Venous-to-arterial pCO$_2$ difference in high-risk surgical patients

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**Abstract:** Alteration of tissue perfusion is a main contributor to organ dysfunction in high-risk surgical patients. The difference between venous carbon dioxide and arterial carbon dioxide pressure (pCO$_2$ gap) has been described as a parameter reflecting tissue hypoperfusion in critically ill patients who are insufficiently resuscitated. The pCO$_2$ gap/CavO$_2$ ratio has also been described as an indicator of the respiratory quotient, thus the relationship between DO$_2$ and VO$_2$. Most of the knowledge about the pCO$_2$ gap and the pCO$_2$ gap/CavO$_2$ ratio has come from studies in the literature on animal models or intensive care unit (ICU) patients. To date, publications pertaining to the operative setting are sparse. In the present review, we will first discuss the physiological background of the pCO$_2$ gap and CO$_2$-O$_2$ derived parameters used in the operating room. Few studies have focused on the clinical relevance of the pCO$_2$ gap in high-risk non-cardiac surgical patients. Prospective observational studies with a small sample size and retrospective studies have shown that the pCO$_2$ gap may be a useful complementary tool to identify patients who remain insufficiently optimized hemodynamically. In a few studies, a high pCO$_2$ gap was associated with postoperative complications following non-cardiac high-risk surgery. Results of observational studies conducted in patients undergoing cardiac surgery are contradictory. We focused on the divergence between non-cardiac surgery, cardiac surgery, and septic critically ill patients. When analyzing the literature, we can find some explanations for the discrepancies in the published results between cardiac and non-cardiac surgery. Finally, we will discuss the clinical utility of the pCO$_2$ gap in high-risk surgical patients.

**Keywords:** Venous-to-arterial pCO$_2$ difference; high-risk surgery; postoperative complications; cardiopulmonary bypass

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**Introduction**

Individualized hemodynamic optimization during high-risk surgery is an essential key to patient care. Several studies have demonstrated that such strategies improve the postoperative course by reducing morbidity and mortality. Hemodynamic optimization is a preventive strategy aiming to adapt oxygen delivery (DO$_2$) to oxygen consumption (VO$_2$) to avoid tissue hypoperfusion during surgery (1). This strategy is based on optimization of blood pressure (fluid and/or vasopressor), cardiac output (CO) (fluid and/or inotrope), and perfusion parameters such as central venous oxygen saturation (ScVO$_2$) or arterial lactate. Nevertheless, normalizing systemic hemodynamic parameters and ScVO$_2$ does not guarantee adequate tissue perfusion, and a substantial number of patients still progress to multiple organ failure and death. Although blood lactate concentration was initially described as a surrogate marker of tissue hypoperfusion, an elevated lactate value may be associated with adrenergic stimulation and surgical stress (2).
Recently, the difference between venous carbon dioxide and arterial carbon dioxide pressure (pCO$_2$ gap) has been described as a parameter reflecting tissue hypoperfusion in critically ill patients who are insufficiently resuscitated (3). Similarly, the pCO$_2$ gap/Cavo$_2$ ratio has been described as an indicator of the respiratory quotient, thus the relationship between DO$_2$ and VO$_2$ (4). Most of the knowledge about the pCO$_2$ gap and the pCO$_2$ gap/Cavo$_2$ ratio comes from studies in the literature on animal models or intensive care unit (ICU) patients (5). These parameters have been demonstrated to be associated with several variables of tissue perfusion, and most importantly with outcomes (mortality, morbidity). To date, publications pertaining to the operative setting have been sparse.

The purpose of the present review is to discuss clinical evidence of the usefulness of the pCO$_2$ gap and CO$_2$-O$_2$ derived parameters in the operating room. We will then discuss the results according to the type of surgery (cardiac vs. non-cardiac) and propose clinical use.

**Physiological background**

According to the Fick equation, CO$_2$ elimination (VCO$_2$) equals the product of the difference between venous blood CO$_2$ content (CvCO$_2$), arterial blood CO$_2$ content (CaCO$_2$), and CO [VCO$_2$ = CO × (CvCO$_2$ – CaCO$_2$)]. Because there is a linear association between CO$_2$ content and CO pressure, the pCO$_2$ gap may be expressed as: pCO$_2$ gap = K * VCO$_2$/CO. Therefore, the pCO$_2$ gap could be associated with CO$_2$ generation and CO. As CO$_2$ is much more soluble than O$_2$, it represents a very sensitive marker of tissue hypoxia (6). Since the pCO$_2$ gap depends on CO and VCO$_2$, it represents an indicator of the capacity of venous blood to eliminate CO$_2$ generated by peripheral tissues, and thus the adequacy of blood flow during shock states. Interestingly, an inverse curvilinear relationship between the pCO$_2$ gap and CO has been described, highlighting the importance of blood flow on venous CO$_2$ accumulation (7,8).

Several studies on septic shock have found that an increase in CO with fluid expansion is associated with a decrease in the pCO$_2$ gap compared to increased CO (9). For a constant production of CO$_2$, the increase in CO is coupled with an increased arterial blood volume having a low CO$_2$ content passing through the tissue, producing a washout effect and lowering the venous CO$_2$ content. Another factor in the lowering of the pCO$_2$ gap is the effect of blood pH on the relationship between pCO$_2$ and total blood CO$_2$ content. This relationship is shifted to the right, with a pH decrease resulting in an increased pCO$_2$ gap for the same value of CvCO$_2$. Consequently, an increase in CO will be associated with lower pCO$_2$ gap if the tissue acid production is decreased by the improvement in oxygen supply (10). Finally, the mechanisms implicated in the elevation of the pCO$_2$ gap during shock states are not completely understood, and interpretation of the pCO$_2$ gap could sometimes be difficult.

The ratio between the pCO$_2$ gap and the arterial-venous oxygen difference (pCO$_2$ gap/Cavo$_2$ ratio) has also been described (11,12). Under situations of tissue hypoxia, we can observe that a decreased VO$_2$ is associated with decreased aerobic CO$_2$ generation, whereas anaerobic CO$_2$ generation can still arise. Knowing that the VCO$_2$ is being reduced less than the VO$_2$, we can observe a rise in the VCO$_2$/VO$_2$ ratio (i.e., the respiratory quotient). Studies have demonstrated that the pCO$_2$ gap/Cavo$_2$ ratio can be used as an indicator of the presence of overall tissue hypoxia in critically ill patients (13). Mekontso-Dessap and colleagues demonstrated, in a retrospective ICU cohort, that the pCO$_2$ gap/Cavo$_2$ ratio may be a substitute for the respiratory quotient and blood lactate. The pCO$_2$ gap/Cavo$_2$ ratio was able to predict the presence of hyperlactatemia (4). Subsequently, Monnet and colleagues demonstrated that this ratio was able to predict an increase in VO$_2$ following fluid expansion in ICU patients. The pCO$_2$ gap/Cavo$_2$ ratio was able to better predict the presence of VO$_2$/DO$_2$ dependency phenomenon than blood lactate and ScVO$_2$ (14). In 2013, Vallet and colleagues proposed an interpretation of different shock states based on the analysis of blood lactate and O$_2$-CO$_2$ derived parameters (15) (Table 1).

**Clinical relevance of the pCO$_2$ gap in high-risk non-cardiac surgical patients**

Several observational studies have been conducted in patients undergoing non-cardiac surgery. A prospective study on 51 elective neurosurgical patients evaluated the correlation between the pCO$_2$ gap and CO. The authors demonstrated a close inverse correlation between CO and the pCO$_2$ gap for both central and mixed venous gas samples. They concluded that the pCO$_2$ gap could represent a useful parameter for CO assessment, and could be utilized in a neurosurgical practice involving postural changers (16). These authors did not evaluate outcomes. Futier and colleagues (17) conducted a retrospective study on 70 patients undergoing major abdominal surgery with an individualized goal-directed fluid replacement therapy. The
pCO\textsubscript{2} gap was measured every hour until the end of the surgery. Of the 70 patients, 34% developed postoperative septic complications. The authors demonstrate that high ScvO\textsubscript{2} was not associated with postoperative complications, and that the pCO\textsubscript{2} gap was the only parameter associated with complications (17). During the course of the surgery, the pCO\textsubscript{2} gap was larger in patients with complications (7.8±2 vs. 5.6±2 mmHg, P<0.05) than in patients without complications. In addition, a pCO\textsubscript{2} gap value >5 mmHg was able to predict postoperative complications with an area under the ROC curve (AUC) of 0.785 (95% CI: 0.74 to 0.83, P<0.05) (17). In patients with normal ScvO\textsubscript{2}, the pCO\textsubscript{2} gap may be a useful complementary tool to identify patients who remain insufficiently optimized hemodynamically. Robin and colleagues later performed a prospective observational study in 115 high-risk non-cardiac surgery patients (mostly abdominal surgery) (18). The pCO\textsubscript{2} gap was evaluated at admission to ICU, immediately after surgery. Seventy-eight patients (68%) developed postoperative complications. The pCO\textsubscript{2} gap was significantly higher at ICU admission in patients who suffered from complications (8.7±2.8 vs. 5.1±2.6 mmHg, P<0.001). The pCO\textsubscript{2} gap predicted the occurrence of postoperative complications, with an AUC of 0.86 (95% CI: 0.77 to 0.95) and a cut off value of 5.8 mmHg. Moreover, the pCO\textsubscript{2} gap has a higher ability to predict postoperative complications than arterial lactate. Taking together the results of their studies, the authors concluded that “the pCO\textsubscript{2} gap might be a useful and complementary tool to detect persistent tissue hypoperfusion that could be included as an additional step in the algorithms of early goal-directed therapy protocols” (18).

Apart from a retrospective study on 66 patients undergoing abdominal surgery, Silva and colleagues demonstrated an association between the pCO\textsubscript{2} gap and mortality (19). A pCO\textsubscript{2} gap of over 5 mmHg was predictive of mortality, with an AUC of 0.73 (95% CI: 0.61 to 0.84, P<0.05) (19). Recently, in a multicenter prospective observational study in non-cardiac surgery, our group demonstrated that the pCO\textsubscript{2} gap and the pCO\textsubscript{2} gap/CavO\textsubscript{2} ratio were associated with the postoperative course (20). In summary, there is evidence supporting the association between the pCO\textsubscript{2} gap, the pCO\textsubscript{2} gap/CavO\textsubscript{2} ratio, and postoperative morbidity and mortality. To date, no study has assessed the ability of hemodynamic protocols based on the pCO\textsubscript{2} gap measurement to decrease postoperative complications.

**Clinical relevance of the pCO\textsubscript{2} gap in high-risk cardiac surgical patients**

A study performed in the 90’s by Cavaliere and colleagues evaluated the pCO\textsubscript{2} gap in 30 patients in the early postoperative hours following cardiac surgery (21). Of the 30 patients, 21 (70%) developed postoperative complications. The pCO\textsubscript{2} gap was significantly higher at ICU admission in patients who suffered from complications (9±2 vs. 5±1 mmHg, P<0.001). By using a multiple linear regression analysis, the authors demonstrated that the pCO\textsubscript{2} gap was associated to the body temperature, the paCO\textsubscript{2} and the arterial mixed venous O\textsubscript{2} content difference. The pCO\textsubscript{2} gap was not associated to CO nor blood lactate (21). Based on the assumption that ScvO\textsubscript{2} remains challenging as a tool to identify patients with adequate circulatory status, Habicher and colleagues performed a study in cardiac surgical patients with normal ScvO\textsubscript{2} (22). The authors hypothesized that the pCO\textsubscript{2} gap could serve as an additional parameter to evaluate the adequacy of tissue perfusion. A retrospective data analysis on 60 patients was performed. The patients had a ScvO\textsubscript{2} ≥70% and were divided into 2 groups: the high-pCO\textsubscript{2} gap group (≥8 mmHg) and the low-pCO\textsubscript{2} gap group (<8 mmHg) (22). Patients with a high pCO\textsubscript{2} gap had worse postoperative courses, with higher lactate levels and worse splanchnic functions. These findings were associated with need for longer mechanical ventilation and longer ICU stays. In 2016, a retrospective study that included 220 consecutive patients after elective cardiac surgery evaluated

### Table 1 Shock type according to lactate and O\textsubscript{2}-CO\textsubscript{2} derived parameters (15)

<table>
<thead>
<tr>
<th>Shock type</th>
<th>Lactate</th>
<th>O\textsubscript{2} extraction</th>
<th>ScvO\textsubscript{2}</th>
<th>pCO\textsubscript{2} gap</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiogenic or hypovolemic</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Anemic or hypoxemic</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Distributive</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Cytopathic</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
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</tbody>
</table>
the association between the pCO$_2$ gap and postoperative complications (23). The pCO$_2$ gap was considered normal for a value less than 6 mmHg. The SOFA score and the mortality rate were higher in the low pCO$_2$ gap group than in the high pCO$_2$ gap group. Moreover, the pCO$_2$ gap had a low ability to predict outcomes (23). Guinot and colleagues subsequently evaluated the association between the pCO$_2$ gap during the ICU course following cardiac surgery and postoperative morbidity and mortality (24). Three hundred thirty-nine patients were enrolled in this prospective observational study. The pCO$_2$ gap was not predictive of the development of major complications. Moreover, the pCO$_2$ gap was poorly correlated with tissue perfusion parameters, and arterial lactate clearance (24).

Du and colleagues conducted an observational retrospective study to establish whether the pCO$_2$ gap/CavO$_2$ ratio could predict the hemodynamic response to resuscitation (25). Seventy-two patients undergoing cardiac surgery were analyzed. VO$_2$ responders were defined by an increased VO$_2$ of over 10%. The ratio appeared to be a reliable marker of overall anaerobic metabolism that predicted VO$_2$ response. Abou-Arab and colleagues later analyzed the ability of the pCO$_2$ gap/CavO$_2$ ratio to predict an increase in VO$_2$ upon fluid challenge in cardiac surgical patients (26). One hundred ten patients, consecutively admitted to a cardiothoracic ICU and in whom fluid expansion was performed, were included. VO$_2$ responders were defined as patients showing more than 15% increase in VO$_2$. Arterial pressure, CO, and arterial and venous blood gas levels were measured before and immediately after the fluid challenge. CO$_2$-O$_2$, derived variables were not predictive of VO$_2$ changes following fluid challenge in this specific population (26). Only ScvO$_2$ was poorly predictive of VO$_2$ changes. The pCO$_2$ gap/CavO$_2$ ratio was not associate to arterial lactate. Interestingly, the authors observed a decrease in the pCO$_2$ gap only in non-VO$_2$ responder patients, suggesting a different pattern of microcirculatory alteration following cardiac surgery than in sepsis.

In summary, association between the pCO$_2$ gap, pCO$_2$ gap/CavO$_2$ ratio, postoperative course and anaerobic metabolism is unclear in cardiac surgical area. Small and retrospective studies demonstrated positive results whereas larger cohort demonstrated negative results.

**Divergence between non-cardiac surgery, cardiac surgery, and septic critically ill patients**

When analyzing the literature, some explanations can be found regarding discrepancies in the published results. The most important is probably the type of surgery (21,27). Cardiac surgery with cardiopulmonary bypass is a specific physiologic situation that may be associated with factors altering the relationship between CO$_2$-O$_2$ derived content and pressure, VCO$_2$, DO$_2$, VO$_2$, and tissue perfusion. On the contrary, non-cardiac major surgery is often abdominal surgery which may be more similar to the macro- and micro-circulatory disturbance observed in ICU patients (19).

Ruokonen and colleagues have already studied the ability of the pCO$_2$ gap to assess tissue perfusion in cardiac surgery patients by using a control group of abdominal surgery patients (27). According to this author, a pCO$_2$ gap rise is frequent after cardiac surgery and better reflects an alteration of systemic and regional perfusion compared to tissue hypoxia (26). In this way, some studies did not demonstrate any association between the pCO$_2$ gap, pCO$_2$ gap/CavO$_2$ ratio, arterial lactate and VO$_2$ (21,26).

The relationship between CO$_2$-O$_2$ derived content and pressure depends on several parameters that can be altered in the operating theatre, specifically in cardiac surgery. Of these parameters, body temperature, alveolar ventilation, and hemodilution may be of importance. Van der Linden and colleagues have demonstrated an increase in the pCO$_2$ gap during acute hemorrhaging in anesthetized dogs. Hemorrhage was associated with a progressive increase in venous pCO$_2$, with a corresponding widening of the pCO$_2$ gap which was correlated with a blood lactate change (28). Nevertheless, hemodilution was demonstrated to have more complex effects on CO$_2$-O$_2$ derived variables than hemorrhage (29,30). During mechanical ventilation, alveolar ventilation may be associated with pCO$_2$ changes. Mallat and colleagues and Morel and colleagues demonstrated similar results when analyzing the pCO$_2$ gap during rising alveolar ventilation (31,32). Both studies demonstrated that rising alveolar ventilation is associated with an increased pCO$_2$ gap. These changes were related to changes in VO$_2$, systemic vasoconstriction, and variations in the PCO$_2$/CO$_2$ content relationship (31,32). By altering the metabolism and the PCO$_2$/CO$_2$ content relationship, body temperature can alter the adequacy of the pCO$_2$ gap. Utoh and colleagues demonstrated, in cardiac surgical patients, that the two main factors associated with high pCO$_2$ gap values were the duration of cardiopulmonary bypass surgery and the minimum rectal temperature. Cardiac surgery was shown to be associated with changes in metabolic rate, CO, and VO$_2$(15,21). Such alterations can occur throughout first postoperative hours.
The extent of microcirculation alterations caused by sepsis, surgery, and cardiopulmonary bypass may differ (33,34). Sepsis is normally associated with impaired microcirculatory regulation, decreased functional capillary index, absent/intermittent capillary flow, increased heterogeneity in the perfusion index, arteriovenous shunting, and cellular hypoxia (35). On the contrary, cardiopulmonary bypass is associated with many reversible alterations in microcirculation, including a decrease in microvascular perfusion, increased heterogeneity in the perfusion index and red blood cell velocity, and arteriovenous shunting (33,36). These changes are associated with alterations in the arteriovenous oxygen difference, VO₂, and CO₂ and O₂ diffusion (37). During major abdominal surgery, the microvascular perfusion is not altered, and it is not associated with postoperative complications (38). Nevertheless, an impaired microvascular flow can appear during the postoperative period when patients suffer from complications (38). These changes are similar to those observed in sepsis (39).

**Use of the pCO₂ gap in high-risk surgical patients**

One has to keep in mind that a high pCO₂ gap may not necessarily indicate an alteration in tissue perfusion or a low flow state. Moreover, studies have demonstrated that a normal pCO₂ gap does not preclude the presence of tissue hypoxia, and thus has poor sensitivity to detect tissue hypoxia (8,40). In patients with low CO and a normal arterial lactate value, the pCO₂ gap was demonstrated to be increased (7). Keeping in mind these limitations and the fact that, to date, no randomized study using the pCO₂ gap has been published, the pCO₂ gap may be interpreted according to the type of surgery (cardiac vs. non-cardiac), medical situation (e.g., sepsis, haemorrhage, cardiogenic), and macro- and micro-hemodynamic parameters (e.g., CO, arterial lactate, ScVO₂). The pCO₂ gap may be considered as a parameter reflecting the ability of blood flow to remove the total CO₂ produced by tissue rather than a marker of tissue dysoxia. Based on these interpretations, several authors have proposed algorithms. Among them, an algorithm based on the lactate value may be useful in the choice of therapeutic treatment for acute circulatory failure (Figure 1).

**Figure 1** Proposed algorithm to guide hemodynamic treatment in high-risk surgical patients. ScVO₂, central venous oxygen saturation; PEEP, positive end-expiratory pressure.

**Conclusions**

The pCO₂ gap can be considered as a marker of CO
adequacy for the overall metabolic demand that has been associated with the postoperative course in non-cardiac major surgery. The pCO$_2$ gap may not always be a marker of tissue hypoxia. During hemodynamic treatment, the interpretation of the pCO$_2$ gap may help physicians to understand which variables can be optimized. In cardiac surgery, results are inconsistent because of many factors altering the pCO$_2$ gap interpretation. In surgical patients without any sign/parameter of tissue hypoperfusion, manipulating the pCO$_2$ gap may be done with caution.

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Footnote
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