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The relationship of CO2 metabolism to tissue perfusion, microcirculation, and treatment response in shock and sepsis

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CHAPTER 11

DETERMINANTS OF TISSUE PCO₂
IN SHOCK AND SEPSIS:
RELATIONSHIP TO THE MICROCIRCULATION
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INTRODUCTION

The development of gastrointestinal tonometry was an important step in the monitoring of tissue dysxia. It rapidly became a useful tool in basic research. In addition, and for the first time, a regional parameter could be used to detect and to treat hypoperfusion. From an experimental point of view, tonometry adequately tracks intramucosal acidosis [1], i.e., the increase in intramucosal-arterial PCO₂ difference (ΔPCO₂). Likewise, the increase in ΔPCO₂ is better than other systemic and intestinal variables to show tissue hypoperfusion in normal volunteers [2] and in experimental models [3]. Intramucosal acidosis is a sensitive predictor of gastric [4] and colonic mucosal ischemia [5]. Furthermore, gastric tonometry is an insightful predictor of outcome. This usefulness has been shown in postoperative [6], critically ill [7], septic [8] and shock [9] patients. Gastric tonometry might also be used to assess the effect of vasoactive drugs [10, 11]. Finally, intramucosal pH (pHi) has been evaluated as a guide for resuscitation. Gutierrez et al. [12] demonstrated in a randomized controlled trial that pHi-guided therapy could decrease mortality in critically ill patients.

Despite having been the only clinically available approach to detect tissue hypoperfusion for many years and despite the scientific evidence supporting its usefulness, gastrointestinal tonometry is not commonly used. Various reasons may explain this issue, including that saline tonometry has poor reproducibility [13], although this was improved by the introduction of air tonometry [14]. Sublingual capnometry remains an attractive approach [15], but this technique has not yet been adequately validated.

Another source of uncertainty lies in the true significance of ΔPCO₂ elevation. In the last few years, new evidence has given a better understanding of the mechanisms underlying intramucosal acidosis. In this chapter, we will discuss the determinants of tissue and venous PCO₂ in shock and sepsis and their relationship to microcirculatory perfusion.

Mechanisms of increase in venous and tissue PCO₂: The Basics

Increased mucosal intestinal PCO₂ has been mainly used to detect tissue dysxia, the condition in which oxygen delivery (DO₂) can no longer sustain oxygen consumption (VO₂) [16]. Twenty years ago, Grum et al. [17] evaluated the adequacy of gut oxygenation by the tonometric measurement of pHi, during DO₂ reductions secondary to ischemia, hypoxemia, or a combination of both. pHi only decreased after critical reductions of DO₂. Consequently, changes in VO₂ and pHi were closely correlated (Fig. 1). The authors concluded that pHi appears to be a sensitive indicator of tissue oxygenation, because it mirrors tissue VO₂. Nevertheless, critical DO₂ was only reached in ischemic experiments. In pure hypoxemic experiments, neither pHi nor VO₂ decreased.

Theoretically, PCO₂ can increase in the intestinal lumen by two mechanisms [18]: First, by bicarbonate buffering of the protons generated during the breakdown of
high-energy phosphates and strong acids, in which case increased PCO₂ would represent tissue dysoxia; alternatively, PCO₂ can increase due to hypoperfusion and decreased washout of CO₂. The Fick Equation applied to CO₂, states that CO₂ production (VCO₂) is the product of cardiac output and venoarterial CO₂ content difference. Consequently, decreases in blood flow result in venous and tissue hypercarbia, regardless of the lack of change in VCO₂.

Trying to solve this controversy, Schlichtig and Bowles [18] presented evidence supporting intramucosal PCO₂ as a marker of dysoxia in extreme hypoperfusion when VO₂ decreases. In a dog model of cardiac tamponade, these authors demonstrated that below critical DO₂, mucosal PCO₂ increases because of anaerobic VCO₂. This conclusion was drawn using the Dill nomogram, which can, theoretically, detect anaerobic VCO₂ from the comparison of the measured (%HbO₂,v) vs. calculated (%HbO₂,v_DILL) venous oxyhemoglobin, within a given value of venous PCO₂. Since venous PCO₂ is considered representative of tissue PCO₂, the authors made the calculation with its intestinal equivalent, intramucosal PCO₂. Similar values of measured (%HbO₂,v) vs. calculated (%HbO₂,v_DILL) venous oxyhemoglobin would represent aerobic VCO₂. If %HbO₂,v_DILL is lower than measured %HbO₂,v, anaerobic VCO₂ is then assumed. Using this approach, we identified an anaerobic source of gut intramucosal CO₂ during moderate hemorrhage [3]. Our %HbO₂,v_DILL values obtained from gastric, jejunal, and ileal mucosal PCO₂ decreased markedly during ischemia, indicating the presence of anaerobiosis. Notwithstanding the original contribution of Schlichtig and Bowles [18] to the analysis of these topics, the use of low flow to produce critical DO₂ and decreased VO₂ may act as a potential confounder, given the impossibility of dissociating tissue dysoxia from hypoperfusion [19].
Vallet et al. [20] explored this issue by measuring venous PCO₂ in isolated dog hindlimb preparations subjected to comparable decreases in DO₂, produced by two mechanisms. In one group, blood flow was progressively decreased (ischemic hypoxia), whereas in the other, arterial PO₂ was lowered at constant perfusion flow (hypoxic hypoxia). Both groups experienced similar declines in DO₂ and VO₂, implying similar degrees of tissue dysoxia. The venoarterial PCO₂ difference, however, remained constant in the hypoxic hypoxia group, and increased more than twofold in the ischemic hypoxia group. The authors concluded that flow is the major determinant of venoarterial PCO₂ difference, not tissue dysoxia [20] (Fig. 3).

Nevière et al. assessed a similar hypothesis in pigs, comparing the effects of reduced inspired oxygen fraction (FiO₂) and decreased blood flow measured with laser-Doppler [21]. In ischemic hypoxia, ΔPCO₂ rose to 60 mmHg. In hypoxic hypoxia, in which mucosal blood flow was maintained constant, ΔPCO₂ increase to 30 mmHg only with the lowest FiO₂ (0.06). The authors concluded that intramucosal PCO₂ elevation in hypoxic hypoxia denotes local CO₂ generation. Some flow heterogeneity could, however, have been present in their experiments that was not assessed by laser-Doppler, a method that only tracks global microvascular changes. In addition, in the two preceding steps of FiO₂ reduction, VO₂/DO₂ dependency had been reached, and ΔPCO₂ remained unchanged.

From a physiologic point of view, it is difficult to understand how VCO₂ might increase during oxygen supply dependency. During progressive exercise, there are corresponding increases in VO₂ and VCO₂ [22]. The slope of the VCO₂/VO₂ relationship is the respiratory quotient. When the exercise reaches the anaerobic threshold, there is an excess of VCO₂ to VO₂ due to the appearance of anaerobic

![Fig. 2. a) Hindlimb oxygen uptake as a function of limb oxygen delivery (DO₂) for ischemic hypoxia (IH) and hypoxic hypoxia (HH). There was no statistically significant difference at any DO₂. Critical DO₂ (DO₂crit) was not different in IH and HH. b) Hindlimb venoarterial PCO₂ difference as a function of limb DO₂ for IH and HH. Despite similar degrees of tissue dysoxia, venoarterial PCO₂ difference remained constant in the HH group and increased more than twofold in the IH group.](image-url)
VCO₂ from the bicarbonate buffering of lactic acid (Fig. 3). In this condition, both VCO₂ and respiratory quotient increase.

In the other extreme of physiology, during oxygen supply dependency, the respiratory quotient also increases [23]. This increase, however, occurs in the context of the reduction of total VCO₂ (Fig. 4). Anaerobic VCO₂ appears, but total VCO₂ decreases.
We further explored this issue in another model of hypoxic hypoxia [24]. In these experiments, venous and tissue PCO$_2$ increased during ischemic hypoxia, but not during hypoxic hypoxia. Therefore, ΔPCO$_2$ was unable to show the presence of tissue dysoxia during hypoxic hypoxia, in which blood flow is preserved (Fig. 5a). To confirm that blood flow is the main determinant of ΔPCO$_2$, we studied these relationships in another model of tissue dysoxia without hypoperfusion, anemic hypoxia [25] (Fig. 5b). We compared the effects of progressive bleeding to those of isovolemic exchange of blood with dextran. Our goal was to evaluate the behavior of CO$_2$ gradients as a function of systemic and intestinal blood flow, and also the other determinants, VCO$_2$ and the CO$_2$Hb dissociation curve. Tissue-arterial and venoarterial PCO$_2$ failed to reflect the dependence of VO$_2$ on DO$_2$. Nevertheless, these gradients increased by a few mmHg (Figs. 5 and 6). Conversely, however, venoarterial CO$_2$ content differences decreased. This apparent paradox might be explained by changes in the CO$_2$Hb dissociation curve induced by anemic hypoxia. The other determinant of PCO$_2$ differences, the VCO$_2$ remained unchanged, both at systemic and intestinal levels. The systemic and intestinal respiratory quotient, however, increased because of VO$_2$ reductions.

In summary, our results [24, 25], together with those of Vallet et al. [20], support the concept that increases in tissue-arterial and venoarterial PCO$_2$ gradients reflect only microcirculatory stagnation, not tissue dysoxia. Tissue and venous PCO$_2$ are insensitive markers of dysoxia and merely indicate hypoperfusion. These experimental findings were confirmed by a mathematical model [26]. Gutierrez developed a two-compartment mass transport model of tissue CO$_2$ exchange for hypoxic hypoxia, to examine the relative contribution of blood flow and cellular dysoxia to the increases in tissue and venous PCO$_2$. The model assumed perfectly

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**Fig. 5.** a) Ileal intramucosal-arterial PCO$_2$ difference (ΔPCO$_2$) as a function of intestinal oxygen transport in hypoxic and ischemic hypoxia. From reference [24] with permission. b) ΔPCO$_2$ as a function of intestinal oxygen transport in anemic and ischemic hypoxia. From reference [25] with permission. In hypoxic and anemic hypoxia, ΔPCO$_2$ fails to reflect tissue dysoxia.
mixed homogeneous conditions, steady-state equilibrium, and VCO₂ occurring exclusively at the tissues. The results of the model supported the idea that changes in tissue and venous blood CO₂ concentrations during dysoxia reflect primarily alterations in vascular perfusion, and not shortage of energy supply.

Intramucosal acidosis in sepsis

Beyond the previous discussion, intramucosal acidosis is a common finding in clinical and experimental sepsis, conditions in which cardiac output is usually normal or increased. In resuscitated endotoxemic pigs, VanderMeer et al. found that intramucosal acidosis developed despite preserved mucosal oxygenation and blood flow measured only at the mucosa [27]. The underlying mechanism was attributed to metabolic disturbances, and led to the concept of “cytopathic hypoxia” [28]. Nevertheless, an important shortcoming of that study was the use of
laser-Doppler flowmetry to measure tissue perfusion and the lack of measurement of tissue oxygenation at the serosal side of the intestines, an important source of gut CO$_2$ [31].

On the other hand, Vallet et al. studied dogs challenged with endotoxin, and then resuscitated them to normalize oxygen transport [29]. Intestinal VO$_2$ and mucosal PO$_2$ and pH, however, remained low. The authors ascribed these findings to blood flow redistribution from the mucosa toward the muscular layer. Nevertheless, Revelly et al. [30] described an inverse redistribution, with increased mucosal and decreased muscular blood flow, using dyed microspheres in endotoxemic pigs [30]. Paradoxically, pH$_i$ was inversely correlated with mucosal flow, though positively correlated with muscular perfusion. The authors concluded that intramucosal acidosis was not explained by mucosal hypoperfusion [30]. 

Siegemund et al. showed, in a similar model, reductions in mucosal and serosal microvascular PO$_2$, and an increase in $\Delta$PCO$_2$ [31]. Fluid resuscitation normalized mucosal PO$_2$ but serosal PO$_2$ and $\Delta$PCO$_2$ remained altered. Inhibition of inducible nitric oxide (NO) however restored serosal PO$_2$ and also $\Delta$PCO$_2$ thereby identifying the source of intraluminal CO$_2$ measured in their model.

Conversely, Tugtekin et al. [32], in a porcine model of 24-hour endotoxin infusion, showed an association between intramucosal acidosis and severe hypoperfusion in ileal villi. In this study, about half of the evaluated villi were heterogeneously-or non-perfused, despite normal portal blood flow. Creteur et al. described, in septic patients, a correlation between sublingual $\Delta$PCO$_2$ and microcirculatory blood flow [33]. In agreement with their results, results from our laboratory showed that endotoxic shock in sheep was associated with sublingual and intestinal microcirculatory alterations and intramucosal acidosis [34]. Fluid resuscitation normalized systemic and intestinal oxygen transport, as well as sublingual and intestinal serosal microcirculation. Nevertheless, a reduced number of perfused intestinal villi and increased $\Delta$PCO$_2$ persisted. This led us to conclude that intramucosal acidosis was related to a persistent decrease in the mucosal microvascular flow index and a reduced number of perfused intestinal villi [34] (Fig. 7). 

There are other studies further supporting the hypothesis that, in endotoxemia, changes in perfusion and not tissue dysoxia determine $\Delta$PCO$_2$. We randomized endotoxemic sheep to saline solution resuscitation to maintain blood flow at baseline values or to increase it by 50%. Increased perfusion prevented intramucosal acidosis, though metabolic acidosis continued due to increased anion gap [35]. Similarly, in endotoxemic sheep, the administration of levosimendan, an inotropic and vasodilator drug, precluded increases in $\Delta$PCO$_2$ but hyperlactatemia was exacerbated [36] or unaffected [37]. The findings of these studies suggest that intramucosal acidosis is mainly related to local hypoperfusion and that metabolic disorders depend on a cellular mechanism which is unresponsive to changes in blood flow.
Venoarterial and tissue-arterial PCO$_2$ gradients are the result of interactions in aerobic and anaerobic VCO$_2$, CO$_2$ dissociation curve, and blood flow to tissues. During VO$_2$/DO$_2$ dependency, opposite changes in aerobic and anaerobic VCO$_2$ occur. Aerobic VCO$_2$ decreases as a consequence of failing aerobic metabolism, but, at the same time, anaerobic VCO$_2$ starts due to bicarbonate buffering of protons derived from fixed acids. Total VCO$_2$ might not increase, as in our experiments. But as VO$_2$ falls, there is an increase in the respiratory quotient [27]. The relative increment of VCO$_2$ with respect to VO$_2$ can only cause venous and tissue hypercarbia during tissue hypoperfusion, in which CO$_2$ removal is reduced. These conditions can be present despite preserved systemic and regional blood flow. Notwithstanding the fact that ΔPCO$_2$ is not a marker of dysoxia but of tissue perfusion, it remains a very useful clinical and experimental monitoring tool, particularly in clinical situations such as sepsis in which cardiac output is increased while microcirculatory flow can be impaired.

**CONCLUSION**

Fig. 7. Effects of endotoxic shock and resuscitation on the percentage of perfused ileal villi and intramucosal-arterial PCO$_2$ difference (ΔPCO$_2$). Endotoxic shock decreased the perfused intestinal villi and fluid resuscitation was unable to restore villus perfusion (a). ΔPCO$_2$ was correlated with perfused intestinal villi (b) but not with superior mesenteric artery blood flow (c).
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gradient does not reflect intestinal dysxia in anemic hypoxia. J Trauma 57: 1211–1217