



# CO<sub>2</sub> gap changes compared with cardiac output changes in response to intravenous volume expansion and/or vasopressor therapy in septic shock

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**Background.** The difference in partial pressure of carbon dioxide (PCO<sub>2</sub>) between mixed or central venous blood and arterial blood, known as the ΔPCO<sub>2</sub> or CO<sub>2</sub> gap, has demonstrated a strong relationship with cardiac index during septic shock resuscitation. Early monitoring of the ΔPCO<sub>2</sub> can help assess the cardiac output (CO) adequacy for tissue perfusion.

**Objectives.** To investigate the value of ΔPCO<sub>2</sub> changes in early septic shock management compared with CO.

**Methods.** This observational prospective study included 76 patients diagnosed with septic shock admitted to Cairo University Hospital's Critical Care Department between December 2020 and March 2022. Patients were categorised by initial resuscitation response, initial ΔPCO<sub>2</sub> and 28-day mortality. The primary outcome was the relationship between the ΔPCO<sub>2</sub> and CO changes before and after initial resuscitation, with secondary outcomes including ICU length of stay (LOS) and 28-day mortality.

**Results.** Peri-resuscitation ΔPCO<sub>2</sub> changes predicted a ≥15% change in the cardiac index (CI) (area under the curve (AUC) 0.727; 95% CI 0.614 - 0.840) with 66.7% sensitivity and 62.8% specificity. The optimal ΔPCO<sub>2</sub> change cut-off value was <-1.85, corresponding to a <-22% threshold for a 15% cardiac index increase. The PCO<sub>2</sub> gap ratio (gap/gap ratio of T1- PCO<sub>2</sub> gap to T<sub>0</sub>-PCO<sub>2</sub> gap) also predicted a ≥15% change in cardiac index (AUC 0.745; 95% CI 0.634 - 0.855) with 63.6% sensitivity and 79.1% specificity. The optimal CO<sub>2</sub> gap/gap ratio cut-off value was <0.71. A significant difference in 28-day mortality was noted based on the gap/gap ratio.

**Conclusion.** Peri-resuscitation ΔPCO<sub>2</sub> and the gap/gap ratio are useful non-invasive bedside markers for predicting changes in CO and preload responsiveness.

**Keywords.**

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## Contribution of the study

The current study provides an insight to the PCO<sub>2</sub> gap changes during and after early resuscitation of septic shock patients, which correlate to cardiac output changes and might also serve as a fluid responsiveness indicator.

The difference in partial pressure of carbon dioxide (PCO<sub>2</sub>) between mixed or central venous blood and arterial blood (ΔPCO<sub>2</sub>) is correlated with patient outcome and mortality.<sup>[1]</sup> The ΔPCO<sub>2</sub> is correlated with patient outcome and mortality.<sup>[2]</sup> Mixed ΔPCO<sub>2</sub> is inversely correlated with the cardiac index. Therefore, substituting central for mixed ΔPCO<sub>2</sub> is an accepted alternative.<sup>[3]</sup> One goal of acute circulatory failure treatment is to increase cardiac output.<sup>[4]</sup> Measurements of central venous oxygen saturation (S<sub>cv</sub>O<sub>2</sub>) and ΔPCO<sub>2</sub> are recommended to assess cardiac output adequacy and guide therapy.<sup>[5]</sup> A ΔPCO<sub>2</sub> value of >6 mmHg indicates insufficient tissue blood flow, even when S<sub>cv</sub>O<sub>2</sub> is >70%.<sup>[1]</sup>

This study aimed to investigate the value of ΔPCO<sub>2</sub> changes in early septic shock management compared with cardiac output.

## Methods

### Study design and patients

This observational prospective cohort non-randomised study was

conducted on 76 consecutive adult patients admitted to the critical care department of Cairo University Hospital between December 2020 and March 2022. The patients had septic shock and elevated blood lactate levels >2 mmol/L requiring fluid resuscitation and/or vasopressor drug infusion. The study was approved by the ethical committee of the faculty of medicine, Cairo University (N-194-2019) and registered on clinicaltrials.gov [NCT05578534]. Written informed consent was obtained from the patient's first-degree relatives.

### Inclusion and exclusion criteria

Patients with septic shock were included and were clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mmHg or greater and serum lactate level greater than 2 mmol/L (>18 mg/dL).<sup>[6]</sup> Patients with advanced cardiac (severe and persistent symptoms of heart failure, reduced LVEF ≤30% or severe valve abnormalities), pulmonary

(severe chronic obstructive pulmonary diseases), hepatic (liver cirrhosis with Child-Pugh C) or renal (stages 4 and 5 of the chronic kidney disease) diseases were excluded from the study (Fig. 1).

## Definitions

Sepsis is identified by suspected or confirmed infection and organ dysfunction as defined by the sequential organ failure assessment (SOFA).<sup>[6]</sup> Organ dysfunction is defined by an increase in SOFA score of 2 points or more (sepsis-related) from up to 48 hours before to up to 24 hours after the onset of suspected infection.<sup>[7]</sup>

## Data collection

Patients' demographic data, comorbidities, acute physiology and chronic health evaluation (APACHE) II score upon intensive care unit (ICU) admission, SOFA score (initial and after 48 hours), arterial lactate,  $\Delta\text{PCO}_2$ , blood gases (ABG, cv VBG) and vital signs were collected. Echocardiographic left ventricular outflow tract (LVOT) cardiac output and index data were measured. The microbiological data, source of sepsis, relevant laboratory data, vasopressor/inotropic support and ventilatory support were recorded.

The first set of measurements ( $T_0$ ) was taken after inserting invasive lines. The second set of measurements ( $T_1$ ) were obtained after the initial resuscitation, once the mean arterial pressure (MAP) stabilised. This stabilisation occurred either through administering a fluid bolus of up to 30 mL/kg intravenously, initiating vasopressor infusion or after 3 hours, whichever came first.

Lactate clearance was determined by calculating the percentage ratio of (initial arterial lactate level at  $T_0$  – arterial lactate level at

3 hours after treatment)/ arterial lactate level at  $T_0$ . The  $\Delta\text{PCO}_2$  (before and after resuscitation),  $\text{PCO}_2$  gap at  $T_1/\text{PCO}_2$  gap at  $T_0$  (gap/gap ratio) and cardiac index responsiveness were also calculated.

The patients were classified based on their initial  $\Delta\text{PCO}_2$ , resuscitation response and 28-day mortality into:

- High gap ( $P_{cv-a}\text{CO}_2 > 6$  mmHg) v. normal gap ( $P_{cv-a}\text{CO}_2 \leq 6$  mmHg)<sup>[8,9]</sup>
- Responsive (15% increase in the cardiac index or stable MAP was achieved) v. non-responsive (<15% increase in the cardiac index or a stable MAP was not achieved)<sup>[10,11]</sup>
- Survivors v. non-survivors
- Positive response to initial resuscitation, defined as an increase in the cardiac index by 15% or a stable MAP (identified by  $\text{MAP} \geq 65$  mmHg for 2 hours with no further fluid boluses or vasopressor increments), achieved within or after completion of the first 3 hours post-enrolment. This cut-off value was chosen based on previous studies.<sup>[10-11]</sup>

## Interventions and study procedures

Our patients were resuscitated according to surviving sepsis campaign recommendations within 1 hour of recognition. The study cohort was included immediately on admission to the ICU and after insertion of invasive lines ( $T_0$ ).

The resuscitation targets were  $\text{MAP} \geq 65$  mmHg, urine output  $\geq 0.5$  mL/kg/min,  $S_{cv}\text{O}_2 \geq 70\%$ , normalisation or significant decrease of serum lactate concentration (a decrease of >10% after 3 hours of early resuscitation). Vasopressors were administered during or after fluid resuscitation if MAP could not be maintained.

Additionally, infusion of dobutamine was initiated in cases of myocardial dysfunction or ongoing hypoperfusion despite optimising intravascular volume. Ventilation parameters and sedation drug settings were kept unchanged during the volume expansion (VE).

## Outcomes

The primary outcome was to evaluate the response of the  $\Delta\text{PCO}_2$  to initial resuscitation and its value for assessing fluid responsiveness in the ICU. Secondary outcomes included ICU length of stay (LOS) and 28-day ICU mortality.

## Statistical analysis and sample size calculation

Based on the previous studies and using G power software version 3.1.3 (Heinrich-Heine-Universität, Germany) with a power of 0.90 and an alpha error of 0.05, the expected mean difference between low and high  $\Delta\text{PCO}_2$  patients for the cardiac index was used to calculate a required sample size of 69 patients. Factoring in a withdrawal/non-evaluable participant rate of 10%, 76 patients were recruited.

The analysis of the data was done using SPSS version 25 (IBM Corp, USA). Quantitative variables were presented as mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate. Qualitative variables were presented as count and percentage. A paired-sample Student's *t*-test was used to compare quantitative variables at two different time points. Student's *t*-test or Mann-Whitney-U test was used to compare quantitative data between two independent groups. The  $\chi^2$  test or Fisher's exact test was used to compare qualitative data between different groups. Pearson's and Spearman's correlation tests were used to measure linear correlation between different quantitative variables. The operating characteristic curve (ROC) analysis was used to measure the predictive ability of different quantitative variables and to identify the best cut-off values.  $P < 0.05$  was considered statistically significant.

## Results

Slightly more than half (53%) of all enrolled patients ( $n=40/76$ ) responded to resuscitation, while 47% ( $n=36/76$ ) were non-responsive. In the studied population, the respiratory system was the most common source of sepsis, with pneumonia emerging as the most common diagnosis (Tables 1 and 2).

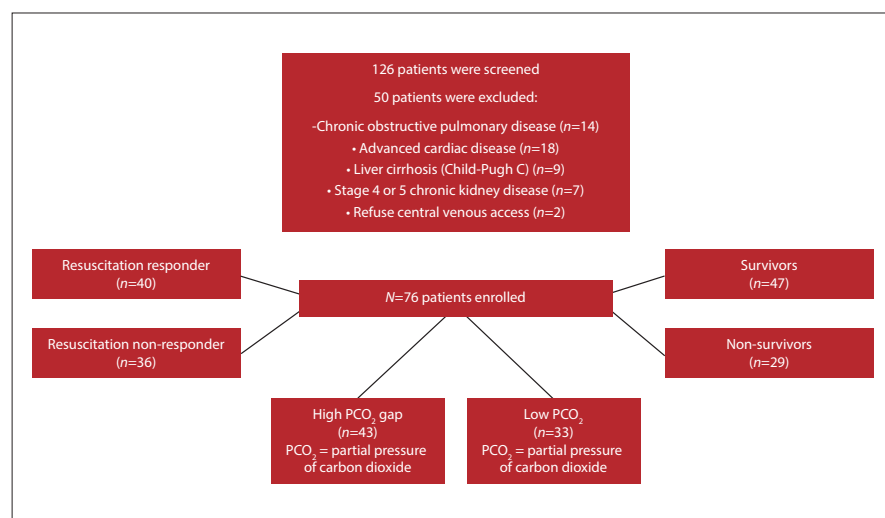


Fig. 1. Flow chart of the study methods.

### Correlation between changes in cardiac index and $\Delta\text{PCO}_2$

A statistically significant negative correlation was found between pre and post-resuscitation cardiac index change and corresponding  $\Delta\text{PCO}_2$  change ( $r = -0.562, p < 0.001$ ).

### Validity of $\Delta\text{PCO}_2$ change to predict 15% or more change in cardiac index

Table 3 provides the predictive characteristics of  $\Delta\text{PCO}_2$  and gap/gap ratio. The optimal threshold values are also provided.

### Comparison between survivors and non-survivors

The post-resuscitation  $\Delta\text{PCO}_2$  was elevated significantly among non-survivors, while a significant decrease was observed among survivors. The gap/gap ratio was significantly higher and lactate clearance was significantly lower among non-survivors (Table 4).

### $\Delta\text{PCO}_2$ at T1 and gap/gap ratio for predicting mortality at day 28

The best predictor of day 28 mortality was a gap/gap ratio  $> 0.75$ . The ROC-AUC was 0.855 (95% CI 0.767 - 0.943,  $p < 0.001$ ), with 82.8% sensitivity and 66% specificity. The performance of  $\Delta\text{PCO}_2$  at T<sub>1</sub> exhibited moderate accuracy (ROC-AUC 0.796; 95% CI 0.672 - 0.920), with a sensitivity of 79.3% and specificity of 72.3%, using a threshold value of 5.85.  $\Delta\text{PCO}_2$  at T<sub>0</sub> was found to be non-predictive ( $p = 0.209$ ). The gap/gap ratio was significantly associated with SOFA score, arterial lactate and APACHE II score (Table 5) Fig. 2).

## Discussion

The cardiac output is adequate when it is matched to global metabolic demand. This could be assessed by  $\Delta\text{PCO}_2$  calculation.<sup>[12]</sup> Septic shock patients can remain under-resuscitated despite optimising O<sub>2</sub>-derived parameters.<sup>[1,12]</sup>

The percentage change in the cardiac index was negatively correlated with the peri-resuscitation changes in  $\Delta\text{PCO}_2$  and gap/gap ratio (pre or post-resuscitation).

Consistent with our findings, Vallée *et al.*<sup>[13]</sup> demonstrated an inverse correlation between cardiac index, as measured by PiCCO monitor, and P<sub>(cv-a)</sub> CO<sub>2</sub> values at the different study times. In contrast, Ospina-Tascon *et al.*<sup>[8]</sup> reported a low agreement between cardiac output, as measured by pulmonary artery catheter (PAC), and P<sub>v-a</sub> CO<sub>2</sub> ( $r^2 = 0.025$ ,

$p < 0.01$ ) at different points of resuscitation. Furthermore, Van Beest *et al.*<sup>[14]</sup> observed a weak relationship between  $\Delta\text{PCO}_2$  and cardiac index.

In our study, we observed a significant negative correlation between the cardiac output trend and the  $\Delta\text{PCO}_2$  trend during early septic shock resuscitation.

Our findings indicate that the percentage change in  $\Delta\text{PCO}_2$  (pre and post-resuscitation) in cases of septic shock, along with the gap/gap ratio, serve as reliable parameters for predicting changes in cardiac index ( $\geq 15\%$  percent increase) and consequently preload (fluid) responsiveness. Interestingly, using  $\Delta\text{PCO}_2$  to calculate the gap/gap ratio provided the best discrimination for cardiac index responsiveness better than the  $\Delta\text{PCO}_2$  change. The ROC curve determined a cut-off value of  $< 0.71$  for the CO<sub>2</sub> gap/gap ratio to predict preload responsiveness.

Furthermore, based on the mean  $\Delta\text{PCO}_2$  value observed (8.37 (SD 3.96)), the threshold of  $\Delta\text{PCO}_2$  decrease corresponding to a 15% increase in the cardiac index is  $< -22.1\%$  (the cut-off value determined earlier by  $< -1.85$ ).

Changes in  $\Delta\text{PCO}_2$  and the gap/gap ratio calculation could be used to predict preload responsiveness non-invasively without the need for specialised skills or expertise.

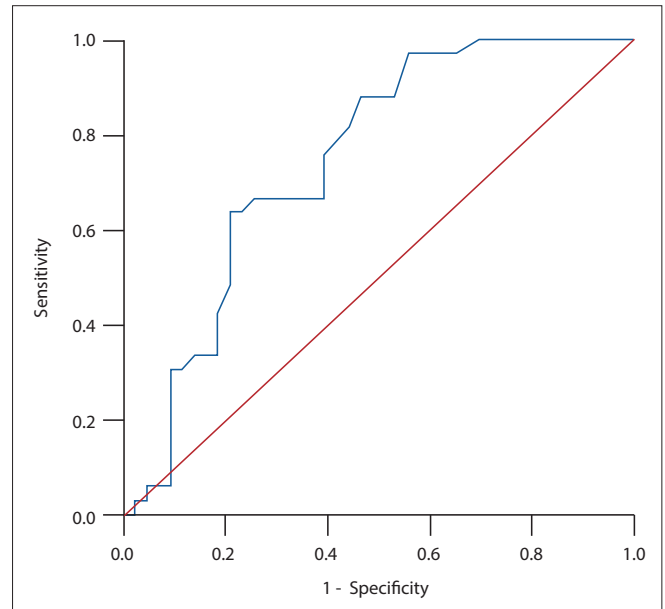


Fig. 2. Validity of the gap/gap ratio to predict cardiac index change.

Table 1. Comparison between responsive (group I) and non-responsive (group II) patients post-resuscitation

Variable	Group I (n=40), mean (SD)	Group II (n=36), mean (SD)	t <sup>†</sup> χ <sup>2‡</sup>	p-value
Age (years),	68.88 (14.60)	72.58 (19.0)	0.96 <sup>†</sup>	0.34
APACHE II	14.75 (4.59)	22.61 (5.64)	6.69 <sup>†</sup>	<0.01**
ICU Length of stay	9.45 (5.08)	7.75 (4.54)	1.53 <sup>†</sup>	0.13
MOD	6 (15.0%)	25 (69.4%)	23.26 <sup>‡</sup>	<0.01**
28 days mortality	4 (10.0%)	25 (69.4%)	28.37 <sup>‡</sup>	<0.01**
$\Delta\text{PCO}_2$ T <sub>0</sub>	8.06 (3.56)	8.47 (3.77)	0.48 <sup>‡</sup>	0.63
$\Delta\text{PCO}_2$ T <sub>1</sub>	4.92 (2.08)	8.28 (3.98)	4.69 <sup>‡</sup>	<0.01**
$\Delta\text{PCO}_2$ change	-3.1 (4.59)	-0.8 (0.70)	3.60 <sup>‡</sup>	<0.01**
Gap/gap ratio	0.65 (0.25)	0.90 (0.13)	4.58 <sup>‡</sup>	<0.01**

\*\*P<0.01

APACHE = acute physiology and chronic health evaluation; ICU = intensive care unit; MOD = Multiple Organ Dysfunction; PCO<sub>2</sub> = partial pressure of carbon dioxide;

T<sub>0</sub> = first set of measurements; T<sub>1</sub> = second set of measurements.

<sup>†</sup>Student t-test

<sup>‡</sup>χ<sup>2</sup>test (Fisher's exact test)

Similar to our findings, a recent study by Nassar *et al.*<sup>[15]</sup> investigated volume expansion (VE)-induced changes in central venous-to-arterial CO<sub>2</sub> difference ( $\Delta\text{-}\Delta\text{PCO}_2$ ) and central venous oxygen saturation ( $\Delta\text{S}_{\text{cv}}\text{O}_2$ ) as a reliable parameter of fluid responsiveness in sedated and mechanically ventilated septic patients. Responders were defined as patients with a >10% increase in cardiac index (transpulmonary thermodilution) after VE.  $\Delta\text{-}\Delta\text{PCO}_2$  and  $\Delta\text{S}_{\text{cv}}\text{O}_2$  were significantly correlated with  $\Delta$ cardiac index after VE ( $r = -0.30, p=0.03$  and  $r = 0.42, p=0.003$ , respectively). The optimal cut-off value (according to Youden index) for  $\Delta\text{-}\Delta\text{PCO}_2$  was  $\leq -23.5\%$ , with a sensitivity of 52% [95% CI 31 - 72%] and specificity of 87% [95% CI 68 - 97%].

Moreover, Pierrakos *et al.*<sup>[16]</sup> conducted a prospective evaluation of the effects of fluid bolus on venous-to-arterial carbon dioxide tension ( $\text{P}_{\text{va}}\text{CO}_2$ ) in critically ill patients with pre-infusion  $\text{P}_{\text{va}}\text{CO}_2 > 6$  mmHg. Fluid bolus caused a decrease in  $\text{P}_{\text{va}}\text{CO}_2$ , from 8.7 [7.6 - 10.9] mmHg to 6.9 [5.8 - 8.6] mmHg ( $p < 0.01$ ). This decrease in  $\text{P}_{\text{va}}\text{CO}_2$  occurred independently of the pre-infusion cardiac index.

These findings were corroborated by Mecher *et al.*<sup>[17]</sup> who found that the reduction in  $\text{P}_{(\text{v-a})}\text{CO}_2$  induced by VE was linked to an

increase in cardiac output specifically in patients with elevated  $\text{P}_{(\text{v-a})}\text{CO}_2$ . Additionally, they noted a correlation between VE-induced changes in cardiac output and changes in  $\text{P}_{(\text{v-a})}\text{CO}_2$  ( $r = -0.46, p < 0.01$ ). This confirms that in patients with septic shock,  $\Delta\text{PCO}_2$  is mainly associated with systemic blood flow rather than tissue hypoxia.

The trend of cardiac output and  $\Delta\text{PCO}_2$  changes before and after early resuscitation of septic shock could reflect the dynamic nature of the  $\Delta\text{PCO}_2$  rather than a static parameter. We recommend this approach based on the behaviour of  $\Delta\text{PCO}_2$  during resuscitation.

Sepsis-induced hypoperfusion may manifest as acute organ dysfunction and/or decreased blood pressure as well as increased serum lactate.<sup>[18]</sup> Volume resuscitation is the mainstay in the treatment of shock. To avoid ineffective or even deleterious VE, a resuscitation guided by a reliable volume status evaluation should be ascertained.<sup>[19]</sup> Rapid optimisation of volume status has been shown to improve outcomes, whereas extended fluid loading is associated with increased morbidity and mortality.<sup>[20,21]</sup>

The 28-day mortality was reported in 10% ( $n=4$ ) of responsive patients and 69.4% ( $n=25$ ) of non-responsive patients ( $p < 0.01$ ).

Our results showed that the overall 28-day mortality rate was 38% ( $n=29$ ), while the survival rate was 62% ( $n=47$ ).

When we calculated the ratio of  $\Delta\text{PCO}_2$  at  $T_1/\Delta\text{PCO}_2$  at  $T_0$ , expressed as the gap/gap ratio, a significant change was observed between low and high-gap patients ( $p=0.03$ ). The higher ratio among low-gap patients suggests that there was no substantial resuscitation-induced change in  $\Delta\text{PCO}_2$  in these patients compared with the high-gap patients.

It was proposed that the gap/gap ratio could be classified into three categories:  $>1$  indicating an increase in  $\Delta\text{PCO}_2$  after initial resuscitation,  $<1$  indicating a decrease in  $\Delta\text{PCO}_2$  after initial resuscitation and  $= 1$  or static consistent with stable  $\Delta\text{PCO}_2$  after initial resuscitation.

The gap/gap ratio serves as an indicator of the trend in  $\Delta\text{PCO}_2$  levels during resuscitation, reflecting prognosis and outcome. Non-survivors exhibited a higher ratio, suggesting less resuscitation-induced change in  $\Delta\text{PCO}_2$  compared with survivors.

We found that a gap/gap ratio  $>0.75$  could predict 28-day mortality with a sensitivity of 82.8% and specificity of 66%.

Also, there was a significant difference in 28-day mortality among all studied patients based on the gap/gap ratio ( $p < 0.001$ ). Specifically, the mean gap/gap ratio for non-survivors was 1.09 (0.46), whereas for survivors it was 0.67 (0.18).

Similar to our findings, the high  $\Delta\text{PCO}_2$  correlation with mortality and clinical outcome was reported by a systematic review of 10 prospective studies.<sup>[2]</sup>

The cardiac index change was markedly lower in non-survivors. Interestingly, although there was no significant difference in  $\Delta\text{PCO}_2$  at  $T_0$  between survivors and non-survivors,  $\Delta\text{PCO}_2$  at  $T_1$  was significantly higher in the non-survivors ( $p < 0.001$ ). This discrepancy highlights the impact of early resuscitation of septic shock on  $\Delta\text{PCO}_2$  levels. The persistent elevation of  $\Delta\text{PCO}_2$  despite resuscitation was indicative of

**Table 2. Patients' demographic data**

Variable	Mean (SD)
Age	70.63 (16.82)
BSA (m <sup>2</sup> )	1.73 (0.17)
Height (cm)	164.76 (6.13)
Weight (kg)	66.54 (12.20)
	<i>n</i> (%)
Sex	
Male	40 (52.6)
Female	36 (47.4)
Venue	
Ward	44 (57.9)
ER	32 (42.1)
Site of infection	
Respiratory	39 (51.3)
Urinary tract	5 (6.6)
Skin/soft tissue	5 (6.6)
Abdominal	7 (9.2)
More than one site	20 (26.3)
Microbiology	
Culture-negative	30 (39.5)
Culture-positive	46 (60.5)
Comorbidities	
Diabetes mellitus	55 (72.4)
Hypertension	58 (76.3)
Renal impairment	20 (26.3)
Cardiac disease	35 (46.1)

SD = standard deviation; BSA = body surface area; ER = emergency room.

**Table 3.  $\Delta\text{PCO}_2$  change and gap/gap ratio for the prediction of a 15% increase in cardiac index**

Variable	$\Delta\text{PCO}_2$ change	Gap/gap ratio
Sensitivity	66.7%	63.6%
Specificity	62.8%	79.1%
AUC-ROC	0.727 (95% CI 0.614 - 0.84)	0.745 (95% CI 0.634 - 0.855)
Negative predictive value	71.1%	73.9%
Positive predictive value	57.9%	70%
Threshold value	$< -1.85$	$< 0.71$

$\text{PCO}_2$  = partial pressure of carbon dioxide; AUC-ROC = area under receiver operating characteristic curve; CI = confidence interval.

**Table 4. Comparison between survivors and non-survivors**

Variable	Survivors (n=47), mean (SD)	Non-survivors (n=29), mean (SD)	t <sup>†</sup>	p-value
Age	68.47 (17.45)	74.14 (15.38)	1.44	0.155
APACHE II (T <sub>0</sub> )	15.04 (4.42)	24.03 (5.20)	8.05	<0.001***
SOFA T <sub>0</sub>	8.19 (1.96)	12.10 (1.59)	9.05	<0.001***
SOFA score (after 48 hours)	5.30 (1.73)	14.28 (2.89)	15.14	<0.001***
A. BE T <sub>0</sub>	-5.13 (3.55)	-7.40 (3.27)	2.80	0.007**
A. BE T <sub>1</sub>	-3.13 (2.84)	-7.93 (3.90)	5.76	<0.001***
CV O <sub>2</sub> sat T <sub>0</sub>	68.77 (7.91)	68.71 (10.08)	0.03	0.976
CV O <sub>2</sub> sat T <sub>1</sub>	82.11 (4.12)	75.88 (6.99)	4.40	<0.001***
ΔPCO <sub>2</sub> T <sub>0</sub>	7.82 (3.41)	8.96 (3.94)	1.34	0.185
ΔPCO <sub>2</sub> T <sub>1</sub>	4.93 (2.10)	9.07 (3.92)	5.24	<0.001***
Gap/gap ratio	0.67 (0.18)	1.09 (0.46)	4.67	<0.001***
Arterial lactate T <sub>0</sub>	3.79 (1.02)	5.66 (3.25)	3.00	0.005**
Arterial lactate T <sub>1</sub>	2.19 (0.67)	6.52 (3.77)	6.12	<0.001***
Arterial lactate clearance <sup>‡</sup>	0.41 (0.31 - 0.51)	-0.14 (-0.25 - 0.02)	6.12	<0.001***

\*\*p&lt;0.01

\*\*\*p&lt;0.001

APACHE = acute physiology and chronic health evaluation; T<sub>0</sub> = first set of measurements; SOFA = sequential organ failure assessment; T<sub>1</sub> = second set of measurements; PCO<sub>2</sub> = partial pressure of carbon dioxide, O.

†Students t-test

‡Mann-Whitney-U test presented as median and interquartile range.

**Table 5. Comparison of patients with a gap/gap ratio less than and more than 0.75**

Variable	Gap/gap ratio (<0.75) n=36	Gap/gap ratio (>0.75) n=40	t <sup>†</sup> χ <sup>2‡</sup>	p-value
SOFA T <sub>0</sub>	9.00 (2.12)	10.30 (2.92)	2.24	0.029*
SOFA (after 48 hours)	6.64 (2.96)	10.60 (5.58)	3.92	<0.001***
APACHE II	16.11 (4.27)	20.60 (7.31)	3.31	0.002**
Arterial lactate T <sub>0</sub>	3.94 (1.12)	5.02 (2.96)	2.15	0.036*
Arterial lactate T <sub>1</sub>	2.47 (0.97)	5.07 (3.91)	4.08	<0.001***
Arterial lactate clearance <sup>§</sup>	0.40 (0.25 - 0.52)	0.02 (-0.17 - 0.40)	3.39	0.001**
Vasopressors need	33 (91.7%)	38 (95.0%)	0.35‡	0.66
28-days mortality	5 (13.9%)	24 (60.0%)	17.07	<0.001***

\*p&lt;0.05

\*\*p&lt;0.01

\*\*\*p&lt;0.001

SOFA = sequential organ failure assessment; T<sub>0</sub> = first set of measurements; APACHE = acute physiology and chronic health evaluation; T<sub>1</sub> = second set of measurements.

†Student t-test

‡χ<sup>2</sup> test

§Mann-Whitney-U test presented as median and interquartile range.

poor outcomes. This suggests a more severe disease state with deranged hemodynamic, metabolic and tissue perfusion parameters.

Similarly, Ronflé *et al.*<sup>[22]</sup> found that increased ΔPCO<sub>2</sub> was associated with poor outcomes in the early phase of septic shock, independent of S<sub>v</sub>O<sub>2</sub> or serum lactate concentrations.

In our study, post-resuscitation ΔPCO<sub>2</sub> predicted the 28-day mortality with a sensitivity of 79.3% and specificity of 72.3%, using a cut-off value of 5.85.

Consistent with our findings, previous studies have validated an association between elevated ΔPCO<sub>2</sub> and increased ICU mortality. Ronflé *et al.*<sup>[22]</sup> reported a P<sub>(v-a)</sub>CO<sub>2</sub> of 6.5 (3.1) mmHg and 5.3 (2.9) mmHg among ICU non-survivors and survivors (p=0.024), respectively. A threshold of P<sub>(v-a)</sub>CO<sub>2</sub> >5.8 mmHg was associated with an increased ICU mortality rate (57% v. 33%, p=0.012). Persistently high P<sub>(v-a)</sub>CO<sub>2</sub> was also associated with an increased risk of ICU mortality. Vallée *et al.*<sup>[13]</sup> also demonstrated a higher mortality in patients with high P<sub>(v-a)</sub>CO<sub>2</sub> (>6 mmHg).

Ospina-Tascon *et al.*<sup>[8]</sup> conducted a prospective study on ΔPCO<sub>2</sub> in septic shock patients. They found that patients with persistently high and increasing P<sub>v-a</sub>CO<sub>2</sub> at T<sub>6</sub> exhibited significantly high SOFA scores on day 3 (p<0.001) and increased mortality rates on day 28 (p<0.001), compared with patients with normal P<sub>v-a</sub>CO<sub>2</sub> at T<sub>6</sub>.

### Study limitations

Our study has some limitations. First, this was a single-centre observational study without randomisation. Second, the selection of the cut-off values, indicating an increase in stroke volume ≥15% with fluid infusion to signify fluid responsiveness, was based on values used in previous studies. However, it is worth noting that the results and predictive effects of resuscitation on ΔPCO<sub>2</sub> might have been different if another cut-off value had been chosen. Similarly, the choice of the cut-off value for ΔPCO<sub>2</sub> (> or <6 mmHg) to indicate high or normal ΔPCO<sub>2</sub> might have impacted the results. Third, central blood samples were chosen for measuring ΔPCO<sub>2</sub> rather than mixed venous samples

owing to the simplicity of acquisition and practicality in routine clinical settings. Fourth, the study focused solely on examining the behaviour of  $\Delta\text{PCO}_2$  without employing it as a therapeutic intervention. Also, patient management and paired blood gas samples were conducted according to the usual ICU practice without intervention from the researchers. Finally, semi-invasive cardiac output measurements like pulse contour analysis catheters were not available at the time of the study. While we aimed to use two methods for cardiac output measurement (non-invasive and semi-invasive), such as echo-Doppler and PiCCO, unfortunately PiCCO catheters or similar methods were not available at the time.

## Recommendations

$\Delta\text{PCO}_2$  is a very useful non-invasive bedside laboratory marker capable of predicting cardiac output changes and guiding therapy during the early resuscitation of septic shock patients.

## Conclusion

The  $\Delta\text{PCO}_2$  is an easily measurable method for evaluating fluid responsiveness in the ICU. The  $\text{PCO}_2$  gap or peri-resuscitation gap/ gap ratio correlates with changes in cardiac output in septic shock patients during and following early resuscitation. Resuscitation responders showed a significant decrease in  $\Delta\text{PCO}_2$  after resuscitation.

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