Review Article

Venous-to-arterial pCO_2 difference in high-risk surgical patients

Pierre Huette[1], Omar Ellouze[2], Osama Abou-Arab[1], Pierre-Grégoire Guinot[2]

[1]Anaesthesiology and Critical Care Department, Cardiothoracic ICU, Amiens University Hospital, Amiens, France; [2]Anaesthesiology and Critical Care Department, Cardiovascular ICU, Dijon University Hospital, Dijon, France

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Correspondence to: Pierre-Grégoire Guinot. Anesthesiology and Critical Care Department, Dijon University Hospital, 2 Bd Maréchal de Lattre of Tassigny, Dijon, France. Email: pierregregoire.guinot@chu-dijon.fr.

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 [$VCO_2 = CO \times (CvCO_2 - CaCO_2)$]. Because there is a linear association between CO_2 content and CO_2 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) conduced a retrospective study on 70 patients undergoing major abdominal surgery with an individualized goal-directed fluid replacement therapy. The

Table 1 Shock type according to lactate and O_2-CO_2 derived parameters (15)

Shock type	Lactate	O_2 extraction	$ScVO_2$	pCO_2 gap
Cardiogenic or hypovolemic	High	High	Low	High
Anemic or hypoxemic	High	High	Low	Low
Distributive	High	Low	High	High
Cytopathic	High	Low	High	Low

pCO_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 $ScvO_2$ was not associated with postoperative complications, and that the pCO_2 gap was the only parameter associated with complications (17). During the course of the surgery, the pCO_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_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 $ScVO_2$, the pCO_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_2 gap was evaluated at admission to ICU, immediately after surgery. Seventy-eight patients (68%) developed postoperative complications. The pCO_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_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_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_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_2 gap and mortality (19). A pCO_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_2 gap and the pCO_2 gap/$CavO_2$ ratio were associated with the postoperative course (20). In summary, there is evidence supporting the association between the pCO_2 gap, the pCO_2 gap/$CavO_2$ ratio, and postoperative morbidity and mortality. To date, no study has assessed the ability of hemodynamic protocols based on the pCO_2 gap measurement to decrease postoperative complications.

Clinical relevance of the pCO_2 gap in high-risk cardiac surgical patients

A study performed in the 90's by Cavaliere and colleagues evaluated the pCO_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_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_2 gap was associated to the body temperature, the $paCO_2$ and the arterial mixed venous O_2 content difference. The pCO_2 gap was not associated to CO nor blood lactate (21). Based on the assumption that $ScvO_2$ remains challenging as a tool to identify patients with adequate circulatory status, Habicher and colleagues performed a study in cardiac surgical patients with normal $ScVO_2$ (22). The authors hypothesized that the pCO_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 $ScvO_2$ ≥70% and were divided into 2 groups: the high-pCO_2 gap group (≥8 mmHg) and the low-pCO_2 gap group (<8 mmHg) (22). Patients with a high pCO_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

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 colleague 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.

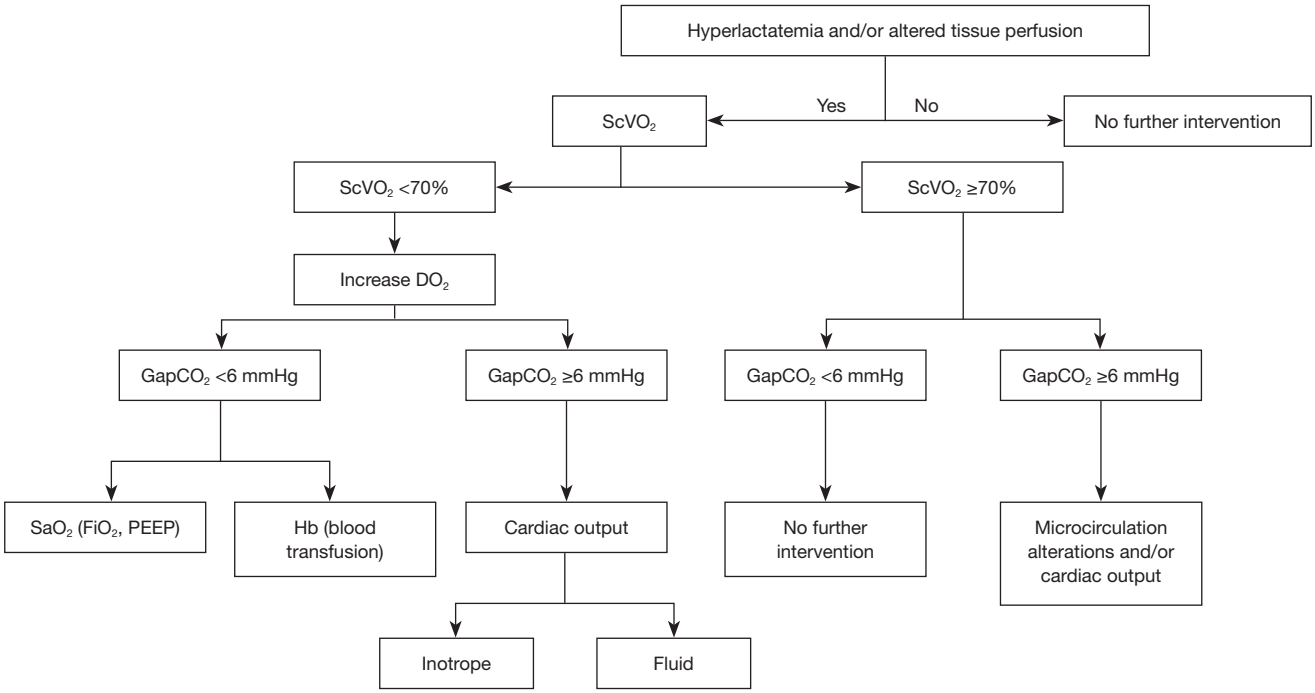

Figure 1 Proposed algorithm to guide hemodynamic treatment in high-risk surgical patients. $ScVO_2$, central venous oxygen saturation; PEEP, positive end-expiratory pressure.

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, VO_2, and CO_2 and O_2 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 pCO_2 gap in high-risk surgical patients

One has to keep in mind that a high pCO_2 gap may not necessarily indicate an alteration in tissue perfusion or a low flow state. Moreover, studies have demonstrated that a normal pCO_2 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 pCO_2 gap was demonstrated to be increased (7). Keeping in mind these limitations and the fact that, to date, no randomized study using the pCO_2 gap has been published, the pCO_2 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, $ScVO_2$). The pCO_2 gap may be considered as a parameter reflecting the ability of blood flow to remove the total CO_2 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*).

Conclusions

The pCO_2 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

Conflicts of Interest: The authors have no conflicts of interest to declare.

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