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Central Venous to Arterial pCO 2 Difference as Complementary Tool for Goal Directed Therapy in Septic Shock

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Abstract

Background: Shock is a life-threatening condition of circulatory failure that most commonly presents with hypotension, it can also be heralded by other vital sign changes or the presence of elevated serum lactate levels, it is important that the clinician rapidly identify the etiology so that appropriate interventions and therapy.

Aim of Study: To investigate the relationship between pCO2 gap and blood lactate concentration and 28 day mortality, as well as the prognostic usefulness of this relationship.

Patients and Methods: The present studywasconducted on 30 adult septic shock patients at general intensive care unit Department of Ain Shams University Hospitals from December 2022 to May 2023, who were divided into two groups regarding pCO 2 gap into normal and high gap after receiving early resuscitation and reaching ScvO 2 >_70%.

Results: There was a non-significant relation between SOFA score and pCO2 gap in first 12 hours of admission, but after 24 hours to end of study, patients with high pCO 2 gap have higher SOFA score. An interesting result obtained in this study was finding that there was no significant relation between APACHE II and pCO 2 gap on admission, but there was a significant increase in APACHE II score in high gap group after 48 hours till end of study. In the present study, there was a non-significant relation between incidence of in-hospital mortality rate and pCO2 gap among studied cases. There was a non-significant relation between 28-day mortality and pCO2 gap among studied cases. This study revealed that there was a significant relation between MAP and pCO 2 gap only after 24 hours of admission and till the end of study, as MAP is lower in high gap group. This study revealed that there was a significant relation between HR and pCO 2 gap only after 24 hours of admission and till the end of study, as HR is higher in high gap group. In the present study, there was a significant low Lactate in normal gap group after 6 hours of enrollment. This study revealed that there was a non-significant relation between CVP and pCO 2 gap among studied cases.An interesting result obtained in this study that there was a non-significant relation between Scvo 2 and pCO2 gap among studied cases.

Conclusion: Targeting ScvO 2 more than 70% alone may not be sufficient to monitor perfusion in septic shock patients, our results suggest that the persistence of high Pv-aCO 2 during the early resuscitation of patients in septic shock is associated with significant higher multi organ dysfunction, higher lactate concentrations, lower MAP and poor outcomes, so the combination of PCO2 gap and ScvO 2 may provide additional information about hemodynamics and the ability to clear lactate, Further research is required to determine the best use of this parameter as a treatment end-point; The predictive value for outcome of the central venous pCO 2 difference is questionable but persistence of an increased central venous pCO 2 difference after 24h of therapy seems to enhance the likelihood of bad outcome so the importance of PCO 2 gap for outcomes might warrant its inclusion as a target in goal-directed treatment protocols.

Key Words: *Central Venous – Arterial pCO 2 – Septic Shock.*

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Introduction

ONE of the most common reasons for ICU admission is sepsis. Depending on the severity of the clinical situation, which is conditioned by the existence of organ failure mediated by diverse mechanisms of cell death, this heterogeneous and complicated disease may result in a 20-50 percent mortality rate **[1]**.

Septic shock is a type of vasodilatory or distributive shock. Septic shock is defined as sepsis that has circulatory, cellular, and metabolic abnormalities that are associated with a greater risk of mortality than sepsis alone **[2]**.

Though sepsis is known to contain microvascular abnormalities, and a decrease in oxygen delivery and/or insufficient use of the available oxygen form a major part of such organ dysfunction, the way the many individual mechanisms interact is not entirely understood **[3]**.

The early detection of tissue injury is consequently critical in the management of these patients, and the monitoring of certain physiological varia-

bles that can be used to determine tissue perfusion status has been advocated in their initial care [4].

Multicenter clinical trials have lately been unable to prove the utility of $SvcO_2$ monitoring as guidance in patient resuscitation [5].

As a result of the above, the most recent version of the Surviving Sepsis Campaign does not propose using this variable as an initial resuscitation aim or target in the management of patients with sepsis [6].

As a result, other metrics for assessing tissue perfusion are required to guide therapy. The venous-to-arterial CO2 pressure difference (pCO_2 delta or $_APCO_2$), which serves as a proxy marker for the venous-to-arterial CO_2 content differential, is one such metric [7].

The difference between PCO_2 in central venous blood and PCO_2 in arterial blood is known as central venous to arterial CO_2 gap (P v-a CO_2) [8].

P v-a CO_2 has been considered as an indicator of the adequacy of venous blood flow to wash out CO_2 in peripheral tissues [8].

Due to CO_2 synthesis at the peripheral level, coupled with oxygen intake and metabolism in general, venous CO_2 concentrations are higher than arterial CO_2 concentrations under healthy conditions [9]. In numerous clinical situations, including sepsis, the pCO_2 delta value has been proposed as a measure capable of reflecting altered tissue perfusion [10].

The purpose of the study is to investigate the behavior of pCO_2 delta and its relationship to blood lactate concentration and 28 day mortality during resuscitation in the very early phase of septic shock and if we could use pCO_2 delta as complementary tool for goal directed therapy in septic shock.

We hypothesized that combination of PCO_2 gap and $ScvO_2$ may provide additional information about hemodynamics and the ability to clear lactate.

Aim of the work:

To investigate the relationship between pCO_2 gap and blood lactate concentration and 28 day mortality, as well as the prognostic usefulness of this relationship.

Subjects and Methods

Type of study: Prospective observational study.

Study setting: General ICU Department, Ain Shams University Hospitals.

Study period: 6 months.

Study population: Patients with the following criteria:

1- Septic shock issued by international sepsis and septic shock treatment guidelines: Patients with septic shock will be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain MAP ›_65mm Hg and Having a serum lactate level >2mmol/L (18mg/dL) despite adequate volume resuscitation.

2- $ScvO_2$ ›_70% achieved 6 hours after resuscitation.

Selection criteria for cases:

Inclusion criteria:

18 years or older, both males and females and patients met the diagnostic criteria of septic shock issued by international sepsis and septic shock treatment guidelines for septic shock: Patients with septic shock will be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain MAP ›_65mm Hg and having a serum lactate level >2mmol/L (1 8mg/dL) despite adequate volume resuscitation.

Exclusion criteria:

Patients with any other type of shock, pregnancy, irreversible underlying disease such as end-stage neoplasm and sever chronic obstructive pulmonary disease

Sampling method: Consecutive sampling.

Sample size: 30 critical care patients with septic shock, by using Power Analysis and Sample Size Software (PASS 11) (Version 11.0.08) for sample size calculation, to reach power 80%, at alpha error 5% and after reviewing previous study results (Bitar et al., 2020).

Study procedure: All selected patients were divided into two groups according to:

P (CV-a) CO_2: Group (1): P (CV-a) CO_2 <6mmHg were considered as belonging to the Low gap group. Group (2): P (CV-a) CO_2 ›_6mmHg were considered as belonging to the High gap group.

All Patients were subjected to the following:a detailed history taking from patient or relatives including the chronic diseases, family history, past history, present history and possible source of sepsis, a complete physical examination: General and local examination carried out for all patients and study patients resuscitated according to surviving sepsis campaign last guidelines: Measure lactate level, obtain blood cultures before administrating

antibiotics, administer broad-spectrum antibiotics, begin rapid administration of 30ml/kg crystalloid for hypotension or lactate ≥4mmol/L and apply vasopressor if hypotensive during or after fluid resuscitation to maintain a mean arterial pressure ≥65mm Hg. The time of inclusion (T0) and study enrolment was considered as the time at which $ScvO_2$ reaches ≥70. The patients' age, sex, diagnosis, Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) score obtained. Early fluid resuscitation started, time points of 0, 6, 12, 18, 24, 36, 48, 60, 72, 84, 96, 108, 120 hours after resuscitation were T0, T6, T12, T18, T24, T36, T48, T60, T72, T84, T96, T108, T120.Data like heart rate (HR), MAP, CVP, lactate, p (CV-a) CO_2 and $ScvO_2$ were collected at each time point. SOFA Score collected at T0, T12, T24, T48. T72,T96, T120. APACHE II Score collected at T0, T48, T96, T120 Full laboratory investigations: At the beginning of the study (CBC, pan cultures, coagulation profile, kidney function tests, liver function tests, cardiac enzymes, CRP, blood gases samples from artery and from central venous line). Central venous catheter insertion to all patients in the superior vena cava (position veried by X-ray, the tip of catheter being superimposed on the 4_{th} right intercostal space), aseptic technique was used. P (CV-a) CO_2 calculated as the difference between $PcvCO_2$ and $PaCO_2$ respectively obtained from central venous blood and arterial blood samples. Patients were separated into two groups according to the initial (T0) value of P (CV-a) CO_2 patients with a P (CV-a) CO_2 <6mmHg will be considered as belonging to Low gap group, those with a P (CV-a) CO_2 ≥6mmHg will be considered as belonging to the High gap group.

The study groups were compared as regard to the following variables: Mortality as primary outcome measure, haemodynamic parameters and lactate concentration at each time and condition improvement, as measured by APACHE II score.

Ethical considerations:

Study Approved by Ethical Committee of Faculty of Medicine of Ain Shams University, all patients or their legal guardians had given their Informed consent to participate. All participants or their legal guardians chose to participate on their own free will and were fully informed regarding the procedures of the Research and any potential risks and all patients' data were highly confidential.

Statistical analysis and data interpretation:

Statistical analysis was done by SPSS v26 (IBM Inc., Armonk, NY, USA). Quantitative variables were presented as mean, standard deviation (SD) and range and were compared between the two groups utilizing unpaired Student's *t*-test. Qualitative variables were presented as frequency and percentage (%) and were analyzed utilizing the Chi-square test or Fisher's exact test when appropriate. A two tailed *p*-value <0.05 was considered statistically significant. Kaplan Meier curve was used to show the mortality rate.

Results

This study is a prospective observational study. The study was conducted at the intensive care unit (ICU) of anesthesiology, critical care medicine and pain management department of Ain Shams University Hospital (ASUH). This study included 30 patients, 14 patients in high gap group and 16 patients in low gap group.

Age and sex were insignificantly different between both groups (Table 1).

Table (1): Demographic data of the studied groups.

	High gap group (n=14)	Low gap group (n=16)	*p*-value
Age (years):			
Mean ± SD	58.3±11.26	60.4±11.02	0.601
Range	39-73	44-79	
Sex:			
Male	6 (20%)	10 (33.33%)	0.282
Female	8 (26.67%)	6 (20%)	

Risk factors (DM, old CVS, IHD, asthmatic, CKD, AF, MV replacement, hypothyroid, HTN, HCV +ve, cirrhosis, COPD and BPH) were insignificantly different between both groups Table (2).

Diagnosis (pneumonia, DKA, ascending cholangitis, UTI, infected bed sores, infected permcath, infective endocarditis, AKI, spontaneous bacterial peritonitis, cellulitis, post-operative sepsis, Fournier's gangrene, meningitis and infected diabetic foot) were insignificantly different between both groups Table (3).

During the study, 5 (35.71%) patients died in high gap group (first patient died after 36 hours, second patient died at 2_{nd} day, third patient died at 3_{rd} day, fourth patient died at 7_{th} day and fifth patient died at 8_{th} day) and 2 (12.05%) patients died in low gap group (first patient died at 11_{th} day and second patient died at 13_{th} day).

SOFA score at T0 and T12 was insignificantly different between both groups. SOFA score at T24, T48, T72, T96 and T120 was significantly higher in high gap group than low gap group (p<0.001) (Table 4).

Table (2): Risk factors of the studied groups.

	High gap group (n=14)	Low gap group (n=16)	*p*-value
DM:			
Yes	6 (20%)	10 (33.33%)	0.282
No	8 (26.67%)	6 (20%)	
Old CVS:			
Yes	8 (26.67%)	5 (16.67%)	0.153
No	6 (20%)	11 (36.67%)	
IHD:			
Yes	4 (13.33%)	3 (10%)	0.526
No	10 (33.33%)	13 (43.33%)	
Asthmatic:			
Yes	1 (3.33%)	1 (3.33%)	0.922
No	13 (43.33%)	15 (50%)	
CKD:			
Yes	3 (10%)	6 (20%)	0.338
No	11 (36.67%)	10 (33.33%)	
AF:			
Yes	5 (16.67%)	2 (6.67%)	0.134
No	9 (30%)	14 (46.67%)	
MV replacement:			
Yes	1 (3.33%)	0 (0%)	0.277
No	13 (43.33%)	16 (53.33%)	
Hypothyroid:			
Yes	1 (3.33%)	2 (6.67%)	0.626
No	13 (43.33%)	14 (46.67%)	
HTN:			
Yes	4 (13.33%)	6 (20%)	0.605
No	10 (33.33%)	10 (33.33%)	
HCV +ve:			
Yes	1 (3.33%)	2 (6.67%)	0.626
No	13 (43.33%)	14 (46.67%)	
Cirrhosis:			
Yes	1 (3.33%)	0 (0%)	0.277
No	13 (43.33%)	16 (53.33%)	
COPD:			
Yes	0 (0%)	1 (3.33%)	0.341
No	14 (46.67%)	15 (50%)	
BPH:			
Yes	0 (0%)	3 (10%)	0.088
No	14 (46.67%)	13 (43.33%)	

* : Significant as *p*-value 50.05.
DM : Diabetes mellitus.
CVS : Cerebrovascular stroke.
IHD : Ischemic heart disease.
CKD : Chronic kidney disease.
AF : Atrial fibrillation.
MV : Mitral valve.
HTN : Hypertension.
HCV : Hepatitis C virus.
COPD : Chronic obstructive pulmonary disease.
BPH : Benign prostatic hyperplasia.

Table (3): Diagnosis of the studied groups.

	High gap group (n=14)	Low gap group (n=16)	*p*-value
Pneumonia:			
Yes	5 (16.67%)	4 (13.33%)	0.523
No	9 (30%)	12 (40%)	
DKA, septic shock:			
Yes	1 (3.33%)	1 (3.33%)	0.922
No	13 (43.33%)	15 (50%)	
Ascending cholangitis:			
Yes	1 (3.33%)	0 (0%)	0.277
No	13 (43.33%)	16 (53.33%)	
UTI:			
Yes	6 (20%)	7 (23.33%)	0.961
No	8 (26.67%)	9 (30%)	
Infected bed sores:			
Yes	3 (10%)	1 (3.33%)	0.222
No	11 (36.67%)	15 (50%)	
Infected permcath:			
Yes	1 (3.33%)	1 (3.33%)	0.922
No	13 (43.33%)	15 (50%)	
Infective endocarditis:			
Yes	1 (3.33%)	0 (0%)	0.277
No	13 (43.33%)	16 (53.33%)	
AKI, septic shock:			
Yes	3 (10%)	5 (16.67%)	0.544
No	11 (36.67%)	11 (36.67%)	
Spontaneous bacterial peritonitis:			
Yes	1 (3.33%)	0 (0%)	0.277
No	13 (43.33%)	16 (53.33%)	
Cellulitis:			
Yes	2 (6.67%)	2 (6.67%)	0.886
No	12 (40%)	14 (46.67%)	
Post operative sepsis:			
Yes	1 (3.33%)	0 (0%)	0.277
No	13 (43.33%)	16 (53.33%)	
Fournier's gangrene:			
Yes	0 (0%)	1 (3.33%)	0.341
No	14 (46.67%)	15 (50%)	
Meningitis:			
Yes	0 (0%)	3 (10%)	0.088
No	14 (46.67%)	13 (43.33%)	
Infected Diabetic foot:			
Yes	0 (0%)	2 (6.67%)	0.171
No	14 (46.67%)	14 (46.67%)	

DKA: Diabetic ketoacidosis.
UTI : Urinary tract infection.
AKI : Acute kidney injury.

Table (4): SOFA score of the studied groups.

	High gap group	Low gap group	*p*-value
T0:			
Mean	6.86	7.81	0.307
SD	2.68	2.34	
T12:			
Mean	7.93	6.19	0.066
SD	2.50	2.48	
T24:			
Mean	9.00	4.38	<0.001 *
SD	3.26	2.58	
T48:			
Mean	9.77	2.56	<0.001 *
SD	3.68	2.53	
T72:			
Mean	9.50	2.13	<0.001 *
SD	4.28	2.16	
T96:			
Mean	10.70	1.63	<0.001 *
SD	4.64	2.19	
T120:			
Mean	11.50	1.50	<0.001 *
SD	4.79	2.25	

*: Significant as *p*-value 50.05.
SOFA: Sepsis-related organ failure assessment.

APACHE II score at T0 was insignificantly different between both groups. APACHE II score at T48, T96 and T120 was significantly higher in high gap group than low gap group (*p*-value <0.001) (Table 5).

Table (5): APACHE II score of the studied groups.

	High gap group	Low gap group	*p*-value
T0:			
Mean	19.71	18.19	0.547
SD	7.52	6.19	
T48:			
Mean	17.31	8.56	<0.001 *
SD	8.12	4.18	
T96:			
Mean	15.70	7.63	<0.001 *
SD	6.11	4.47	
T120:			
Mean	18.90	7.19	<0.001 *
SD	7.25	4.35	

*: Significant as *p*-value 50.05.
APACHE: Acute physiology and chronic health evaluation.

Heart rate at T0, T6, T12 and T18 was insignificantly different between both groups. Heart rate at T24, T36, T48, T60, T72, T84, T96, T108 and T120 was significantly higher in high gap group than low gap group (*p*-value <0.05) (Table 6).

Table (6): Heart rate (beats/min) of the studied groups.

	High gap group	Low gap group	*p*-value
T0:			
Mean	123.57	115.75	0.129
SD	15.94	11.30	
T6:			
Mean	121.79	114.00	0.087
SD	13.04	10.98	
T12:			
Mean	114.50	106.56	0.068
SD	12.59	10.33	
T18:			
Mean	112.00	104.88	0.061
SD	9.01	10.76	
T24:			
Mean	111.36	98.00	0.010*
SD	15.29	10.93	
T36:			
Mean	109.00	94.56	<0.001 *
SD	11.98	6.48	
T48:			
Mean	110.85	93.19	<0.001 *
SD	15.42	11.43	
T60:			
Mean	112.42	92.69	<0.001 *
SD	12.74	12.43	
T72:			
Mean	115.80	92.31	<0.001 *
SD	14.39	11.45	
T84:			
Mean	110.00	89.50	<0.001 *
SD	12.87	9.70	
T96:			
Mean	110.30	87.94	<0.001 *
SD	13.81	11.21	
T108:			
Mean	109.10	86.81	<0.001 *
SD	12.35	8.53	
T120:			
Mean	111.20	87.00	<0.001 *
SD	13.54	11.13	

*: Significant as *p*-value 50.05.

Mean arterial pressure at T0, T6, T12 and T18 was insignificantly different between both groups. Mean arterial pressure at T24, T36, T48, T60, T72, T84, T96, T108 and T120 was significantly lower in high gap group than low gap group (*p*-value <0.05) (Table 7).

CVP at T0, T6, T12, T18, T24, T36, T48, T60, T72, T84, T96, T108 and T120 was insignificantly different between both groups (Table 8).

Table (7): Mean arterial pressure (mmHg) of the studied groups.

	High gap group	Low gap group	*p*-value
T0:			
Mean	67.36	68.69	0.305
SD	1.34	4.59	
T6:			
Mean	69.93	72.38	0.068
SD	3.27	3.72	
T12:			
Mean	72.57	76.56	0.059
SD	4.62	6.24	
T18:			
Mean	73.64	77.19	0.103
SD	5.83	5.67	
T24:			
Mean	71.00	81.31	<0.001*
SD	5.99	9.18	
T36:			
Mean	71.21	84.81	<0.001*
SD	6.60	10.16	
T48:			
Mean	70.46	85.94	<0.001*
SD	8.26	9.50	
T60:			
Mean	70.33	87.00	<0.001*
SD	6.58	9.54	
T72:			
Mean	68.90	88.50	<0.001*
SD	5.95	10.50	
T84:			
Mean	70.50	89.13	<0.001*
SD	10.15	10.09	
T96:			
Mean	70.00	91.56	<0.001*
SD	4.50	10.09	
T108:			
Mean	69.20	91.81	<0.001*
SD	4.83	10.36	
T120:			
Mean	68.80	93.31	<0.001*
SD	5.29	10.64	

*: Significant as *p*-value ≤0.05.

Table (8): CVP (cmH2O) of the studied groups.

	High gap group	Low gap group	*p*-value
T0:			
Mean	10.36	8.50	0.266
SD	5.09	3.85	
T6:			
Mean	13.57	12.13	0.123
SD	2.93	2.03	
T12:			
Mean	13.57	13.13	0.565
SD	2.47	1.71	
T18:			
Mean	15.00	13.69	0.117
SD	2.66	1.74	
T24:			
Mean	15.00	13.75	0.092
SD	2.11	1.81	
T36:			
Mean	15.21	13.81	0.108
SD	2.89	1.64	
T48:			
Mean	15.15	13.69	0.104
SD	1.57	2.80	
T60:			
Mean	15.25	13.31	0.081
SD	3.67	1.92	
T72:			
Mean	15.10	13.19	0.099
SD	2.56	2.88	
T84:			
Mean	15.60	13.56	0.087
SD	3.34	2.48	
T96:			
Mean	15.60	14.88	0.429
SD	2.99	1.63	
T108:			
Mean	15.80	14.06	0.092
SD	1.69	2.82	
T120:			
Mean	15.90	14.19	0.052
SD	3.03	1.17	

*: Significant as *p*-value ≤0.05. CVP: Central venous pressure.

Lactate at T0 was insignificantly different between both groups. Lactateat T6, T12, T18, T24, T36, T48, T60, T72, T84, T96, T108 and T120 was significantly higher in high gap group than low gap group (*p*-value <0.001) (Table 9).

ScvO2 at T0 T6, T12, T24 T36, T48, T60, T72, T84, T96, T108 and T120 was insignificantly different between both groups (Table 10).

p(CV-a) CO2 at T0, T6, T12, T18, T24, T36, T48, T60, T72, T84, T96, T108 and T120 were significantly higher in high gap group than low gap group (*p*-value < 0.001) (Table 11).

The mortality rate was insignificantly different between high gap group and low gap group. The mortality rate was 3 (21.43%) patients in high gap group while no mortalities in low gap group (Table 12).

Table (9): Lactate (mmol/l) of the studied groups.

	High gap group	Low gap group	*p*-value
T0:			
Mean	7.97	8.01	0.964
SD	2.51	2.43	
T6:			
Mean	9.08	4.78	<0.001*
SD	2.14	2.04	
T12:			
Mean	9.84	2.52	<0.001*
SD	3.47	1.47	
T18:			
Mean	10.23	1.76	<0.001*
SD	3.35	1.68	
T24:			
Mean	10.00	1.41	<0.001*
SD	3.64	2.34	
T36:			
Mean	9.86	1.21	<0.001*
SD	3.50	1.48	
T48:			
Mean	10.11	1.25	<0.001*
SD	3.89	1.85	
T60:			
Mean	10.28	1.34	<0.001*
SD	3.67	2.03	
T72:			
Mean	10.49	1.52	<0.001*
SD	4.01	2.35	
T84:			
Mean	10.85	1.36	<0.001*
SD	4.11	2.61	
T96:			
Mean	10.79	1.48	<0.001*
SD	4.31	3.11	
T108:			
Mean	11.43	1.43	<0.001*
SD	4.67	2.65	
T120:			
Mean	12.13	1.51	<0.001*
SD	5.04	3.31	

*: Significant as *p*-value ≤0.05.

Table (10): $ScvO_2$ (%) of the studied groups.

	High gap group	Low gap group	*p*-value
T0:			
Mean	72.29	73.63	0.071
SD	1.77	2.09	
T6:			
Mean	71.57	73.56	0.129
SD	3.01	3.85	
T12:			
Mean	72.00	73.94	0.065
SD	2.22	3.15	
T18:			
Mean	71.86	73.81	0.094
SD	3.46	2.71	
T24:			
Mean	73.07	74.63	0.173
SD	2.87	3.18	
T36:			
Mean	73.14	75.00	0.082
SD	2.68	2.92	
T48:			
Mean	72.31	74.44	0.063
SD	2.63	3.16	
T60:			
Mean	72.67	74.88	0.054
SD	2.81	2.92	
T72:			
Mean	73.30	74.69	0.271
SD	2.16	3.48	
T84:			
Mean	72.40	74.19	0.119
SD	1.51	3.27	
T96:			
Mean	73.20	75.44	0.061
SD	2.04	3.20	
T108:			
Mean	72.30	74.88	0.080
SD	3.62	3.42	
T120:			
Mean	72.10	74.13	0.103
SD	2.69	3.12	

*: Significant as *p*-value ≤0.05.
ScvO :Central venous oxygen saturation.

Table (11): p(CV-a) CO 2 (mmHg) of the studied groups.

	High gap group	Low gap group	*p*-value
T0:			
Mean	7.29	4.25	<0.001*
SD	1.54	1.13	
T6:			
Mean	8.14	3.38	<0.001*
SD	1.70	1.45	
T12:			
Mean	8.07	2.88	<0.001*
SD	2.13	1.96	
T18:			
Mean	8.00	3.13	<0.001*
SD	2.18	1.93	
T24:			
Mean	7.36	3.00	<0.001*
SD	2.02	2.13	
T36:			
Mean	7.71	2.94	<0.001*
SD	2.13	1.53	
T48:			
Mean	8.00	2.38	<0.001*
SD	2.16	1.71	
T60:			
Mean	8.42	3.00	<0.001*
SD	2.23	2.00	
T72:			
Mean	8.90	2.75	<0.001*
SD	2.64	1.98	
T84:			
Mean	9.00	2.50	<0.001*
SD	2.05	1.75	
T96:			
Mean	8.10	2.44	<0.001*
SD	2.51	2.42	
T108:			
Mean	8.20	2.81	<0.001*
SD	2.49	2.04	
T120:			
Mean	9.10	2.38	<0.001*
SD	2.38	1.89	

*: Significant as *p*-value 50.05.
P(cv-a) CO2: Central venous-arterial carbon dioxide difference.

Table (12): Kaplan-Meier survival curve at ^{5th} day mortality.

	High gap group (n=14)	Low gap group (n=16)	*p*-value
Number of mortalities	3 (21.43%)	0 (0.0%)	0.054
Mean survival	4.393	5.000	
SE	0.320	0.00	

SE: Standard error.

Table (13): Kaplan-Meier survival curve at 28 th day mortality.

	High gap group (n=14)	Low gap group (n=16)	*p*-value
Number of mortalities	5 (35.71 %)	2 (12.05%)	0.101
Mean survival	19.536	26.000	
SE	3.056	1.326	

SE: Standard error.

The mortality rate was insignificantly different between high gap group and low gap group. The mortality rate was 5 (35.71%) patients in high gap group and 2 (12.05%) patients in low gap group (Table 13).

Discussion

Sepsis exists on a continuum of severity ranging from infection and bacteremia to sepsis and septic shock, which can lead to multiple organ dysfunction syndrome (MODS) and death. The definitions of sepsis and septic shock have rapidly evolved since the early 1990s **[11]**.

The systemic inflammatory response syndrome (SIRS) is no longer included in the definition since it is not always caused by infection, sepsis is a clinical syndrome that has physiologic, biologic, and biochemical abnormalities caused by a dysregulated host response to infection. Sepsis and the inflammatory response that ensues can lead to multiple organ dysfunction syndrome and death **[12]**.

Septic shock is a type of vasodilatory or distributive shock. Septic shock is defined as sepsis that has circulatory, cellular, and metabolic abnormalities that are associated with a greater risk of mortality than sepsis alone **[2]**.

ABG is a test have been used for identification of respiratory, metabolic, and mixed acid-base disorders, with or without physiologic compensation, by means of pH and CO 2 levels, measurement of the partial pressures of respiratory gases involved in oxygenation and ventilation, monitoring of acid-base status, as in patient with diabetic ketoacidosis (DKA), assessment of the response to mechanical ventilation in a patient with respiratory failure, determination of arterial blood gases in advanced chronic pulmonary disease for assessment of the need for home oxygen **[12]**.

The difference between PCO 2 in central venous blood and PCO 2 in arterial blood is known as central venous to arterial CO 2 gap (P v-a CO 2) **[8]**, P v-a CO 2 has been considered as an indicator of

the adequacy of venous blood flow to wash out CO2 in peripheral tissues **[8]**, Elevated P v-a CO_2 (›_ 6 mmHg) occurs in cases of decreased systemic blood flow. Normalization of P v-a CO_2 during resuscitation was associated with normalization of serum lactate **[13]**.

Early hemodynamic optimization using resuscitation bundles targeting central venous oxygen saturation ($ScvO_2$) and macro hemodynamics were initially associated with significant reduction of mortality in septic shock **[14]**, however; the usefulness of oxygen-derived parameters has been strongly questioned **[15]**, and recent studies not succeeded to prove its benefits **[16]** and **[17]**, Meanwhile other studies claim that using P v-a CO_2 has been linked to beneficial outcomes for shocked patients resuscitation.

The present studywasconducted on 30 adult septic shock patients at general intensive care unit Department of Ain Shams University Hospitals from December 2022 to May 2023, who were divided into two groups regarding pCO_2 gap into normal and high gap after receiving early resuscitation and reaching $ScvO_2$ ›_70%.

Thus the aim of our study was to evaluate the use of central venous to arterial pCO_2 difference in patients with septic shock as a complementary tool for goal directed therapy and its relation to outcome.

Regarding co-morbidities, there was insignificant statistical difference in the distribution of co-morbidities between both groups, there were 6 (20%) diabetic patients in high gap group versus 10 (33.33%) in normal gap group (*p*-value 0.282), 8 (26.67%) old cerebrovascular stroke in high gap group versus 5 (16.67%) in normal gap group (*p*-value 0.153), 4 (13.33%) ischemic heart disease in high gap group versus 3 (10 %) in normal gap group (*p*-value 0.526), 1 (3.33%) asthmatic patient in high gap group versus 1 (3.33%) in normal gap group (*p*-value 0.922), 3 (10%) chronic kidney disease in high gap group versus 6 (20%) in normal gap group (*p*-value 0.338), 5 (16.67%) atrial fibrillation in high gap group versus 2 (6.67%) in normal gap group (*p*-value 0.134), 1 (3.33%) mitral valve replacement in high gap group versus 0 (0%) in normal gap group (*p*-value 0.277), 1 (3.33%) hypothyroid in high gap group versus 2 (6.67%) in normal gap group (*p*-value 0.626), 4 (13.33%) hypertensive in high gap group versus 6(20%) in normal gap group (*p*-value 0.605), 1 (3.33%) hepatitis C positive in high gap group versus 2 (6.67%) in normal gap group (*p*-value 0.626), 1 (3.33%) liver cirrhosis in high gap group versus 0(0%) in normal gap group (*p*-value 0.277), 0 (0%) chronic obstructive pulmonary disease in high gap group versus 1 (3.33%) in normal gap group (*p*-value 0.341), 0 (0%) benign prostatic hyperplasia in high gap group versus 3 (10%) in normal gap group (*p*-value=0.088).

According to cause of admission, all patients are diagnosed with septic shock with no statistically difference between both groups regarding the cause of sepsis (*p*-value >0.05).

Such results indicated that both groups were comparable and both the demographic characteristics, risk factors and cause of admission were not interfering with net results of the study.

PCO_2 gap and Outcome: As regard to SOFA score, in the present study we collect SOFA score in 7 different points and results showed that SOFA score was insignificantly different between both groups at T0 and T12 and was significantly higher in high gap group than normal gap group at T24, T48, T72, T96 and T120.

Vallée's study, shows that regarding SOFA score there was no significant relationship with pCo_2 gap at T0, At T24 the low gap patients had a significantly lower SOFA score than the High gap patients **[18]** (this came in accordance to our study). However, there is a difference with Vallée's study in that they did not measure SOFA score after 24 hours.

In Mallat's study, there was no significant difference in SOFA score between both high and normal gap groups at T0. From T0 to T24, the decrease in SOFA score was significantly greater for patients who achieved a normal compared with high pCO_2 gap at T6 (which is consistent with our study) **[13]**.

According to APACHE II score, in the present study we correlate APACHE II score with both groups at 4 different points T0, T48, T96 and T120 and that reveal no significant correlation in both normal and high groups at T0. The correlation shows significant increase in APACHE II score in high gap group at T48, T96 and T120 in comparison with normal gap group.

Vallée F's study, APACHE II score collected only in one point at T0 and there was no significant difference between both high and normal gap groups **[18]**.

In Mallat's study, at T0 there was no significant difference inAPACHE II score between both groups **[13]**.

Our studyis different from these studies in that we collectAPACHE II score at 4 different points T0, T48, T96 and T120 which could help more about prediction of outcome.

In our study, in terms of in-hospital mortality rate, it was insignificantly different between high gap group and low gap group. The mortality rate was 3 (21.43%) patients in high gap group while no mortalities in low gap group.

As regard 28-day mortality; the overall mortality was 47.76% and the mortality rate was insignificantly different between high gap group and low gap group. The mortality rate was 5 (35.71%) patients in high gap group and 2 (12.05%) patients in low gap group.

This came in accordance with Van Beest's study, the hospital mortality rate for all patients was 24.5% (13/53). The in-hospital mortality rate was 21% for low gap group and 29% for the high gap group **[19]**.

In Vallée F's study, mortality rate at day 28 for all patients was 44% (22/50) and there was no significant difference between both groups: 34% (9/26) for low gap group and 54% (13/24) for high gap group and that agree with our results **[18]**.

On the other hand, In Mallat's study, the overall 28-day mortality was 55% (44/80), with 75% mortality within 28-days for high pCO 2 gap versus 42% for the normal group which is against our study **[13]**.

In addition, in Ospina-Tascón's study, the final sample was 85 patients, the 28-day mortality was 37.6%, and they calculated the mortality risk ratios at day 28 in patients with ScvO $_2$ >_70% and persistent high pCo $_2$ gap and was considered significant **[20]**.

PCO2 gap and Hemodynamics:

According to MAP, in our result the relationship between MAP and PCO 2 gap was not significant between both groups at T0, T6, T12 and T18 and there were significant improvement observed in normal gap group from T24.

In Vallée's study, performed prospective observational case series study on septic shock patients with ScvO $_2$ >70% after early resuscitation in the emergency unit evaluating pCO 2, MAP, HR and lactate every 6 hours over 12 hours (T0, T6 and T12), MAP was insignificantly different in both groups at T0, T6 and T12 and that is consistent with first 12 hours in our study **[18]**.

In Ospina-Tascón's study, performed on septic shock patients and collect measurements of pCO 2 gap, lactate and hemodynamics at T0 and 6 hours (T6), 12 hours (T12) and 24 hours (T24) later. According to pCO 2 gap developed during the first 6 hours of resuscitation patients were classified into 4 groups: Persistently high PCO 2 gap (high at T0 and T6); increasing pCO 2 gap (normal at T0 and high at T6); decreasing pCO 2 gap (high at T0 and normal at T6); persistently normal (normal at T0 and T6). Patients with decreasing pCO 2 gap had significantly improvement in MAP than patients with persistent high pCO 2 gap at T6 **[20]**.

AS regard to HR, our study show no significant difference in both groups at T0, T6, T12, T18 and there was significantly higher HR in high gap group than low gap group from T24 to T120. This is explained by the compensatory sympathetic stimulation which increases heart rate in hypoxic hypoperfused patients to maintain cardiac output and organ perfusion.

In Mallat's study, HR was insignificantly different in both groups at T0 and at T6 which support our results in first 6 hours of study **[13]**.

In Ospina-Tascón's study, HR was insignificantly different in both high and normal gap groups at T0 and T6 which agrees with our results in first 6 hours **[20]**.

Concerning Lactate, in our study, Lactate was insignificantly different in both high and low gap groups at T0 and displayed significant decrease in normal gap group than high gap group from T6 to T120. These results suggest that the presence of a high P (CV-a) CO 2 value could be a useful tool to identify patients who still remain inadequately resuscitated despite a ScvO $_2$ larger than 70% have already been reached.

This came in accordance withVallée F's study, there was no correlation between pCO 2 gap and lactate concentration at T0. From T0 to T12 the clearance of lactate concentration was significantly larger in low gap group than high gap group **[18]**.

In addition, in Mallat's study, as our study no significant difference in lactate in both high and low gap groups at T0, from T0 to T6, lactate decrease was significantly greater in patients reached normal pCO 2 gap at T6 **[13]**.

As regard to CVP, in our study, CVP was insignificantly different at all-time points from T0 to T120.

Similarly, In Du's study, revealed that CVP was insignificantly different in both high and low gap groups on admission at T0 and after 6hr of resuscitation at T6 **[21]**.

By contrast, In Ospina-Tascón G's study, CVP showedno significant differnce in both high and low gap groups at T0, but after resuscitation (T6) there was a significant increase in CVP in patients with persistent high gap more than in patients with decreasing gap.

In our study, p (CV-a) CO_2 showed a significant difference in both high and low gap groups at each point from T0 to T120.

In Vallée F's study, low gap group patients had a significantly lower pCO_2 gap than patients in high gap group at T0, T6 and T12 **[18]**.

In Mallat's study, p (CV-a) CO_2 was significantly higher in the group of patients with high versus normal pCO_2 gap **[13]**.

In terms of $Scvo_2$, in our study, there was no significant difference in $Scvo_2$ and pCo_2 gap between both high and low gap groups at all-time points.

In agreement with this, in Vallée F's study, all patients had $Scvo_2$ larger than 70% with no statistical difference between groups at T0, T6 and T12.

In Van Beest's study, there was a significant relationship in $Scvo_2$ and pCo_2 gap between both high and low gap groups on admission at T0 but after resuscitation there was no significant difference at T6, T 12, T 18, T24 **[22]**.

$ScvO_2$ have been well accepted as target to guide resuscitation in sepsis. However, sometimes it is not sufficient to reflect tissue perfusion as when capillary shunting occurred, $ScvO_2$ could be elevated and mask tissue hypo perfusion. Recently, P (v-a) CO_2 has gained attention as a complementary tool to reflect global perfusion in the resuscitation of septic shock patients when $ScvO_2$ is more than 70%, however We are aware that complementary studies are warranted in order to confirm our results.

Conclusion:

Targeting $ScvO_2$ more than 70% alone may not be sufficient to monitor perfusion in septic shock patients, our results suggest that the persistence of high Pv-aCO_2 during the early resuscitation of patients in septic shock is associated with significant higher multi organ dysfunction, higher lactate concentrations, lower MAP and poor outcomes, so the combination of PCO_2 gap and $ScvO_2$ may provide additional information about hemodynamics and the ability to clear lactate, Further research is required to determine the best use of this parameter as a treatment end-point; The predictive value for outcome of the central venous pCO_2 difference is questionable but persistence of an increased central venous pCO_2 difference after 24h of therapy seems to enhance the likelihood of bad outcome so the importance of PCO_2 gap for outcomes might warrant its inclusion as a target in goal-directed treatment protocols.

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فرق الوريدى المركزى إلى الشريانى لثانى أكسيد الكربون كاداه تكميلية للعلاج الموجه نحو الهدف فى الصدمة الانتانيه

الخلفية : الصدمة هى حالة حيوية تهدد الحياة تتميز فى معظم الأحيان بأنخفاض ضغط الدم، ويمكن أيضاً أن تكون مصحوبة بتغيرات فى علامات الحيوية الأخرى أو وجود ارتفاع فى مستويات اللاكتات فى الدم، ومن المهم أن يحدد الطبيب بسرعة السبب الكامن لهذه الحالة حتى يتم اتخاذ التدخلات والعلاج المناسب.

هدف العمل : تحقيق العلاقة بين فجوة ثانى أكسيد الكربون وتركيز اللاكتات فى الدم ومعدل الوفيات خلال ٢٨ يوماً، بالإضافة إلى فائدة هذه العلا قة كعامل تنبؤى.

المرضى والطرق : أجريت هذه الدراسة على ٣٠ مريضاً بصدمة تعفنية فى وحدة العناية المركزة العامة فى مستشفيات جامعة عين شمس من ديسمبر ٢٠٢٢ إلى مايو ٢٠٢٣، حيث تم تقسيمهم إلى مجموعتين وفقاً لفجوة ثانى أكسيد الكربون إلى فجوة طبيعية وفجوة عالية بعد استلام العلاج المبكر والوصول إلى مستوى $ScvO_2 \geq 70\%$.

النتائج : لم تظهر علاقة ذات دلالة بين درجة الصدمة وفجوة ثانى أكسيد الكربون فى الفترة الأولى من ١٢ ساعة من الدخول، ولكن بعد ٢٤ ساعة وحتى نهاية الدراسة، كانت لدى المرضى ذوى فجوة ثانى أكسيد الكربون العالية درجة صدمة نسبية أعلى. أظهرت الدراسة أيضاً أنه لا توجد علاقة ذات دلالة بين مؤشر APACHE II وفجوة ثانى أكسيد الكربون عند الدخول ، ولكن هناك زيادة معنوية فى درجة APACHE II فى مجموعة الفجوة العالية بعد ٤٨ ساعة حتى نهاية الدراسة. فى هذه الدراسة، لم تظهر علاقة ذات دلالة بين معدل وفيات المستشفى وفجوة ثانى أكسيد الكربون بين الحالات المدروسة. ولم تظهر علا قة ذات دلالة بين معدل الوفيات خلال ٢٨ يوماً وفجوة ثانى أكسيد الكربون بين الحالات المدروسة. كشفت هذه الدراسة أن هناك علا قة ذات دلالة بين ضغط الدم المتوسط وفجوة ثانى أكسيد الكربون بعد ٢٤ ساعة من الدخول وحتى نهاية الدراسة، حيث يكون ضغط الدم المتوسط أقل فى جموعة الفجوة العالية. كشفت هذه الدراسة أيضاً أن هناك علاقة ذات دلالة بين معدل ضربات القلب وفجوة ثانى أكسيد الكربون بعد ٢٤ ساعة من الدخول وحتى نهاية الدراسة، حيث تكون معدل ضربات القلب أعلى فى مجموعة الفجوة العالية. فى هذه الدراسة، كان هناك انخفاض معنوى فى مستوى اللاكتات فى مجموعة الفجوة الطبيعية بعد ٦ ساعات من البدء. ولم تظهر علاقة ذات دلالة بين الضغط الوريدى المركزى وفجوة ثانى أكسيد الكربون بين الحالات المدروسة. أظهرت هذه الدراسة أيضاً أنه لا توجد علاقة ذات دلالة بين مستوى $ScvO_2$ وفجوة ثانى أكسيد الكربون بين الحالات المدروسة.

الأستنتاج : قد لا يكون استهداف مستوى $ScvO_2$ أكثر من ٧٠٪ وحدة كافياً لمراقبة التروية فى مرضى الصدمة التعفنية، تشير نتائجنا إلى أن استمرار وجود فجوة $Pv\text{-}aCO_2$ عالية أثناء إعادة الإنعاش المبكر للمرضى فى حالة صدمة التعفن يرتبط بزيادة كبيرة في اضطراب وظائف الأعضاء المتعددة وزيادة تركيز اللاكتات وانخفاض ضغط الدم المتوسط وسوء النتائج، لذا يمكن أن يوفر توافر فجوة ثانى أكسيد الكربون و $ScvO_2$ معلومات إضافية حول الديناميات الهيموديناميةوالقدرة على تخليص اللاكتات، ويتطلب الأمر مزيداً من البحث لتحديد أفضل استخدام لهذا المعلم كهدف للعلاج، القيمة التنبؤية لفرق ثانى أكسيد الكربون فى الوريد المركزى مشكوك فيها، ولكن استمرار زيادة فرق ثانى أكسيد الكربون فى الوريد المركزى بعد ٢٤ ساعة من العلاج يبدو أنه يزيد من احتمالية حدوث نتائج سيئة، لذا فإن أهمية فجوة ثانى أكسيد الكربون للنتائج قد تبرر تضمينها كهدف فى بروتوكولات العلاج الموجهة نحو الأهداف.