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# Prognostic Significance of Central Venous Compared to Arterial Carbon Dioxide Difference in Postoperative Critically Ill Patients

**Nashwa M. Abed[1], Mohamed S. Asker[2], Sherif M. Samir[1], Mahmoud M. Kenawy*[1]**
[1]Department of Critical Care Medicine, Faculty of Medicine, Cairo University, Egypt
[2]Department of Critical Care Medicine, Faculty of Medicine, Al-Azhar University, Egypt
***Corresponding author:** Mahmoud M. Kenawy, **Mobile:** (+20) 01006029033, **E-Mail:** drqenawi@kasralainy.edu.eg

## ABSTRACT

**Background:** Following major surgery, hypoxia is considered a key contributor to organ failure postoperatively, as well as mortality. Decreased oxygen saturation in the central veins ($ScvO_2$) has been linked to organ failure in the postoperative period. However, there are data suggesting that variables based on oxygen availability have a weak relationship with anaerobic metabolism.

**Objective:** To evaluation of clinical significance of elevated values of the central venous to arterial carbon dioxide gap ($PCO_2$ gap) among critical care unit cases at high risk for complications following surgery.

**Patients and Methods:** Our study was randomized controlled trial (RCT) study, performed in El Sahel Teaching Hospital in duration from March 2019 to March 2021. We included 30 postoperative patients. Patients were categorized according to presence of complication to group I and II, and according to $PCO_2$ gap to groups A and B.

**Results:** Cases who had high $PCO_2$ gap equal or more than 6 mmHg experienced significantly extended duration of mechanical ventilation (median1 day among group I vs. 0 days among group II, p-value = 0.017), length of ICU stay (median 5.5 days among group I vs. 4 days among group II, p-value = 0.03), length of hospital stay (median 17.5 days among group I vs. 11.5 days among group II, p-value <0.001), and organ failure (15 cases among group I vs. 1 case among group II, p-value = 0.007).

**Conclusion:** High-risk surgical patients benefited from fewer complications, shorter times on mechanical ventilation and in the intensive care unit (ICU), and shorter hospital stays when their hemodynamic status was optimized after surgery using a $PCO_2$ gap of less than 6 mmHg as a guide.

**Keywords:** Arterial carbon dioxide, Central venous carbon dioxide, $PCO_2$ gap, Postoperative critically ill.

## INTRODUCTION

Postoperative organ failure and mortality are directly related to tissue hypoxia following major surgery[1]. Patient outcome improves when hemodynamic therapy is optimized depending on the desired level of oxygenation and/or perfusion[2].

Postoperative organ failure is associated with decreased central venous $O_2$ saturation ($ScvO_2$) [3]. However, there is a weak relationship between $O_2$-derived variables and anaerobic metabolism[4]. In the context of decreased $O_2$ extraction capacities, tissue hypoxia can exist despite a normal or high $ScvO_2$ (higher than 75%)[5].

Excess $CO_2$ clearance from tissues can be measured by the $PCO_2$ gap, which is inversely proportional to cardiac output (CO)[6]. Thus, inadequate tissue perfusion due to decreased blood flow is the primary predictor of $PCO_2$ gap growth. On the other hand, large surgical trauma $PCO_2$ gaps have only been studied in a limited fashion[7].

This study aimed to evaluation of clinical significance of elevated values of the central venous to arterial carbon dioxide gap ($PCO_2$ gap) among critical care unit cases at high risk for complications following surgery.

## PATIENTS AND METHODS

El Sahel Teaching Hospital was the site of this March 2019 to March 2021 randomized controlled trial (RCT). We included 30 postoperative patients, and further categorized them according to presence of complication to group I (with complications, n=20) and II (without complications, n=10), and according to $PCO_2$ gap to group A (high gap ≥6 mmHg, n=22) and B (normal gap <6 mmHg, n=8).

The following conditions were applied to all patients who underwent abdominal or vascular surgery: (i) Both demographic and surgical factors were taken into account; (ii) Minimum of three demographic factors; or (iii) Minimum of three surgical criteria and at least one intensive care unit (ICU) criterion.

### Demographic criteria included:

(i) Age ≥70 years, (ii) ASA (American Society of Anesthesiology) class equal or higher than 3, (iii) Severely nutritional problem, (iv) Past history of severe respiratory disease, (v) Chronic kidney failure, (vi) Chronic hepatic failure, (vii) Ischemic heart disease, and (viii) Malignancy. *Surgical criteria* included; (i) Major abdominal surgeries, (ii) Prolonged surgery equal or more than 8 hours, (iii) Urgent surgeries, (iv) Septic surgeries, (v) Vascular clamping for or more than 1 hour, or (vi) Esophagectomy, gastrectomies, small bowel resections, large bowel resections, hepatectomies, pancreaticectomies, intraabdominal vascular procedures, and other abdominal surgeries. *Intensive care criteria* included; (i) Shock, (ii) Acute respiratory failure, (iii) Hemorrhage (hemoglobin <7 g/dl), or (iv) Acute coronary syndrome.



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All patients have been subjected to; (i) Medical history taking, (ii) Clinical assessment using Simplified Acute Physiology Score (SAPS II score), (iii) Organ failure postoperatively assessment utilizing the Sequential Organ Failure Assessment (SOFA) score, (iv) Laboratory data collected immediately after ICU admission; $PCO_2$ gap, $ScvO_2$, $SaO_2$, $PaO_2$, serum lactate, serum bicarbonate and hemoglobin level.

The ICU course was recorded concerning catecholamine infusion, duration of mechanical ventilation (if needed), presence of organ failure or mortality. *Criteria of organ failure was*; (i) Circulation failure; injection of a catecholamine to keep the mean arterial pressure above 65 mm Hg after optimal fluid load, (ii) Acute respiratory failure; requirement to be mechanically ventilated, (iii) Acute renal injury, or (iv) Neurological impairment; stroke or delirium. ICU and total hospital stay times were also assessed.

The presence of postoperative complications was considered the primary outcome. These complications included sepsis, acute respiratory, renal, or cardiac failure, bleeding, ischemic events, organ failure, and death.

**Ethical approval:**

**The study was authorized by the El Sahel Teaching Hospital Ethical Committee for Intensive Care Medicine. All participants or their legal guardians gave written consent after receiving all information. The Helsinki Declaration was followed throughout the study's conduct.**

***Statistical analysis***

Information was analysed with SPSS 20.0 software (SPSS Inc., Chicago, Illinois, USA). Quantitative data were presented as mean and standard deviation for parametric data or median and range for nonparametric data. Qualitative data were presented as frequency and proportion. Statistically significant group comparisons of quantitative data were made using the independent-samples t-test for parametric data and Mann–Whitney U test for nonparametric data. Comparison of percentages was done using the chi-square ($X^2$) test. The optimal cut-off value for detection of sensitivity and specificity was determined, and the parameter's overall predictivity was determined, using receiver operating characteristic (ROC) curve analysis. $P<0.05$ was considered significant.

## RESULTS

We enrolled 30 patients: 17 men (57%) and 13 women (43%) who had mean age of 67.38±9.79 years and ASA class ≥3 in 18 patients. Malignancy and ischemic heart disease were the most common co-morbidities. Twenty-one patients had major abdominal surgeries and 12 patients presented with shock. (Table 1).

**Table (1):** Distribution of criteria among study population

| Criterion | No. | % |
|---|---|---|
| Age (years) | | |
| <70 years | 19 | 63.3 |
| ≥70 years | 11 | 36.7 |
| ASA class | | |
| Class <3 | 12 | 40.0 |
| Class ≥3 | 18 | 60.0 |
| Severely nutritional issues | 3 | 10.0 |
| History of previous severe respiratory disease | 3 | 10.0 |
| Chronic kidney failure | 2 | 6.7 |
| Chronic hepatic failure | 2 | 6.7 |
| Ischemic heart disease (angina or infarction) | 13 | 43.3 |
| Malignant neoplasia | 17 | 56.7 |
| Shock | 12 | 40.0 |
| Acute respiratory failure | 7 | 23.3 |
| Hemorrhage (hemoglobin lower than 7 g/dl) | 3 | 10.0 |
| Acute coronary syndrome | 3 | 10.0 |

Statistically significant differences in serum lactate, serum bicarbonate, $PaO_2$, and $PCO_2$ gap were found between the 2 groups in the present study (Table 2).

**Table (2):** Comparing cases with and without postoperative complications according to laboratory parameters

| Lab Parameter | Group I (n=20) | Group II (n=10) | p-value |
|---|---|---|---|
| Serum lactate (mmol/l) | 3.53±0.51 | 1.72±0.35 | <0.001* |
| Serum bicarbonate (mmol/l) | 17.30±2.67 | 19.90±2.06 | 0.012* |
| Hemoglobin (g/dl) | 10.51±1.13 | 10.88±1.13 | 0.406 |
| $PCO_2$ gap (mmHg) | 8.22±1.48 | 5.66±1.40 | <0.001* |
| $PcvCO_2$ (mmHg) | 47.92±4.63 | 48.21±4.48 | 0.870 |
| $PaCO_2$ (mmHg) | 39.55±3.73 | 42.54±4.04 | 0.053 |
| $ScvO_2$ % | 58.85±4.31 | 59.36±3.64 | 0.751 |
| $SaO_2$ % | 98.20±1.20 | 98.91±0.69 | 0.095 |
| $PaO_2$ (mmHg) | 88.78±8.17 | 102.72±12.58 | 0.002* |

*: Significant

Patients of group A experienced significantly longer duration of mechanical ventilation, length of ICU stay, length of hospital stay and organ failure (Table 3).

**Table (3):** Outcome of cases with high and normal $PCO_2$ gap

| Outcome | Group A (n=22) | Group B (n=8) | p-value |
|---|---|---|---|
| Total duration of MV, days[¥] | 1 (0-3) | 0 (0-0) | 0.017* |
| Length of ICU stay, days[¥] | 5.5 (3-8) | 4 (3-6) | 0.030* |
| Length of hospital stay, days[¥] | 17.5 (12-29) | 11.5 (7-17) | <0.001* |
| Organ failure | 15 (68.2%) | 1 (12.5%) | 0.007* |
| 28-day mortality | 2 (9.1%) | 0 (0%) | 0.377 |

[¥]Data are expressed median and interquartile range (IQR), *: Significant

The following table shows that $PCO_2$ Gap, SOFA score and serum lactate had a significant effect on the development of postoperative complications. (Table 4)

**Table (4):** Multiple linear regression model for postoperative complications

| | Unstandardized Coefficients | | Standardized Coefficients | 95% Cl for B | | T-test | |
|---|---|---|---|---|---|---|---|
| | B | Std. Error | Beta | Lower | Upper | t | p-value |
| Emergency surgery | -0.164 | 0.092 | -0.139 | -0.354 | 0.026 | 1.788 | 0.087 |
| $PCO_2$ gap | 0.060 | 0.029 | 0.237 | 0.000 | 0.120 | 2.074 | 0.048* |
| Lactate | 0.364 | 0.054 | 0.745 | 0.253 | 0.476 | 6.750 | <0.001* |
| Bicarbonate | 0.035 | 0.021 | 0.199 | -0.009 | 0.079 | 1.640 | 0.115 |
| SOFA at admission | 0.071 | 0.021 | 0.427 | 0.027 | 0.115 | 3.348 | 0.003* |
| SAPS II | -0.021 | 0.011 | -0.255 | -0.044 | 0.002 | 1.866 | 0.075 |

R-square=0.95, Model ANOVA: F=35.065, *: Significant

ROC curve showed that $PCO_2$ gap, serum lactate and SOFA score on admission were significantly correlated with postoperative complications (p-value = 0.048, <0.001, 0.003, respectively). The cutoff value was >6.8 mmHg for $PCO_2$ gap, >2.11 mmol/l for serum lactate and >2 for SOFA score on admission. Areas under the curve were 0.93, 0.99, and 1, respectively (Figure 1).

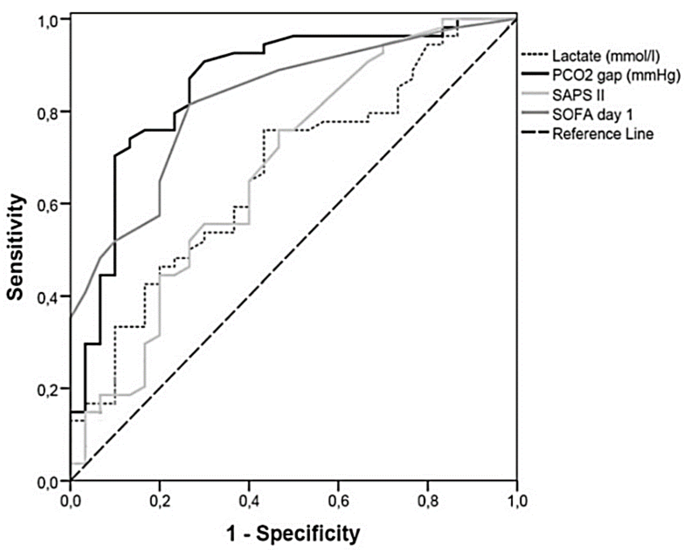


**Figure (1):** ROC curve showing correlation with postoperative complications.

## DISCUSSION

In high-risk patients, maintaining adequate tissue perfusion of all organs is crucial. Critically sick individuals are at a higher risk for hypoperfusion because of their increased resting energy expenditure and oxygen use. Recognizing and treating hypovolemia as soon as possible with fluid therapy without intravascular volume overload is crucial for resuscitation. Different methods of resuscitation can have varying effects on the prognosis of critically ill patients[8].

This study demonstrates that a straightforward assessment of $PCO_2$ gap that is equal or higher than 6.0 mmHg in the preoperative period is a relevant marker for postoperative complications, despite the vast amount of resources dedicated to monitoring perioperative risk of complications. The $PCO_2$ gap's diagnostic performance is comparable to that of the SOFA score and serum lactate, but it has the added benefit of being detectable at the time of admission. Measurement of the $PCO_2$ gap is straightforward at the bedside and is significantly more responsive than the SOFA score [8].

**Futier *et al.* [9],** who found that an elevated $PCO_2$ gap is linked to a high prevalence of postoperative problems if volume loading is inadequate, corroborate these findings. Similarly, cases who had septic shock or severe sepsis who have a substantial $PCO_2$ gap are more likely to experience organ failure and death, according to research by **van Beest *et al.*[10]**. Serum lactate was significantly higher in high $\Delta PCO_2$ group in the same study (mean 3.53±0.51 mmHg in group I vs. 1.72±0.35 mmHg in group II, p-value <0.001). Furthermore, after 24 hours, the $PCO_2$ gap was inversely connected with serum lactate clearance and improvement in the SOFA score.

**Bakker and colleagues[11]** found that, despite having virtually similar CO, $O_2$ supply, and $O_2$ intake, the $PCO_2$ difference was less in survivors of septic shock. The $PCO_2$ gap was shown to be reduced in septic shock patients who underwent fluid challenge.

A positive association between $PCO_2$ and the SOFA score was shown by **Wang *et al.* [12]** (r = 0.318, p <0.001). In the high $PCO_2$ group, the GCS was lower, but not statistically significant (p = 0.062). Hypoperfusion of the brain could account for this change.

As regard to organ dysfunction, high $PCO_2$ gap group showed significantly higher number of organ dysfunction (p-value = 0.001). Similar findings were obtained by **Robin *et al.* [7]**, in which a significant proportion of individuals with elevated $\Delta PCO_2$ also experienced organ failure.

There was an increase in the 28-day mortality rate in the high $PCO_2$ gap group (9.1% vs. 0%), but there was no statistically significant difference between the two groups (p-value = 0.377). **Mallat *et al.*[13]** found a similar pattern, reporting a higher rate of mortality in the high $PCO_2$ group (75%) compared to the normal group (42%; p = 0.003) within 28 days. Mortality was reported to be greater in the high $PCO_2$ group than in the normal group (29 percent versus 21 percent) by **van Beest *et al.* [10]**, but this difference was not statistically significant.

High $PCO_2$ ratios have also been linked to an increased death rate, as documented by **Mesquida *et al.* [14] and Ospina-Tascon *et al.*[15]** performed a multivariate analysis on a number of hemodynamic variables in septic shock and found that lactate and $PCO_2$ were independently related with death. Consistent results were also discovered by **Gavelli *et al.* [16].**

## CONCLUSIONS

Postoperative hemodynamic optimization in high-risk surgical patients, guided by $\Delta PCO_2$ <6 mmHg, reduced mechanical ventilation duration, length of hospital stay as well as organs failure. High $PCO_2$ gap, high serum lactate and high SOFA score on admission were significantly correlated with postoperative complications.

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**Competing interests:** Nil.

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