

Statistical analysis

We conducted statistical tests to determine the relationship between serum lactate, MAP, and other variables and the outcome variable, PCO2 Gap.We have studied the correlation between the outcome variable PCO2 gap and the other independent variables, interpreted them, and provided a pictorial representation of the correlation.If the variable was parametric, Pearson's correlation test was used.If the variable is non-parametric, for example, rank, frequency, etc., we use the Spearman correlation test.We used STATA Ver 17.0 for the statistical analysis and correlation test, and we used a t-test to find whether there was a significant difference between the two groups.

RESULTS

Table 1. Demographic data of the study

		Number (%)
Age	16-30	9
	31-50	41
	51-75	155
	76-90	19
Sex	Male	141(62.9)
	Female	83(37.1)
BMI	17.6 -20.9	33
	21.6 -24	37
	24.1-27.8	120
	27.9-30.7	34

Regarding age, most people fell into categories 51-75 and 155, followed by categories 31–50.The fewest patients were in the age group of 16-30.In terms of sex, men were found in more numbers than women.BMI distribution showed that most patients had a BMI of approximately 24.1-27.8, followed by 21.6-24 (Table 1).

Table 2.Comparison of various mean parameters between the PCO2

		PCO2 GAP		P-value
		<8	> 8	
Serum lactate	0 hours	3.166581±1.850631	3.213623±2.848373	0.9
	6 hours	2.709032±2.143318	3.407246±3.573296	0.1335
MAP	0 hours	89.30968±13.31417	92.01449±14.83982	0.1953
	6 hours	88.79355±11.94995	90.47826±13.01652	0.3603
Cardiac index	0 hours	3.291097±0.950816	2.95971±0.779859	0.0067
	6 hours	3.291742±0.969454	2.95971±0.806373	0.0082
Urine output	0 hours	52.48387±42.12063	46.81159±34.42779	0.29
	6 hours	55.16447±51.31844	51.66667±61.0127	0.6784
Cardiac output	0 hours	5.349871±1.200477	4.994493±1.153933	0.0367
	6 hours	5.342516±1.228882	4.965217±1.193732	0.0315

IV fluid	0 hours	179.2169±182.8725	115.3846±134.6554	0.0039
	6 hours	170±205.6596	188.9286±245.9019	0.5773
Nor adrenaline	0 hours	9.814815±4.532252	9.047619±4.188988	0.2186
	6 hours	11.53704±6.234097	12.42857±5.714643	0.2958

There was no significant difference between the serum lactate level and the PCO2 gap at the 0th hour and 6th hour.MAP at both the 0th hour and 6th hour shows no significant difference between the PCO2 gap and MAP. There was a significant difference between the PCO2 gap and CI at the 0th hourand 6th hour (p=0.006 and p=0.008, respectively).

There was no significant difference between the PCO2 gap and urine output at the 0th hour and 6th hour.There was a significant difference between the PCO2 gap and cardiacoutputat the 0th hour and 6th hour (p=0.036 and p=0.031, respectively).

When comparing fluid IV at the 0th hour and the PCO2 gap, the p-value is 0.0039, which is highly significant.At the 6th hour and the PCO2 gap, the p-value was 0.5773, which wasinsignificant.There was no significant difference between the 0th and 6th-hour adrenaline and PCO2 gaps (Table 2).

Table 3. Comparison of correlation between PCO2 at 0th hour and 6th hours

	PCO2	
	0 hours	6 hours
Serum lactate	-0.0103	-0.089
Cardiac index	-0.0104	-0.0484
Cardiac output	-0.0513	-0.0078
MAP	0.0478	0.029
IV fluid	0.0463	-0.0974
Urine output	0.1094	-0.0369
Nor adrenaline	-0.0591	-0.0029

At 0 h, the correlation between the PCO2 gap and serum lactate level was -0.0103; at 6 h, it was -0.089.This indicates a negative correlation between these two parameters, implying that serum lactate levels decrease with an increase in the PCO2 gap.

At 0 h, the correlation between the PCO2 gap and CI was -0.0104; at 6 h, it was -0.0484.This indicates a negative correlation between these two parameters, implying that CI decreases with an increased PCO2 gap.

At 0 h, the correlation between the PCO2 gap and CO was -0.0513; at 6 h, it was -0.0078.This shows a negative correlation between these two parameters, implying that CO decreases with an increase in the PCO2 gap.

At 0 h, the correlation between the PCO2 gap and SL was -0.0103; at 6 h, it was -0.089.This indicates that there is a negative correlation between these two parameters.This implies that the SL decreases with an increase in the PCO2 gap.

At 0 h, the correlation between the PCO2 gap and MAP was 0.0478; at 6 h, it was 0.029.This shows a positive correlation between these two parameters, which implies that the MAP increases with an increase in the PCO2 gap.

At 0 h, the PCO2 and noradrenaline correlations were -0.0591.This shows a negative correlation between the PCO2 gap and noradrenaline at 0 h, implying that noradrenaline decreases with an increased PCO2 gap.However, after 6 h, a positive correlation of 0.0029.This shows a negative correlation between the PCO2 gap and noradrenaline at 6 h, implying that noradrenaline decreases with an increased PCO2 gap.

At 0 h, the PCO2 and IV fluid correlations are 0.046.This shows a positive correlation between the PCO2 gap and fluid IV at 0 h, implying that fluid IV increases with an increase in the PCO2 gap.However, at 6 h, a negative correlation of -0.0974 was shown.This shows a negative correlation between the PCO2 gap and fluid IV at 6 h, implying that fluid IV decreases with an increase in the PCO2 gap.

The correlation between these parameters, the PCO2 gap, and UO was 0.1094.This shows a positive correlation between the PCO2 gap and UO at 0 h, which implies that UO increased with an increase in the PCO2 gap (Table 3).

DISCUSSION

Demographic data analysis showed that out of 224 patients, 141 were male and 83 were female; the number of men was higher than that of women.The most common causes of early sepsis are urosepsis, lower respiratory infections, and secondary infections.Of the 224 patients analysed, the average age of patients admitted to the ICU was 51–75 years, followed by 31–50 years.Most of the patients' BMI ranged from 24.1-27.8.

Our study found that in the high PCO2gap group, there was a significant change in the cardiac index at admission and at 6 h.Similarly, there was a significant change in the cardiac index in the low PCO2 group (p=0.0067, p=0.0082).The correlation between these two parameters was -0.0104.This indicates a negative correlation between the PCO2 gap and CI at baseline (-0.0104) and 6th hour (-0.0097), implying that the cardiac index decreases with increasing PCO2 gap.This follows the prospective study by **Mallat et al.** that investigated the behaviour of ΔPCO2 and its relationship with CI, blood lactate concentration, and 28-day mortality during resuscitation in the early phase of septic shock.In their study, there were significant differences (p< 0.0001) between the normal (ΔPCO2 ≤0.8 kPa) and high ΔPCO2 groups for CI (3.9 [3.3 to 4.7] vs. 2.9 [2.3 to 3.1] l min) and ScvO2 (73 [65 to 80] vs. 61 [53 to 63] %).The correlation between the changes in CI and ΔPCO2 was r = -0.62, p< 0. 0001. It was further concluded that monitoring ΔPCO2 may be a useful tool for assessing the adequacy of tissue perfusion during resuscitation.NormalisingbothΔPCO2 and ScvO2 is associated with a greater decrease in blood lactate concentration than ScvO2 alone.[11]

Our study found that in the high PCO2gap group, there was a significant change in cardiac output at admission and at 6 h. Similarly, there is a significant change in the low PCO2 group with cardiac output. (p=0.0367, p=0.0315)

Our study found that in the high PCO2 gap group, there was no significant change in serum lactate levels on admission or at 6 h.Similarly, we found no significant change in serum lactate levels in the low PCO2 group (p=0.9, p=0.1335).

In an observational study conducted by **Mesquida et al.** in septic shock patients within the first 24 h of ICU admission, after restoration of mean arterial pressure and central venous oxygen saturation, the $PCVACO_2$ gap and the $PcvaCO_2/CavO_2$ ratio were calculated.Consecutive arterial and central venous blood samples were obtained from each patient within 24 hours. The result of this study Those patients whose lactate values did not decrease had higher $PcvaCO_2/CavO_2$ ratio values at inclusion (1.8 ± 0.8vs. 1.4 ± 0.5, p=0.02). The results of this studyare comparable to those of the present study.During follow-up, 97 paired blood samples were obtained.No improvement in lactate values was associated with a higher $PcvaCO_2/CavO_2$ ratio in the control group.He further concluded that in a population of septic shock patients with normalised MAP and $ScvO_2$, the presence of elevated $PcvaCO_2/CavO_2$ ratio significantly reduced the odds of adequate lactate clearance during the following hours.[12]

Our study found no significant change in the high PCO2 gap group in the mean arterial pressure at admission and 6 h.Similarly, we found no significant change in the low PCO2 group with mean arterial pressure (p=0.1953 and p=0.36030, respectively).

Our study found that in the high PCO2 gap group, there was a significant change in IV fluid on admission (p=0.0039).However, we found no significant change in the low PCO2 group with IV fluid(p=0.5773).

Our study found that in the high PCO2 gap group, there was no significant change in adrenaline levels on admission or at 6 h.Similarly, we found no

significant change in the low PCO2 group with noradrenaline administration (p=0.2186, p=0.2958).

Our study found that in the high PCO2 gap group, there was no significant change in urine output at admission or at 6 h.Similarly, we found no significant change in urine output in the low PCO2 group (p=0.29, p=0.6784).

At 0^{th} hours, the correlation between the PCO2 gap and CI was -0.0104; at 6 h, it was -0.0484.This indicates a negative correlation between these two parameters, implying that the CI decreases with an increased PCO2 gap.

At the 0^{th} hour, the correlation between the PCO2 gap and CO was -0.0513, and atthe 6^{th} hour, it was -0.0078.This shows a negative correlation between these two parameters, implying that CO decreases with an increased PCO2 gap.

At 0 h, the correlation between the PCO2 gap and SL was -0.0103; at 6 h, it was -0.089.This shows a negative correlation between these two parameters, implying that SL decreases with an increased PCO2 gap.

At 0 h, the correlation between the PCO2 gap and MAP was 0.0478; at 6 h, it was 0.029.This shows a positive correlation between these two parameters, which implies that the MAP increases with an increase in the PCO2 gap.

At the 0th hour, the PCO2 gap and noradrenaline correlation were -0.0591.This shows a negative correlation between the PCO2 gap and noradrenaline at 0 h, implying that adrenaline decreases with an increased PCO2 gap.However, after 6 h, a positive correlation of 0.0029.This showed a negative correlation between the PCO2 gap and noradrenaline at 6 h, implying that neither adrenaline decreased with an increase in the PCO2 gap.

At 0 h, the PCO2 and IV fluid correlations are 0.046.This shows a positive correlation between the PCO2 gap and fluid IV at 0 h, which implies that fluid IV increases with an increase in the PCO2 gap.However, at 6 h, there was a negative correlation of -0.0974.This shows a negative correlation between the PCO2 gap and fluid IV at 6 h, which implies that fluid IV decreases with an increase in the PCO2 gap.

The correlation between these parameters, the PCO2 gap, and UO was 0.1094.This shows a positive correlation between the PCO2 gap and UO at 0 h, which implies that UO increased with an increase in the PCO2 gap.

CONCLUSION

The PCO2 gap can be used as an index to assess the severity of sepsis and its progression since it directly correlates with the cardiac index and cardiac output.

Limitations

We analysed the PCO2 gap only at 0 and 6 h of early sepsis, did not monitor the PCO2 gap trend for 24 h, and did not include the causes of early sepsis in the study population. Indicators of early sepsis, pro-BNP, and procalcitonin (PCT) levels were not measured as unavailable at our institute.The length of hospital stay and mortality rate were not studied.

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