The relationship of CO2 metabolism to tissue perfusion, microcirculation, and treatment response in shock and sepsis
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Shock is a life-threatening condition characterized by the inability of the cardiovascular system to support tissue perfusion and oxygenation. Classically, circulatory shock has been divided into four key types—hypovolemic, cardiogenic, obstructive, and distributive—according to its pathophysiological features (1). Regardless of the etiology, the outcome is related to the magnitude of oxygen debt. Experimental and clinical studies have shown that survival is linked to the normalization of different markers of tissue perfusion and oxygenation. Crowell and Smith described that irreversible hemorrhagic shock occurs when the oxygen deficit, evaluated as the area under the curve of basal oxygen utilization, is higher than 140 ml/kg (2). Accordingly, observational studies showed that survivors of different types of shock exhibited higher values of oxygen transport and consumption (DO₂ and VO₂) than nonsurvivors (3, 4). In addition, clinical trials demonstrated that the rapid correction of oxygen debt improves the outcome (5-7).

The monitoring of carbon dioxide at different levels might be an important surrogate for tissue perfusion and oxygenation. End-tidal PCO₂ (PETCO₂) is a useful and simple method of tracking cardiac output during cardiopulmonary resuscitation (8) and a prognostic tool in cardiac arrest (9). The value of this parameter, however, has been only little studied in other low-flow states.

Another approach for the detection and treatment of tissue hypoxia is the monitoring of CO₂ at the regional level. The development of gastrointestinal tonometry was an important step in the monitoring of tissue dysoxia and 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 tracked intramucosal acidosis (10)—i.e., the increase in intramucosal-arterial PCO₂ difference (ΔPCO₂). Likewise, the increase in ΔPCO₂ was better than other systemic and intestinal variables for evidencing tissue hypoperfusion in normal volunteers (11). Intramucosal acidosis was a sensitive predictor of gastric (12) and colonic mucosal ischemia (13) as well as an insightful indicator of outcome. This usefulness has been shown in postoperative (14), critically ill (15), septic (16) and shock (17) patients. Gastric tonometry might also be used to assess the effect of vasoactive drugs (18, 19). Finally, intramucosal pH (pHi) has been evaluated as a guide for resuscitation. Gutierrez et al. demonstrated in a randomized controlled trial that pHi-guided therapy could decrease mortality in critically ill patients (20).

Despite its 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 is poorly reproducible (21), although reproducibility was improved by the introduction of air tonometry (22).
Sublingual capnometry remains an attractive approach (23), but this technique has not yet been adequately validated.

Another source of uncertainty lies in the true significance of ΔPCO₂ elevation (24): Does it reflect increased anaerobic CO₂ production or merely a decreased tissue clearance of CO₂ related to hypoperfusion?

Lastly, the introduction of orthogonal polarization spectral (OPS) (25) and more recently sidestream dark field (SDF) (26) imaging devices now allows an easier visualization of microcirculation in basic research and in the bedside monitoring of critically ill patients.

Hopefully, a comprehensive approach including CO₂ and microcirculation monitoring will improve our understanding of the pathophysiology of shock states.

OUTLINE OF THE THESIS

The monitoring of CO₂ production, tissue washout, and excretion might allow different insights in the pathophysiology of shock and its response to treatment. The pulmonary excretion of CO₂ monitored as PETCO₂ is a sensitive marker of global hypoperfusion. In Chapter 1, we describe the logarithmic relationship between PETCO₂ and cardiac output, during progressive bleeding in dogs. This phenomenon is an expression of decreased pulmonary blood flow and increased dead space as shown by the correlation between the reduction in cardiac output and the increase in the difference between arterial and end-tidal PCO₂.

These issues are further investigated in Chapter 2 where we describe the determinants of the logarithmic relationship between PETCO₂ and cardiac output. With the use of an improved methodology that includes continuous measurements of pulmonary blood flow, CO₂ production (VCO₂), DO₂, and VO₂, we demonstrate that the sharper decreases in PETCO₂ during the critical reductions of cardiac output are the result not only of reduced pulmonary blood flow but also decreased metabolic VCO₂. In addition, beyond a critical value of DO₂, an increase in the respiratory quotient (R = VCO₂/VO₂) arises. The increase in R means that despite the progressive reductions of VCO₂ and VO₂, the former is less affected. This increase in R is an evidence of anaerobic metabolism and results from anaerobic VCO₂ produced by the bicarbonate buffering of anaerobically generated protons.

In Chapter 3, we show that despite the preservation of systemic and intestinal VO₂, intramucosal acidosis can develop during experimental bleeding. Since increased tissue PCO₂ might theoretically occur by anaerobic CO₂ generation or decreased CO₂ washout, the Dill monogram is used in this study to assert the anaerobic source of CO₂. Nevertheless, the use of low flow may act as a potential source of ambiguity, given the impossibility of dissociating tissue dysoxia from hypoperfusion.

To demonstrate that intestinal tissue hypercarbia mainly depends on tissue hypoperfusion, we tested this hypothesis in two sheep models of tissue hypoxia.
with preserved blood flow. As shown in chapters 4 and 5, the ileal $\Delta$PCO$_2$ remains unchanged during oxygen-supply dependency induced by hypoxic and anemic hypoxia compared to ischemic hypoxia. The behaviors of tissue PCO$_2$ determinants during anemic hypoxia—blood flow, VCO$_2$, and the $\mathrm{CO}_2\mathrm{Hb}$ dissociation curve—are comprehensively analyzed in Chapter 5. Our conclusion is that intramucosal acidosis is determined by hypoperfusion and that tissue and venous PCO$_2$ are poor markers of tissue dysoxia when blood flow is maintained.

To show that tissue hypercarbia is a ubiquitous finding in low-flow states, in Chapter 6 we show the behavior of urinary bladder PCO$_2$ during hemorrhagic shock and reperfusion compared to other PCO$_2$ gradients. Although tissue and venous hypercapnia is a widespread consequence of hypoperfusion, our experiments reveal that the increase in PCO$_2$ is higher in ileal mucosa than in bladder mucosa and in mixed and mesenteric venous blood. As another expression of response heterogeneity, only bladder intramucosal acidosis remains after reperfusion.

The presence of gut intramucosal acidosis in septic shock has been considered an evidence of cytopathic hypoxia because this condition develops despite the presence of normal mesenteric blood flow and tissue PO$_2$. Nevertheless, intramucosal acidosis might be explained by villi hypoperfusion, which state may not be detected by regional measurements of blood flow. To further emphasize that CO$_2$ gradients mostly depend on tissue perfusion, we demonstrate in Chapter 7 that supranormal values of blood flow may avoid the development of tissue and venous hypercarbia in endotoxemic sheep. In this model, immediately after the start of endotoxin infusion sheep were randomized to receive fluid resuscitation either to normalize cardiac output and intestinal blood flow or to increase those parameters to supranormal values. Our results show that increased blood flow prevents intramucosal acidosis but not other manifestations of tissue dysoxia such as anion gap metabolic acidosis.

A valuable therapeutic goal could be the correction of tissue hypercarbia. For this purpose, vasoactive drugs may be useful to recruit microcirculation. The response of intramucosal acidosis to vasoactive drugs is evaluated in chapters 8 and 9. First, we show that high doses of levosimendan, an inotropic and vasodilatory drug, improves oxygen transport and prevents intramucosal acidosis in experimental endotoxemia. Nevertheless, systemic hypotension and lactic acidosis occur as a probable consequence of excessive vasodilation. Then, we compare the effects of lower doses of levosimendan with those of dobutamine, the drug commonly used to increase tissue perfusion in septic shock. This dosage increases systemic and intestinal oxygen transport and diminishes intramucosal acidosis without the side effects previously reported. On the other hand, in this model dobutamine lacks beneficial effects on gut perfusion.

In Chapter 10, we show that the persistent villi hypoperfusion accounts for the intramucosal acidosis in sheep endotoxemia. In an experimental model of septic shock and fluid resuscitation, the normalization of systemic and intestinal hemodynamics corrects sublingual and gut serosal microcirculatory alterations.
Ileal mucosal hypoperfusion, however, still remains present after the resuscitation and correlates with $\Delta$PCO$_2$. Consequently, villi perfusion is the determinant of gut luminal PCO$_2$. The determinants of tissue PCO$_2$ in shock and sepsis and their relationship to microcirculation are broadly discussed in Chapter 11.

The systemic and microcirculatory responses to progressive hemorrhage are studied in Chapter 12. A mild to moderate stepwise bleeding that does not affect systemic and intestinal VO$_2$ induces sublingual and intestinal mucosal and serosal microcirculatory changes. These microvascular changes appear from the first step of bleeding and not only reflect systemic alterations but might also express local adjustments that exceed the changes in cardiac output. Despite similar reductions in microvascular flow index (MFI) and red blood cell velocity (RBCV), the intestinal mucosa is the territory most affected because of higher reductions of capillary density and greater heterogeneity. In this study, we also show that the MFI—a semiquantitative score frequently used to characterize the microcirculatory perfusion—strongly correlates with the RBCV directly measured by means of software. This finding indicates that MFI is an adequate evaluation of the microcirculation.

In Chapter 13, we evaluate the effects of increasing mean arterial blood pressure (MAP) with norepinephrine on the sublingual microcirculation of septic shock patients. There are no changes in MFI and in the percent of perfused capillaries when MAP is increased from 65 to 85 mm Hg. There is, however, a trend toward a decreased perfused capillary density. In addition, the changes of perfused capillary density at increased MAP are inversely correlated with the basal perfused capillary density. Thus, the change in the perfused capillary density is strongly dependent on the basal state of microcirculation. Consequently, perfused capillary density improves in patients with altered sublingual perfusion at baseline, and decreases in those with preserved basal microvascular perfusion.

Finally, in a randomized controlled pilot study (Chapter 14), we compare 6% hydroxyethyl starch (HES) 130/0.4 and saline solution for resuscitation of the microcirculation during the early goal directed therapy (EGDT) of septic patients. After 24 hours of EGDT, patients allocated to HES 130/0.4 show better MFI, fraction of perfused capillaries and perfused capillary density than patients in the saline solution group. Our results suggest that EGDT may allow a better recruitment of the microcirculation when 6% HES 130/0.4 is used for the expansion of intravascular volume compared to saline solution.
REFERENCES


