Determinants of Tissue PCO_2 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 dysoxia. 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 PCO_2 difference (ΔPCO_2). Likewise, the increase in ΔPCO_2 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 ΔPCO_2 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 PCO_2 in shock and sepsis and their relationship to microcirculatory perfusion.

Mechanisms of Increase in Venous and Tissue PCO_2: The Basics

Increased mucosal intestinal PCO_2 has been mainly used to detect tissue dysoxia, the condition in which oxygen delivery (DO_2) can no longer sustain oxygen consumption (VO_2) [16]. Twenty years ago, Grum et al. [17] evaluated the adequacy of gut oxygenation by the tonometric measurement of pHi, during DO_2 reductions secondary to ischemia, hypoxemia, or a combination of both. pHi only decreased after crit-

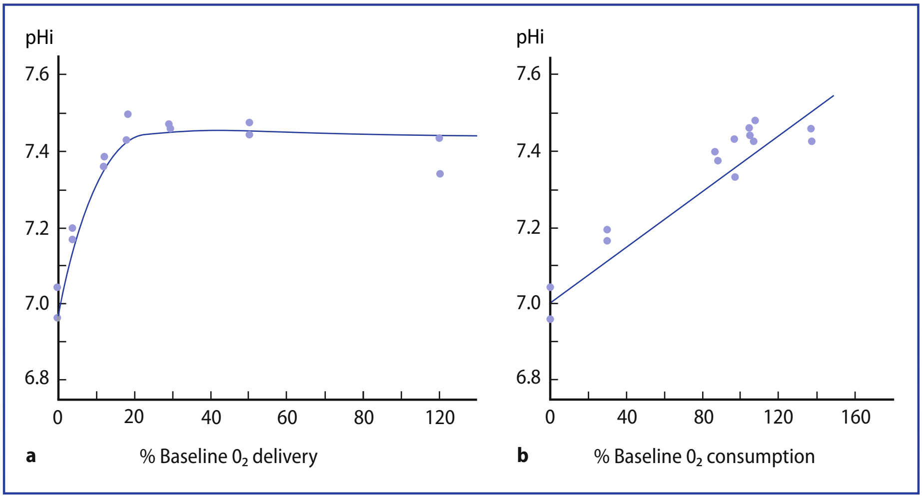

Fig. 1a. Intestinal intramucosal pH (pHi) as a function of oxygen (O_2) delivery. **b** Intestinal intramucosal pH as a function of intestinal O_2 consumption. Reductions of intramucosal pH are only present with critical reductions of O_2 delivery. From [17] with permission.

ical reductions of DO_2. Consequently, changes in VO_2 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 VO_2. Nevertheless, critical DO_2 was only reached in ischemic experiments. In pure hypoxemic experiments, neither pHi nor VO_2 decreased.

Theoretically, PCO_2 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 PCO_2 would represent tissue dysoxia; alternatively, PCO_2 can increase due to hypoperfusion and decreased washout of CO_2. The Fick Equation applied to $CO_{2,}$ states that CO_2 production (VCO_2) is the product of cardiac output and venoarterial CO_2 content difference. Consequently, decreases in blood flow result in venous and tissue hypercarbia, regardless of the lack of change in VCO_2.

Trying to solve this controversy, Schlichtig and Bowles [18] presented evidence supporting intramucosal PCO_2 as a marker of dysoxia in extreme hypoperfusion when VO_2 decreases. In a dog model of cardiac tamponade, these authors demonstrated that below critical DO_2, mucosal PCO_2 increases because of anaerobic $VCO_{2.}$ This conclusion was drawn using the Dill nomogram, which can, theoretically, detect anaerobic VCO_2 from the comparison of the measured ($\%HbO_{2v}$) vs. calculated ($\%HbO_{2v}{}^{DILL}$) venous oxyhemoglobin, within a given value of venous PCO_2. Since venous PCO_2 is considered representative of tissue $PCO_{2,}$ the authors made the calculation with its intestinal equivalent, intramucosal PCO_2. Similar values of measured ($\%HbO_{2v}$) vs. calculated ($\%HbO_{2v}{}^{DILL}$) venous oxyhemoglobin would represent aerobic VCO_2. If $\%HbO_{2v}{}^{DILL}$ is lower than measured $\%HbO_{2v}$, anaerobic VCO_2 is then assumed. Using this approach, we identified an anaerobic source of gut intramucosal CO_2 during moderate hemorrhage [3]. Our $\%HbO_{2v}{}^{DILL}$ values obtained from gastric, jejunal, and ileal mucosal PCO_2 decreased markedly during ischemia, indicating the presence of anaerobia (**Fig. 2**). Notwithstanding the original contribu-

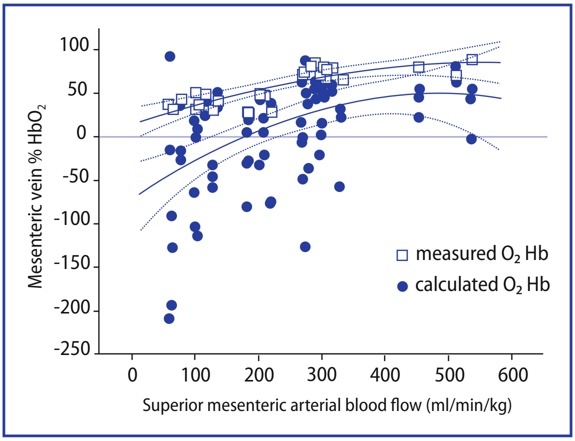

Fig. 2. Measured venous oxygen saturation ($\%HbO_{2v}$) (□) and venous oxygen saturation calculated from gut tissue PCO_2 ($\%HbO_{2v}{}^{DILL}$) (●) as a function of superior mesenteric artery blood flow. Since $\%HbO_{2v}{}^{DILL}$ is lower than measured $\%HbO_{2v}$, anaerobic production of CO_2 may be assumed. From [3] with permission.

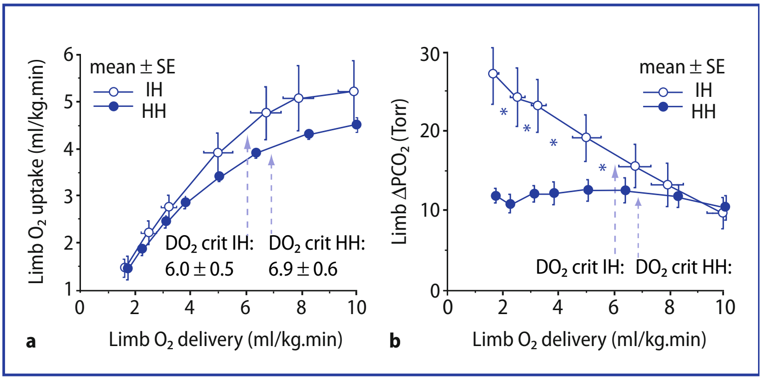

Fig. 3. a Hindlimb oxygen uptake as a function of limb oxygen delivery (DO_2) for ischemic hypoxia (IH) and hypoxic hypoxia (HH). There was no statistically significant difference at any DO_2. Critical DO_2 (DO_2crit) was not different in IH and HH. **b** Hindlimb venoarterial PCO_2 difference as a function of limb DO_2 for IH and HH. Despite similar degrees of tissue dysoxia, venoarterial PCO_2 difference remained constant in the HH group and increased more than twofold in the IH group. From [20] with permission.

tion of Schlichtig and Bowles [18] to the analysis of these topics, the use of low flow to produce critical DO_2 and decreased VO_2 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 PCO_2 in isolated dog hindlimb preparations subjected to comparable decreases in DO_2, produced by two mechanisms. In one group, blood flow was progressively decreased (ischemic hypoxia), whereas in the other, arterial PO_2 was lowered at constant perfusion flow (hypoxic hypoxia). Both groups experienced similar declines in DO_2 and VO_2, implying similar degrees of tissue dysoxia. The venoarterial PCO_2 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 PCO_2 difference, not tissue dysoxia [20] (**Fig. 3**).

Nevière et al. assessed a similar hypothesis in pigs, comparing the effects of reduced inspired oxygen fraction (FiO_2) and decreased blood flow measured with

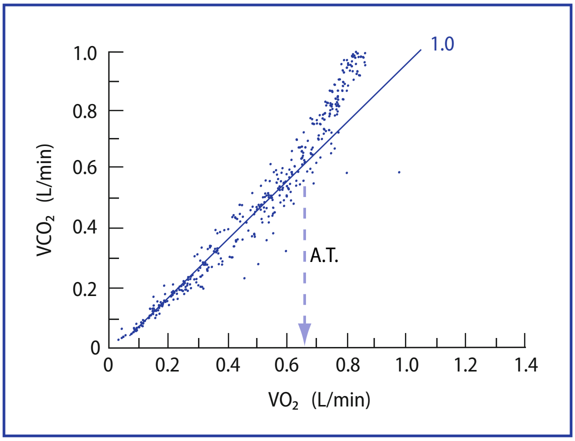

Fig. 4. Plot of carbon dioxide production (VCO_2) as a function of oxygen uptake (VO_2) in response to incremental work rate during a test of exercise. Line with slope 1.0 is the approximate mean of data points up to the point where VCO_2 breaks away and increases rapidly. When data points rise more steeply than a slope of 1.0 is theoretically the VCO_2 at which HCO_3^- starts buffering lactic acid (anaerobic threshold). From [22] with permission.

laser-Doppler [21]. In ischemic hypoxia, ΔPCO_2 rose to 60 mmHg. In hypoxic hypoxia, in which mucosal blood flow was maintained constant, ΔPCO_2 increase to 30 mmHg only with the lowest FiO_2 (0.06). The authors concluded that intramucosal PCO_2 elevation in hypoxic hypoxia denotes local CO_2 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 FiO_2 reduction, VO_2/DO_2 dependency had been reached, and ΔPCO_2 remained unchanged.

From a physiologic point of view, it is difficult to understand how VCO_2 might increase during oxygen supply dependency. During progressive exercise, there are corresponding increases in VO_2 and VCO_2 [22]. The slope of the VCO_2/VO_2 relationship is the respiratory quotient. When the exercise reaches the anaerobic threshold, there is an excess of VCO_2 to VO_2 due to the appearance of anaerobic VCO_2 from the bicarbonate buffering of lactic acid (**Fig. 4**). In this condition, both VCO_2 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 VCO_2 (**Fig. 5**). Anaerobic VCO_2 appears, but total VCO_2 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. 6a**). 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. 6b**). 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_2Hb 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. 6** and **7**). Conversely, however, venoarterial CO_2 content differences decreased. This apparent paradox might be explained by changes in the CO_2Hb dissociation curve induced by anemic hypoxia. The other determinant of PCO_2 differences, the VCO_2 remained unchanged, both at systemic and intestinal

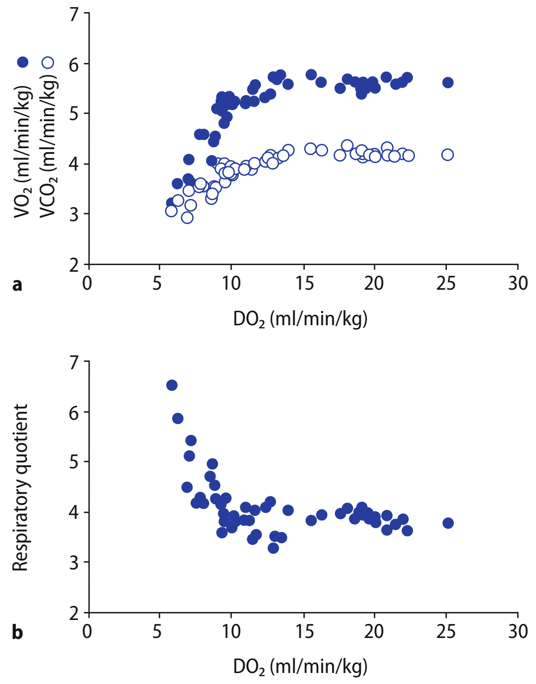

Fig. 5. Effects of progressive bleeding on oxygen consumption (VO_2), carbon dioxide production (VCO_2), and respiratory quotient. Panel **a**. After critical reductions in DO_2, VO_2 and VCO_2 decreased. Panel **b**. After critical reductions in DO_2, respiratory quotient increased [23].

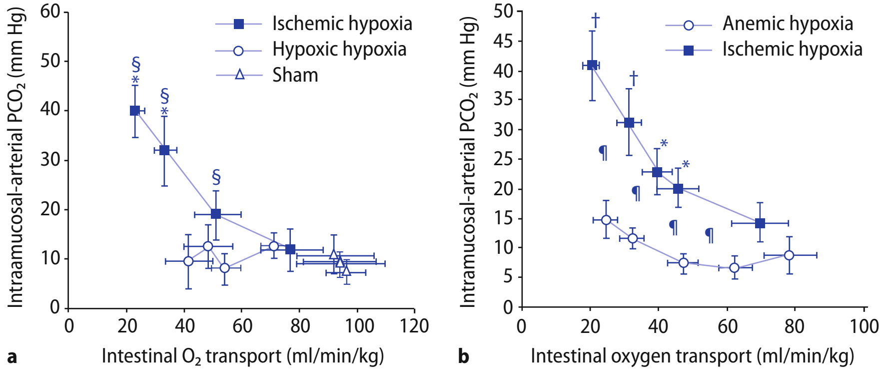

Fig. 6. a Ileal intramucosal-arterial PCO_2 difference (ΔPCO_2) as a function of intestinal oxygen transport in hypoxic and ischemic hypoxia. From [24] with permission. **b** ΔPCO_2 as a function of intestinal oxygen transport in anemic and ischemic hypoxia. From [25] with permission. In hypoxic and anemic hypoxia, ΔPCO_2 fails to reflect tissue dysoxia.

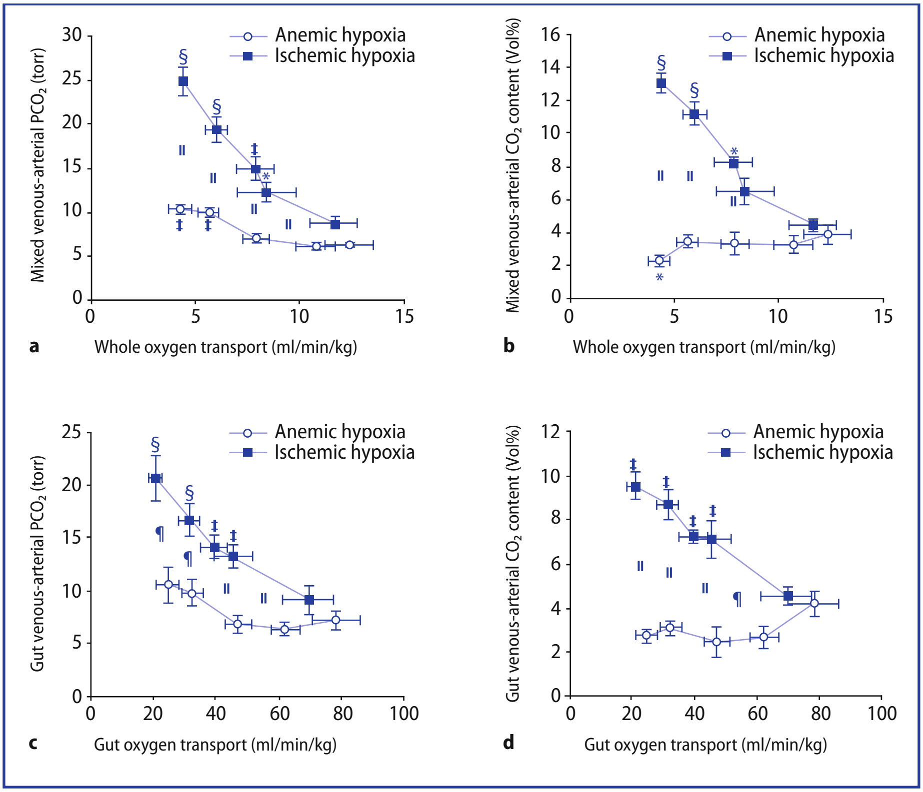

Fig. 7. a Mixed venous-arterial PCO_2 difference as a function of systemic oxygen transport (DO_2) in ischemic and anemic hypoxia. **b** Mixed venous-arterial CO_2 content difference as a function of systemic DO_2 in ischemic and anemic hypoxia. **c** Mesenteric venous-arterial PCO_2 difference as a function of intestinal DO_2 in ischemic and anemic hypoxia. **d** Mesenteric venous-arterial CO_2 content difference as a function of intestinal DO_2 in ischemic and anemic hypoxia. Differences were higher in ischemic than in anemic hypoxia. Venoarterial PCO_2 differences slightly increased while venoarterial CO_2 content differences decreased in anemic hypoxia, implying changes in the CO_2Hb dissociation curve. From [25] with permission.

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 mixed homogeneous conditions, steady-state equilibrium, and VCO_2 occurring exclusively at the tissues. The results of the model supported the idea that changes in tissue and venous blood CO_2 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, pHi 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 ΔPCO_2 [31]. Fluid resuscitation normalized mucosal PO_2 but serosal PO_2 and ΔPCO_2 remained altered. Inhibition of inducible nitric oxide (NO) however restored serosal PO_2 and also ΔPCO_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 ΔPCO_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 ΔPCO_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. 8**).

There are other studies further supporting the hypothesis that, in endotoxemia, changes in perfusion and not tissue dysoxia determine ΔPCO_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 ΔPCO_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.

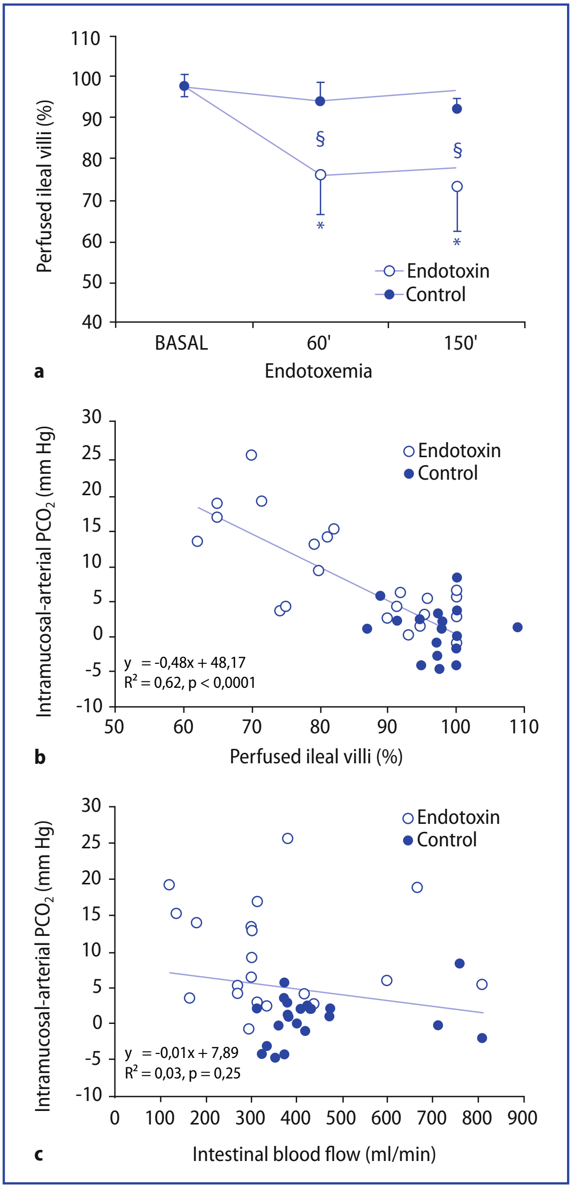

Fig. 8. Effects of endotoxic shock and resuscitation on the percentage of perfused ileal villi and intramucosal-arterial PCO_2 difference (ΔPCO_2). Endotoxic shock decreased the perfused intestinal villi and fluid resuscitation was unable to restore villus perfusion (**a**). ΔPCO_2 was correlated with perfused intestinal villi (**b**) but not with superior mesenteric artery blood flow (**c**). From [34] with permission.

Conclusion

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.

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