

Mechanisms of tissue hypercarbia in sepsis

Arnaldo Dubin¹, Elisa Estenssoro²

¹*Catedra de Farmacología Aplicada, Facultad de Ciencias Medicas, Universidad Nacional de La Plata and Sanatorio Otamendi y Mirolí, Buenos Aires, Argentina,* ²*Unidad de Terapia Intensiva, Hospital Interzonal General de Agudos "Gral. San Martín", La Plata, Argentina*

TABLE OF CONTENTS

1. Abstract
2. Introduction
3. Mechanisms of increase of venous and tissue PCO₂
4. Intramucosal acidosis in sepsis
5. Acknowledgements
6. References

1. ABSTRACT

Intramucosal acidosis, that it is to say, an increased intramucosal-arterial PCO₂ difference, is a common finding in clinical and experimental sepsis. Nevertheless, the physiologic significance of increases in tissue PCO₂ is controversial, since CO₂ can be generated by both aerobic and anaerobic biochemical processes. PCO₂ can rise after buffering of protons produced in the hydrolysis of high-energy phosphate compounds by bicarbonate, or after the anaerobic production of acids, like lactate. In this case, it could represent tissue dysoxia. Alternatively, an increase in tissue PCO₂ could denote hypoperfusion and diminished removal of the CO₂ produced during the oxidation of pyruvate. In this last situation, aerobic metabolism might be preserved. In the present review, we discuss the physiologic mechanisms that determine tissue and venous hypercarbia during the three classic forms of hypoxia: stagnant, hypoxic and anemic hypoxia. The results of experimental studies suggest that tissue minus arterial and venoarterial PCO₂ gradients primarily reflect alterations in tissue perfusion. These conclusions are further confirmed by a mathematical model of CO₂ transport. In sepsis, however, tissue hypercarbia might develop despite normal or high cardiac output. This phenomenon has been initially interpreted as secondary to alterations in energetic metabolism, the so-called cytopathic hypoxia. Yet, new evidences show that the underlying mechanism to tissue hypercarbia in sepsis might be due to severe microcirculatory derangements. In summary, experimental results support the hypothesis that increases in tissue and venous CO₂ are insensitive markers of tissue dysoxia, and merely reflect vascular hypoperfusion.

2. INTRODUCTION

Almost fifty years ago in Hungary, Boda and Muranyi developed gastric tonometry as a method to approximate arterial PCO₂ in intubated, mechanically ventilated children with polio (1). These investigators advanced a latex balloon into the stomach and filled it with air. After an equilibration time of approximately 2 hours, infrared measurement of CO₂ were performed in more than 400 ventilated patients, together with CO₂ determinations in expired air. These observations made them conclude that "the CO₂ tension of arterial blood could be estimated with reasonable accuracy" from gastric CO₂. Nevertheless, they underscored that "gastric PCO₂ may be misleadingly high in severe shock accompanied by an excessive slowing of the circulation." This landmark observation was overlooked until the 1980s, when Fiddian-Green *et al.* (2) introduced the notion that the pH of the gut mucosa could be calculated by sampling gastric CO₂. These investigators based their hypothesis on three assumptions: (1) CO₂ diffuses freely in tissue, (2) PCO₂ in the luminal fluid is in equilibrium with the mucosal PCO₂, and (3) arterial bicarbonate concentration ([HCO₃⁻]) equals intestinal mucosal bicarbonate. Given these assumptions, the application of the Henderson-Hasselbalch equation allows the calculation of the intramucosal pH (pHi):

$$pHi = 6.1 + \log ([HCO_3^-] / \alpha \cdot \text{tonometer PCO}_2)$$

where α represents the solubility of CO₂ in plasma ($\alpha = 0.03$). The assumptions underlying the calculation of pHi, particularly the equivalence between mucosal and arterial blood bicarbonate, held surprisingly well. Intestinal ischemia, in which mucosal bicarbonate may be

Mechanisms of tissue hypercarbia in sepsis

significantly lower than arterial bicarbonate, was a notable exception. Under these conditions, the absolute decrease in tonometric pHi underestimates local pHi, although the change in the signal intensity may still serve as a useful clinical warning (3).

Another problem arises in the interpretation of low mucosal pHi in the presence of systemic acidosis. In this situation, low pHi probably does not suggest local tissue hypoxia but reflects instead low arterial pH. Because of these potential drawbacks in the interpretation of pHi, many investigators currently favor the use of the intramucosal-arterial PCO₂ difference (Δ PCO₂) (4).

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 was used to detect and to treat hypoperfusion.

From an experimental point of view, tonometry adequately tracks intramucosal acidosis (3), that it to say, the increase in Δ PCO₂. Likewise, the increase in Δ PCO₂ is better than other systemic and intestinal variables to show tissue hypoperfusion, both in normal volunteers (5) and experimental models (6). Intramucosal acidosis is a sensitive predictor of gastric (7) and colonic mucosal ischemia (8). Furthermore, gastric tonometry is an insightful predictor of outcome. This usefulness has been shown in postoperative (9) critically ill (10), septic (11) and shock patients (12). Gastric tonometry might be also used to assess the effect of vasoactive drugs (13, 14). Finally, pHi has been evaluated as a guide of resuscitation. Gutierrez *et al.* demonstrated in a randomized controlled trial that pHi-guided therapy could decrease mortality in critically ill patients (15).

Despite of having been the only clinically available approach to tissue perfusion during many years, and of the scientific evidence supporting its usefulness, gastrointestinal tonometry is not commonly used. Different reasons might explain this issue. Saline tonometry has a poor reproducibility (16), which has been improved by the use of air tonometry (17). Sublingual capnometry remains an attractive approach (18), but this technique has not been adequately validated yet.

Another source of uncertainty lies in the true significance of Δ PCO₂ elevation. In the last few years, new evidence allowed a better understanding of the mechanisms underlying intramucosal acidosis. In this review, we will discuss the pathophysiology of tissue and venous CO₂ accumulation in shock states, particularly in septic shock.

3. MECHANISMS OF INCREASE OF VENOUS AND TISSUE PCO₂

Increased mucosal intestinal PCO₂ is used to detect tissue dysoxia, a condition in which O₂ delivery (DO₂) can no longer sustain O₂ uptake (VO₂) (19). Twenty years ago, Grum *et al.* (20) evaluated the adequacy of gut oxygenation by the tonometric measurement of pHi, during

oxygen transport reductions secondary to ischemia, hypoxemia, or a combination of both. pHi only decreased after critical reductions of DO₂. Consequently, changes of VO₂ and pHi were closely correlated (Figure 1). The authors concluded that pHi appears to be a sensitive indicator of tissue oxygenation, because it mirrors tissue VO₂ consumption. Nevertheless, critical DO₂ was only reached in ischemic experiments. In pure hypoxemic experiments, neither pHi nor VO₂ fell.

PCO₂ can increase in the intestinal lumen by two mechanisms (21): 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, in an aerobic state, PCO₂ might increase after hypoperfusion and decreased washout. In this case, oxygen metabolism would be preserved.

Trying to solve this controversy, Schlichtig and Bowles (21) presented evidence supporting intramucosal PCO₂ as a marker of dysoxia in extreme hypoperfusion, when VO₂ falls. In a dog model of cardiac tamponade, they demonstrated that below critical DO₂, mucosal PCO₂ could rise because of anaerobic production of CO₂. This conclusion was drawn using the Dill nomogram, which can theoretically detect anaerobic CO₂ production from the comparison of the measured (%HbO₂v) vs. calculated (%HbO₂vDILL) venous oxyhemoglobin, within a given value of venous PCO₂. As venous PCO₂ is considered representative of tissue PCO₂, they made the calculation with its intestinal equivalent, intramucosal PCO₂. Similar values of measured (%HbO₂v) vs. calculated (%HbO₂vDILL) venous oxyhemoglobin would represent aerobic CO₂ generation. If %HbO₂vDILL is lower than measured %HbO₂v, anaerobic production of CO₂ might be assumed. Using this approach, we identified an anaerobic source of gut intramucosal CO₂ during a hemorrhage of moderate degree (6). Our %HbO₂vDILL values obtained from gastric, jejunal and ileal mucosal PCO₂ became remarkably negative during ischemia, indicating an anaerobic process in course (Figure 2). Notwithstanding the original contribution of Schlichtig and Bowles (21) to the analysis of these topics, the use of low flow to produce critical oxygen delivery and decrease oxygen uptake might act as a potential confounder, given the impossibility of dissociating tissue dysoxia from hypoperfusion (22).

Vallet *et al.* (23) 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 experienced similar declines in DO₂ and VO₂, implying similar degrees of tissue dysoxia (24). The venoarterial PCO₂ difference, however, remained constant in the hypoxic hypoxia group, and increased more than twofold in the ischemic hypoxia group. Vallet *et al.* concluded that it was flow, not tissue dysoxia, the major

Mechanisms of tissue hypercarbia in sepsis

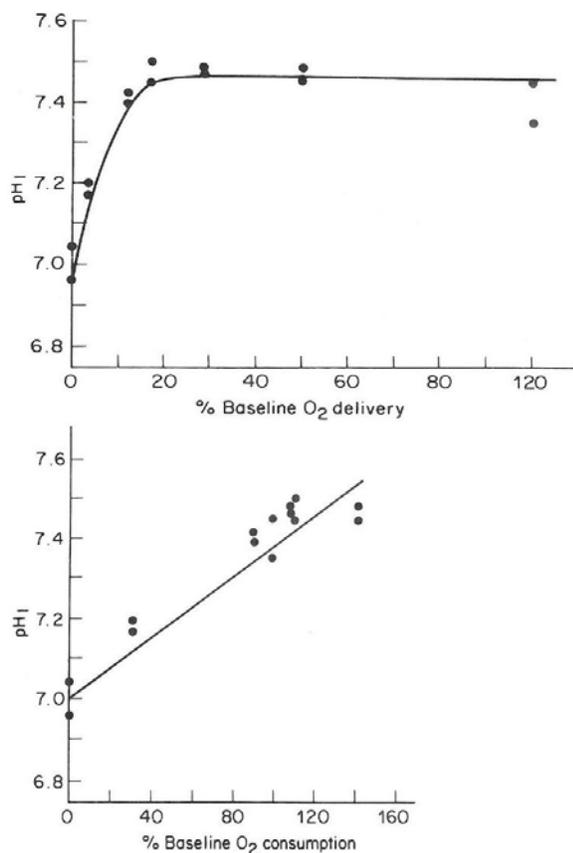


Figure 1. Panel A. Intestinal intramucosal pH as a function of O₂ delivery. Panel B. Intestinal intramucosal pH as a function of intestinal O₂ consumption (Reproduced from reference 16 with permission). Reductions of intramucosal pH are only present with critical reductions of O₂ delivery.

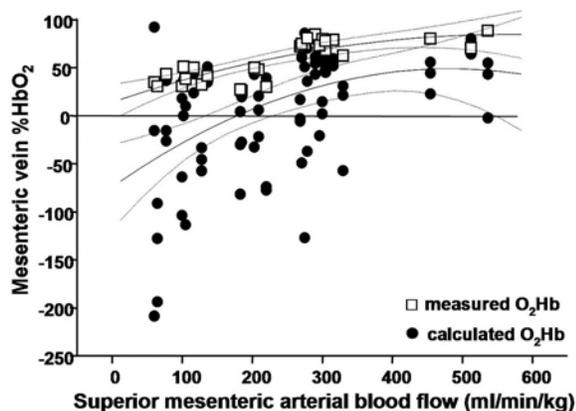


Figure 2. Measured venous oxygen saturation (%HbO_{2v}) (□) and venous oxygen saturation calculated from gut tissue PCO₂ (%HbO_{2v}^{DILL}) (●) as a function of superior mesenteric arterial blood flow. Since %HbO_{2v}^{DILL} is lower than measured %HbO_{2v}, anaerobic production of CO₂ might be assumed (Reproduced from reference 4 with permission).

determinant of venoarterial PCO₂ difference (23) (Figure 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 (25). In ischemic hypoxia, ΔPCO₂ rose to 60 mm Hg. 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 denoted local CO₂ generation. Some flow heterogeneity, however could have been present in their experiments not assessed by laser-Doppler, a method that only tracks global microvascular changes. In addition, in the two preceding steps of FiO₂ reductions, VO₂/DO₂ dependency had been reached, and ΔPCO₂ remained unchanged.

We further explored this issue in another model of hypoxic hypoxia (26). In these experiments, venous and tissue PCO₂ increased during ischemic hypoxia, but not during hypoxic hypoxia. Therefore, ΔPCO₂ was unable to show the presence of tissue dysoxia during hypoxic hypoxia, in which blood flow is preserved (Figure 4). To confirm that blood flow is the main determinant of ΔPCO₂, we studied these relationships in another model of tissue dysoxia without hypoperfusion, anemic hypoxia (27) (Figure 4). We compared the effects of progressive bleeding with those of isovolemic exchange of blood with dextran. Our goals were to evaluate the behavior of CO₂ gradients as a function of systemic and intestinal blood flow, and also its other determinants, like CO₂ production and CO₂Hb dissociation curve. Tissue-arterial and venoarterial PCO₂ failed to reflect the dependence of VO₂ on DO₂. Nevertheless, these gradients increased few mmHg (Figures 4 and 5). Conversely, venoarterial CO₂ content differences decreased. This apparent paradox might be explained by changes in the CO₂Hb dissociation curve (Figure 6). The other determinant of PCO₂ differences, the CO₂ production remained unchanged, both at systemic and intestinal level. The systemic and intestinal respiratory quotient, however, increased because of VO₂ reductions (Figure 7).

In summary, our results (26, 27), together with those of Vallet *et al.* (23) support that increases in tissue-arterial and venoarterial PCO₂ gradients reflect only microcirculatory stagnation, and not tissue dysoxia. Tissue and venous PCO₂ are insensitive markers of dysoxia and merely might reflect hypoperfusion. These experimental findings were confirmed by a mathematical model (28). Gutierrez developed a two-compartment mass transport model of tissue CO₂ exchange during hypoxic hypoxia conditions, to examine the relative contributions of blood flow and cellular dysoxia to the increases in tissue and venous PCO₂. The model assumes perfectly mixed homogeneous conditions, steady-state equilibrium, and CO₂ production occurring exclusively at the tissues. The results of the model applications support that changes in tissue and venous blood CO₂ concentrations during dysoxia reflect primarily alterations in vascular perfusion, and not shortage of energy supply.

Mechanisms of tissue hypercarbia in sepsis

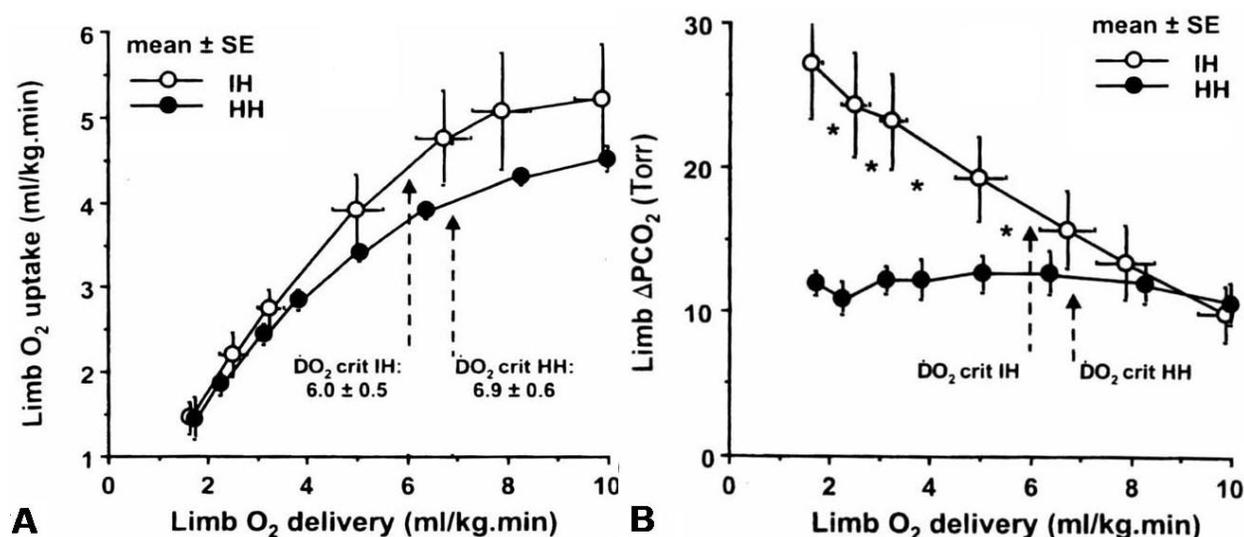


Figure 3. Panel A. Hindlimb O₂ uptake as a function of limb O₂ delivery (DO₂) for ischemic hypoxia (IH) and hypoxic hypoxia (HH). There was no statistically significant difference at any DO₂. Critical DO₂ (DO₂crit) was not different in IH and HH. Panel B. Hindlimb venoarterial PCO₂ difference as a function 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. (Reproduced from reference 19 with permission).

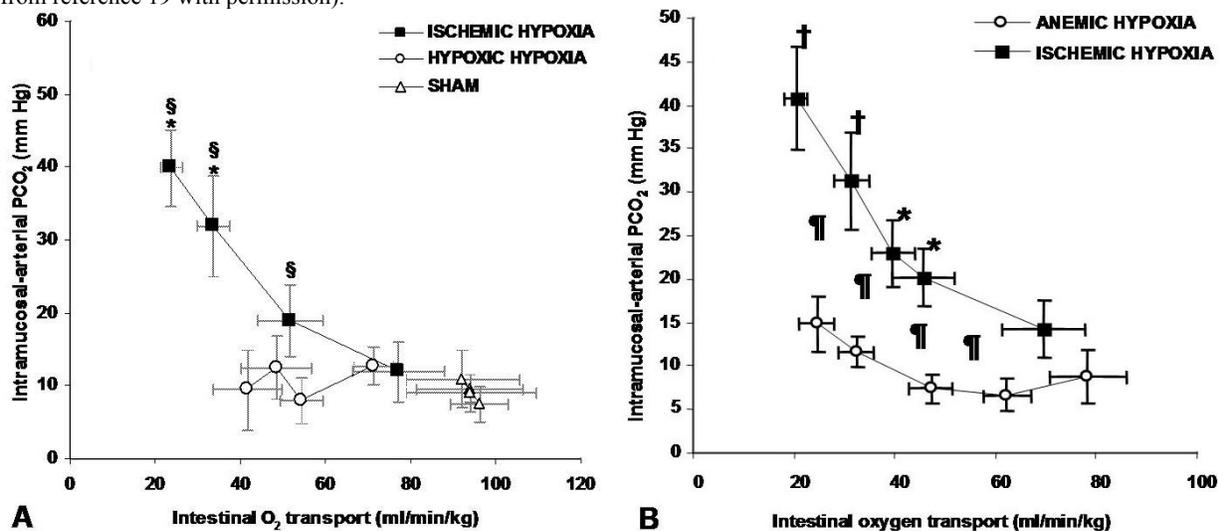


Figure 4. Panel A. Ileal intramucosal-arterial PCO₂ difference (ΔPCO₂) as a function of intestinal O₂ transport in hypoxic and ischemic hypoxia (Reproduced from reference 21 with permission). Panel B. ΔPCO₂ as a function of intestinal O₂ transport in anemic and ischemic hypoxia (Reproduced from reference 22 with permission). In hypoxic and anemic hypoxia, ΔPCO₂ fails to reflect tissue dysoxia.

4. INTRAMUCOSAL ACIDOSIS IN SEPSIS

Beyond the previous discussion, intramucosal acidosis is common in conditions with normal or increased cardiac output, like clinical and experimental sepsis. In resuscitated endotoxemic pigs, Van der Meer *et al.* found that intramucosal acidosis developed, despite preserved mucosal oxygenation and blood flow (29) (Figure 8). The underlying mechanism was attributed to metabolic disturbances, and led to the concept of “cytopathic

hypoxia” (30). Nevertheless, an important shortcoming of that study was the use of laser-Doppler flowmetry to measure tissue perfusion.

On the other hand, Vallet *et al.* studied dogs challenged with endotoxin, and then resuscitated them to normalize oxygen transport (31). Intestinal VO₂ and mucosal PO₂ and pH, however, remained low. The authors ascribed this to blood flow redistribution from mucosa toward muscular layer. Nevertheless, Revelly *et al.*,

Mechanisms of tissue hypercarbia in sepsis

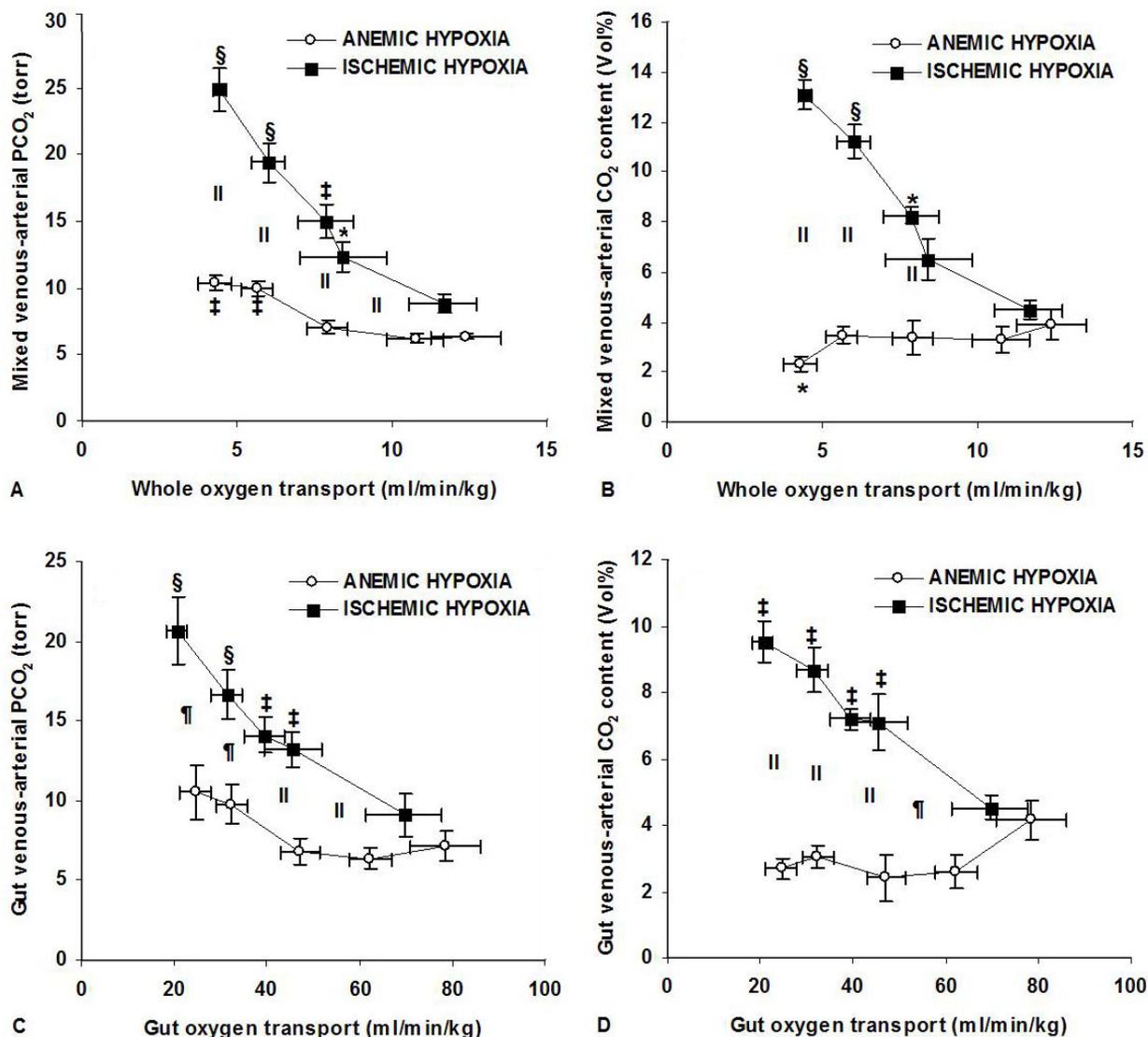


Figure 5. Panel A. Mixed venous-arterial PCO₂ difference as a function of systemic O₂ transport (DO₂) in ischemic and anemic hypoxia. Panel B. Mixed venous-arterial CO₂ content difference as a function of systemic DO₂ in ischemic and anemic hypoxia. Panel C. Mesenteric venous-arterial PCO₂ difference as a function of intestinal DO₂ in ischemic and anemic hypoxia. Panel D. Mesenteric venous-arterial CO₂ content difference as a function of intestinal DO₂ in ischemic and anemic hypoxia. (Reproduced from reference 22 with permission). Differences were higher in ischemic than in anemic hypoxia. Venoarterial PCO₂ differences slightly increased while venoarterial CO₂ content differences decreased in anemic hypoxia, implying changes in CO₂Hb dissociation curve.

described an inverse redistribution, with increased mucosal and decreased muscularis blood flow, using dyed microspheres in endotoxemic pigs (32). Paradoxically, pHi was inversely correlated with mucosal flow, though positively correlated with muscularis perfusion. The authors concluded that intramucosal acidosis was not explained by mucosal hypoperfusion (32). Siegemund *et al.* showed, in a similar model, reductions in mucosal and serosal microvascular PO₂, and a ΔPCO₂ increase (33). Fluid resuscitation normalized mucosal PO₂ but serosal PO₂ and ΔPCO₂ remained altered.

Conversely, Tugtekin *et al.*, in a porcine model of 24-hour endotoxin infusion, showed an association between intramucosal acidosis and severe hypoperfusion in ileal villi (34). In this study, about half of the evaluated villi were heterogeneously or unperfused, despite normal portal blood flow. Creuter *et al.* described, in septic patients, a correlation between sublingual ΔPCO₂ and microcirculatory blood flow (35). Accordingly, results from our laboratory show that endotoxic shock in sheep was associated with sublingual and intestinal microcirculatory alterations and intramucosal acidosis (36). Fluid resuscitation could normalize sublingual and intestinal

Mechanisms of tissue hypercarbia in sepsis

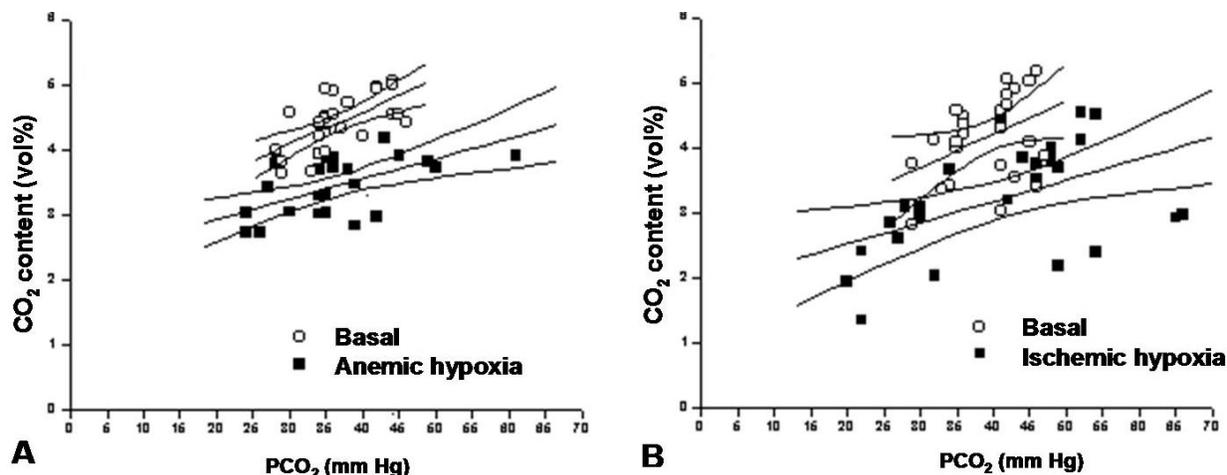


Figure 6. Panel A. CO₂ content as a function of PCO₂ in basal and anemic hypoxia conditions. Panel B. CO₂ content as a function of PCO₂ in basal and ischemic hypoxia conditions. In both anemia and ischemic hypoxia there were shifts in CO₂Hb dissociation curve that might contribute to subtle increases in tissue-arterial and venoarterial PCO₂ differences (22).

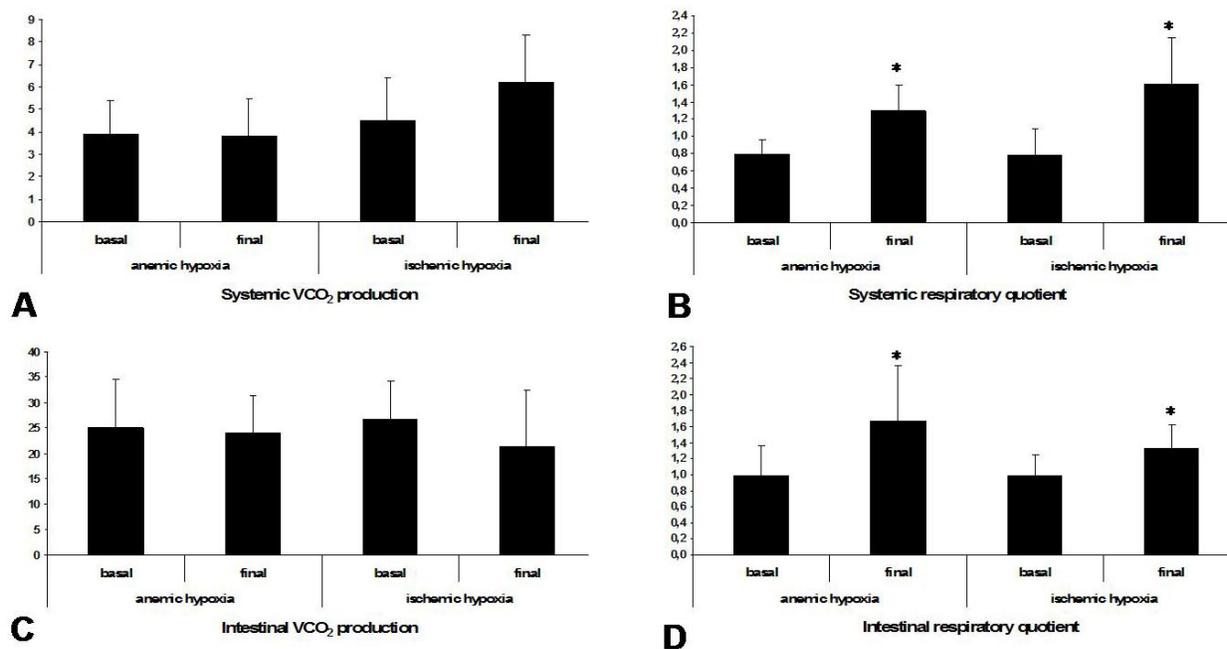


Figure 7. Panel A. Systemic CO₂ production (VCO₂) in anemic and ischemic hypoxia. Panel B. Systemic respiratory quotient (RQ) in anemic and ischemic hypoxia. Panel C. Intestinal VCO₂ in anemic and ischemic hypoxia. Panel D. Intestinal respiratory RQ in anemic and ischemic hypoxia. Both systemic and intestinal VCO₂ remained unchanged. Since VO₂ decreased as a result of oxygen supply dependence, both systemic and intestinal RQ increased (22).

serosal microcirculation, yet reduced number of perfused intestinal villi and increased Δ PCO₂ persisted. Intramucosal acidosis was related to persistent decrease of microvascular flow index and reduced number of perfused intestinal villi (36) (Figure 9).

There are other studies further supporting the hypothesis that, in endotoxemia, changes in perfusion and not tissue dysoxia determine Δ PCO₂. We randomized endotoxemic sheep to saline solution resuscitation to

maintain blood flow at baseline values or to increase it 50%. Increased perfusion prevented intramucosal acidosis, though metabolic acidosis due to increased anion gap continued (37) (Figure 10). Similarly, in endotoxemic sheep, the administration of levosimendan, an inotropic and vasodilator drug, precluded increases in Δ PCO₂ but hyperlactatemia was exacerbated (38) or unaffected (39). The findings of these studies suggest that intramucosal acidosis is mainly related to local hypoperfusion and that

Mechanisms of tissue hypercarbia in sepsis

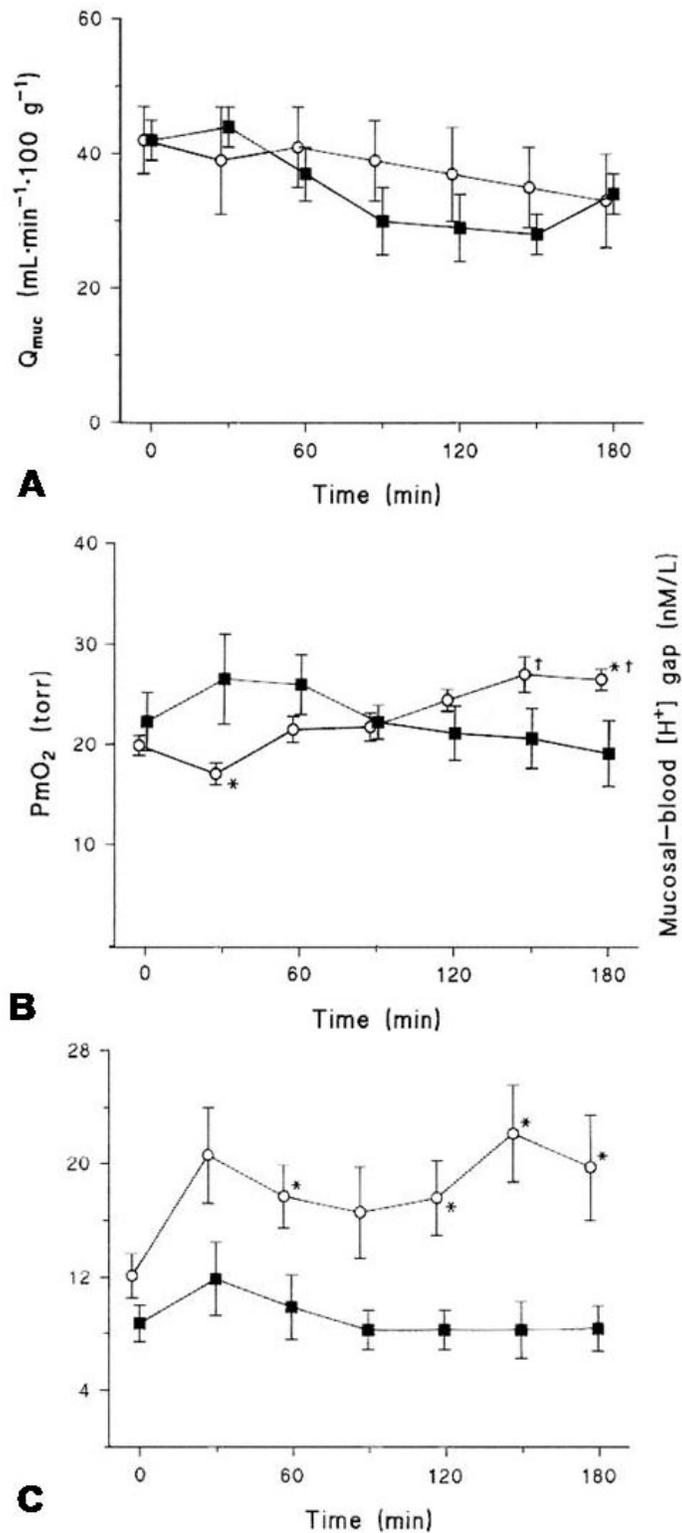


Figure 8. Effects of lipopolysaccharide on mucosal perfusion (Q_{muc} ; panel A), mucosal PO_2 (PmO_2 ; panel B), and mucosal-blood hydrogen ion concentration gap (mucosal-blood $[H^+]$ gap; panel C). Lipopolysaccharide was administered to pigs in the lipopolysaccharide group (open circles) but not to pigs in the control group (solid squares) (Reproduced from reference 24 with permission).

Mechanisms of tissue hypercarbia in sepsis

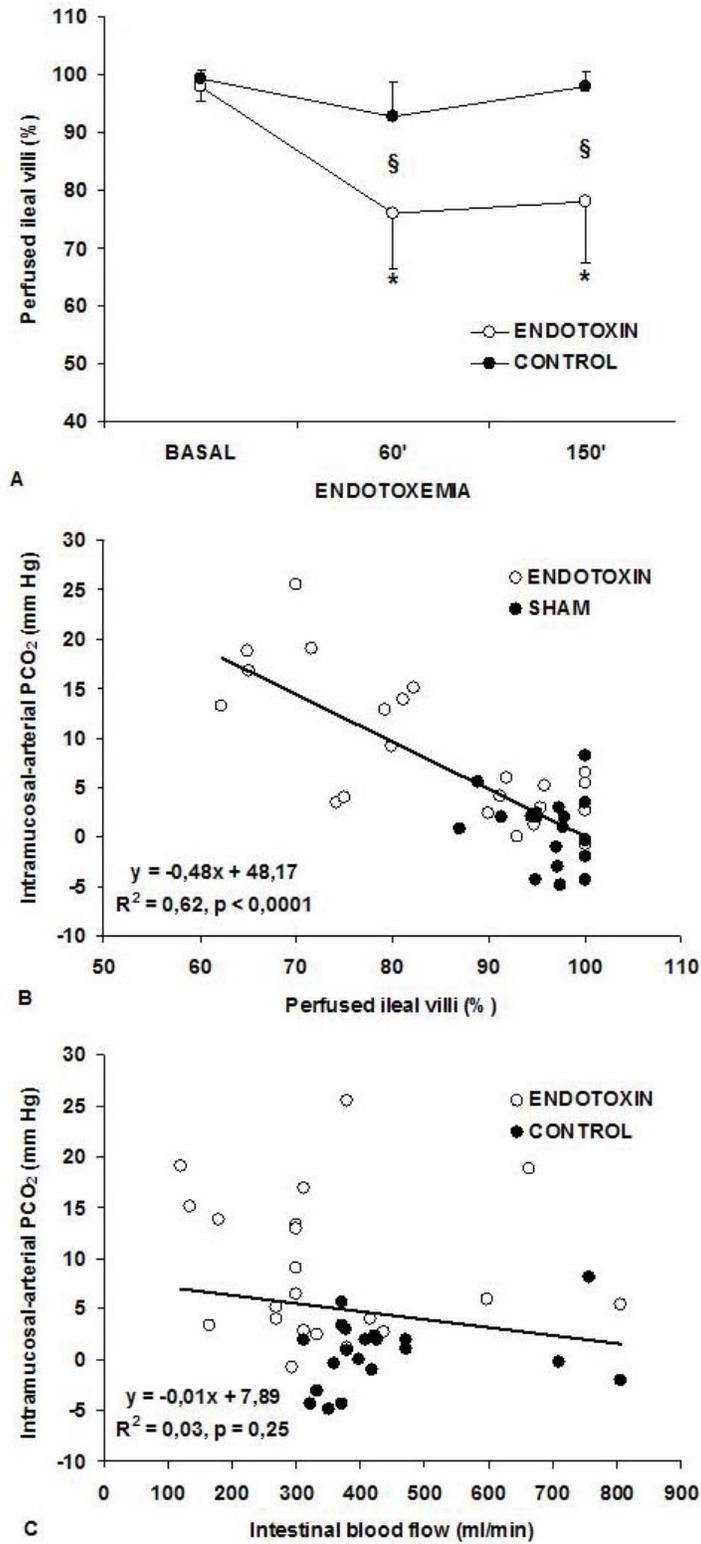


Figure 9. Effects of endotoxin on the percentage of perfused ileal villi and intramucosal-arterial PCO₂ difference (Δ PCO₂) (36). Endotoxic shock decreased the perfused intestinal villi and fluid resuscitation was unable to restore villi perfusion (Panel A). (Δ PCO₂ was correlated with perfused intestinal villi (Panel B) but not with superior mesenteric artery blood flow (Panel C).

Mechanisms of tissue hypercarbia in sepsis

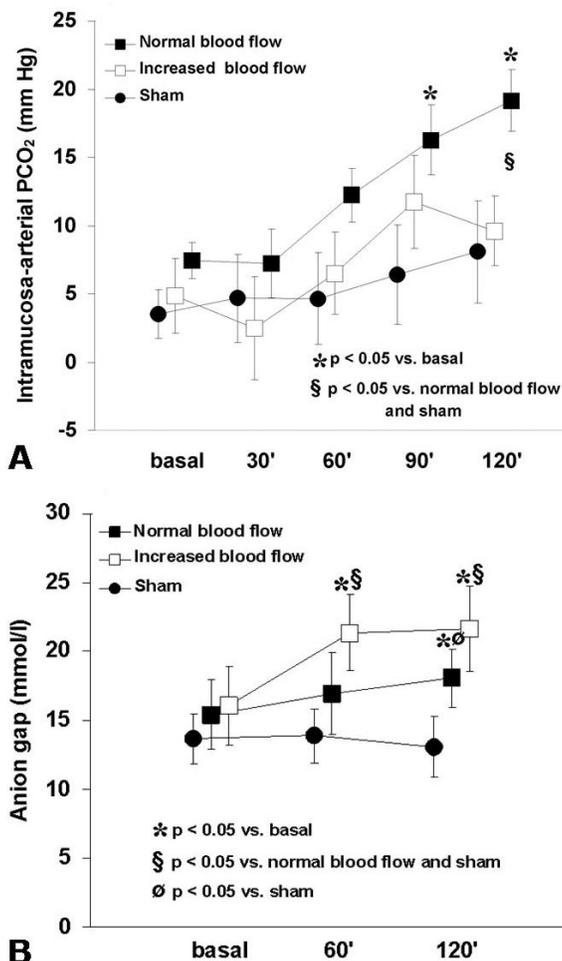


Figure 10. Effects of supranormal elevation of blood flow in a normodynamic model of endotoxemia. Panel A. Increased blood flow precluded the increase in intramucosal-arterial PCO₂ difference, suggesting that intramucosal acidosis is mainly related to local hypoperfusion. Panel B. Despite an increased blood flow, anion-gap metabolic acidosis worsened, which suggests an effect on cellular metabolism (Reproduced from reference 37 with permission).

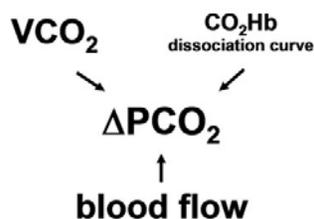


Figure 11. Determinants of intramucosal-arterial PCO₂ difference (Δ PCO₂). Venoarterial and tissue-arterial PCO₂ gradients are the result of interactions in aerobic and anaerobic CO₂ production (VCO₂), CO₂ dissociation curve, and blood flow to tissues. During VO₂/DO₂ dependency, opposite changes in aerobic and anaerobic CO₂ productions occur. CO₂ aerobic production decreases as a consequence of the fall in aerobic metabolism, but at the same time, CO₂ anaerobic production starts because of bicarbonate buffering of protons derived of fixed acids. Total CO₂ production, however, never increases. Consequently, venous and tissue hypercarbia can only arise in low flow states, in which CO₂ removal is reduced.

metabolic disorders depends on a cellular mechanism which is unresponsive to changes in blood flow.

In conclusion, venoarterial and tissue-arterial PCO₂ gradients are the result of interactions in aerobic and

anaerobic CO₂ production, CO₂ dissociation curve, and blood flow to tissues (Figure 11). During VO₂/DO₂ dependency, opposite changes in aerobic and anaerobic CO₂ productions occur. CO₂ aerobic production decreases as a consequence of failing aerobic metabolism, but, at the

Mechanisms of tissue hypercarbia in sepsis

same time, CO₂ anaerobic production starts due to bicarbonate buffering of protons derived of fixed acids. Total CO₂ production might not increase, as in our experiments. But as VO₂ falls, there is an increase in the respiratory quotient (27). The relative increment of CO₂ production with respect to VO₂ can only cause venous and tissue hypercarbia in low flow states, in which CO₂ removal is reduced.

Notwithstanding the fact that Δ PCO₂ is not a marker of dysoxia but of regional perfusion, it remains a very useful clinical and experimental monitoring tool, particularly in clinical situations in which cardiac output is generally increased, like sepsis.

5. ACKNOWLEDGEMENTS

Arnaldo Dubin and Elisa Estenssoro equally contributed to this article.

6. REFERENCES

1. Domokos Boda, László Murányi: Gastrotonometry: An aid to the control of ventilation during artificial respiration. *Lancet* 273, 181-182 (1959)
2. Richard Fiddian-Green: Studies in splanchnic ischemia and multiple organ failure. In: *Splanchnic ischemia and multiple organ failure*. By Martson A, Bulkley GB, Fiddian-Green RG, Haglund U eds. CV Mosby, St Louis, London. 349-363, (1989)
3. Jan Antonsson, Charles Boyle 3rd., Keith Kruthoff, Hailong Wang, Emil Sacristan, Heidie Rothschild, Mitchell Fink: Validation of tonometric measurement of gut intramural pH during endotoxemia and mesenteric occlusion in pigs. *Am J Physio* 259, G519-G523 (1990)
4. Robert Schlichtig, Navdeep Mehta, Timothy Gayowski: Tissue-arterial PCO₂ difference is a better marker of ischemia than intramural pH (pHi) or arterial pH-pHi difference. *J Crit Care* 11:51-56 (1996)
5. Colin Hamilton-Davies, Monty Mythen, Salmon JB, Jacobson D, Shukla A, Andrew Webb: Comparison of commonly used clinical indicators of hypovolaemia with gastrointestinal tonometry. *Intensive Care Med* 23, 276-281 (1997)
6. Arnaldo Dubin, Elisa Estenssoro, Gastón Murias, Héctor Canales, Pablo Sottile, Julio Badie, Marcelo Baran, Fernando Palizas, Mercedes Laporte, Mariana Rivas Diaz: Effects of hemorrhage on gastrointestinal oxygenation. *Intensive Care Med* 27, 1931-1936 (2001)
7. Richard Fiddian-Green, Edwin McGough, Gary Pittenger, E Rothman: Predictive value of intramural pH and other risk factors for massive bleeding from stress ulceration. *Gastroenterology* 85, 613-620 (1983)
8. MG Schiedler, BS Cutler, Richard Fiddian-Green: Sigmoid intramural pH for prediction of ischemic colitis during aortic surgery. A comparison with risk factors and inferior mesenteric artery stump pressures. *Arch Surg* 122, 881-886 (1987)
No DOI found
9. Monty Mythen, Andrew Webb: Intra-operative gut mucosal hypoperfusion is associated with increased post-operative complications and cost. *Intensive Care Med* 20, 99-104 (1994)
10. Guillermo Doglio, Jorge Pusajo, Monica Egurrola, Graciela Bonfigli, Carlos Parra, Liliana Vetere, Maria Hernandez, Sofia Fernandez, Fernando Palizas, Guillermo Gutierrez: Gastric mucosal pH as a prognostic index of mortality in critically ill patients. *Crit Care Med* 19, 1037-1040 (1991)
11. Gilberto Friedman; Giorgio Berlot, Robert Kahn, Jean-Louis Vincent: Combined measurements of blood lactate concentrations and gastric intramucosal pH in patients with severe sepsis. *Crit Care Med* 23, 1184-1193 (1995)
12. Nicholas Maynard, David Bihari, Richard Beale, Mark Smithies, Graham Baldock, Robert Mason, Ian McColl: Assessment of splanchnic oxygenation by gastric tonometry in patients with acute circulatory failure. *JAMA* 270, 1203-1210 (1993)
13. Gutierrez Gutierrez, Clark C, Brown SD, Price K, Ortiz L, Nelson C: Effect of dobutamine on oxygen consumption and gastric mucosal pH in septic patients. *Am J Respir Crit Care Med* 150, 324-329 (1994)
14. Remi Nevière, Daniel Mathieu, Jean-Luc Chagnon, Nathalie Lebleu, Francis Wattel: The contrasting effects of dobutamine and dopamine on gastric mucosal perfusion in septic patients. *Am J Respir Crit Care Med* 154, 1684-1688 (1996)
15. Guillermo Gutierrez, Fernando Palizas, Guillermo Doglio, Néstor Wainsztein, Antonio Galesio, Juan Pacin, Arnaldo Dubin, Eduardo Schiavi, Miguel Jorge, Jorge Pusajo, Francisco Klein, Eduardo San Román, Bernardo Dorfman, Shottlender Juan, Roberto Giniger: Gastric intramucosal pH as a therapeutic index of tissue oxygenation in critically ill patients. *Lancet* 339, 195-199 (1992)
16. Lavi Oud, James Kruse: Poor *in vivo* reproducibility of gastric intramucosal pH determined by saline-filled balloon tonometry. *J Crit Care* 11, 144-150 (1996)
17. David Taylor, Guillermo Gutierrez, Cinda Clark, Susan Hainley: Measurement of gastric mucosal carbon dioxide tension by saline and air tonometry. *J Crit Care* 12, 208-213 (1997)
18. Alexandre Toledo Maciel, Jacques Creteur, Jean-Louis Vincent: Tissue capnometry: does the answer lie under the tongue? *Intensive Care Med* 30, 2157-2165 (2004)

Mechanisms of tissue hypercarbia in sepsis

19. Carl Honig, Richard Connett, Thomas Gayeski, George Brooks: Defining hypoxia: a systems view of VO₂, glycolysis, energetics, and intracellular PO₂. *J Appl Physiol* 68, 833-842 (1990)
20. Cyril Grum, Richard Fiddian-Green, Gary Pittenger, Brydon Grant, Edward Rothman, David Dantzker: Adequacy of tissue oxygenation in intact dog intestine. *J Appl Physiol* 56, 1065-1069 (1984)
No DOI found
21. Robert Schlichtig, Stephen Bowles: Distinguishing between aerobic and anaerobic appearance of dissolved CO₂ in intestine during low flow. *J Appl Physiol* 76, 2443-2451 (1994)
22. Benoit Vallet, Benoit Tavernier, Niels Lund: Assessment of tissue oxygenation in the critically ill. In: Yearbook of intensive care and emergency medicine. By Vincent JL ed. Springer-Verlag, Berlin Heidelberg New York. 715-725 (2000)
23. Benoit Vallet, Jean-Louis Teboul, Stephen Cain, Scott Curtis: Venous-arterial CO₂ difference during regional ischemic or hypoxic hypoxia. *J Appl Physiol* 89, 1317-1321 (2000)
24. Guillermo Gutierrez, Richard Pohil, James Andry, Roger Strong, Ponnada Narayana: Bioenergetics of rabbit skeletal muscle during hypoxemia and ischemia. *J Appl Physiol* 65, 608-616 (1988)
25. Rémi Nevière, Jean-Luc Chagnon, Jean-Louis Teboul, Benoit Vallet, Francis Wattel: Small intestine intramucosal PCO₂ and microvascular blood flow during hypoxic and ischemic hypoxia. *Crit Care Med* 30, 379-384 (2002)
26. Arnaldo Dubin, Gastón Murias, Elisa Estenssoro, Héctor Canales, Julio Badie, Mario Pozo, Juan Sottile, Marcelo Barán, Fernando Palizas, Mercedes Laporte: Intramucosal-arterial PCO₂ gap fails to reflect intestinal dysoxia in hypoxic hypoxia. *Crit Care* 6, 514-520 (2002)
27. Arnaldo Dubin, Elisa Estenssoro, Gastón Murias, Mario Pozo, Juan Sottile, Marcelo Barán, Enrique Piacentini, Héctor Canales, Graciela Etcheverry: Intramucosal-arterial PCO₂ gradient does not reflect intestinal dysoxia in anemic hypoxia. *J Trauma* 57, 1211-1217 (2004)
28. Guillermo Gutierrez: A mathematical model of tissue-blood carbon dioxide exchange during hypoxia. *Am J Respir Crit Care Med* 169, 525-533 (2004)
29. Thomas VanderMeer, Hailong Wang, Mitchell Fink: Endotoxemia causes ileal mucosal acidosis in the absence of mucosal hypoxia in a normodynamic porcine model of septic shock. *Crit Care Med* 23, 1217-1226 (1995)
30. Mitchell Fink: Bench-to bedside review: Cytopathic hypoxia. *Crit Care* 6, 491-499 (2002)
31. Benoit Vallet, Niels Lund, Scott Curtis, David Kelly, Stephen Cain: Gut and muscle tissue PO₂ in endotoxic dogs during shock and resuscitation. *J Appl Physiol* 76, 793-800 (1994)
32. Jean-Pierre Revelly, Takao Ayuse, Nicola Brienza, Henry Fessler, James Robotham: Endotoxic shock alters distribution of blood flow within the intestinal wall. *Crit Care Med* 24, 1345-1351 (1996)
33. Martin Siegemund, Jasper van Bommel, Lothar Schwarte, Wolfgang Studer, Thierry Girard, Stephan Marsch, Peter Radermacher, Ince C: Inducible nitric oxide synthase inhibition improves intestinal microcirculatory oxygenation and CO₂ balance during endotoxemia in pigs. *Intensive Care Med* 31, 985-992 (2005)
34. IF Tugtekin, Peter Radermacher, Marc Theisen, Martin Matejovic, Alexander Stehr, Franz Ploner, Keshen Matura, Can Ince, Michael Georgieff, Karl Trager: Increased ileal-mucosal-arterial PCO₂ gap is associated with impaired villus microcirculation in endotoxic pigs. *Intensive Care Med* 27, 757-766 (2001)
35. Jacques Creteur, Daniel De Backer, Yasser Sakr, Marc Koch, Jean-Louis Vincent: Sublingual capnometry tracks microcirculatory changes in septic patients. *Intensive Care Med* 32, 516-523 (2006)
36. Arnaldo Dubin, Vanina Kanoore Edul, Gastón Murias, Carlos Canullán, Enrique Martins, Gonzalo Ferrara, Héctor Canales, an Ince: Persistent villi hypoperfusion explains intramucosal acidosis in sheep endotoxemia. *Intensive Care Medicine* 32, S7 (2006)
37. Arnaldo Dubin, Gastón Murias, Bernardo Maskin, Mario Pozo, Juan Sottile, Marcelo Barán, Vanina Kanoore Edul, Héctor Canales, Julio Badie, Graciela Etcheverry, Elisa Estenssoro: Increased blood flow prevents intramucosal acidosis in sheep endotoxemia: a controlled study. *Crit Care* 9, R66-73 (2005)
38. Arnaldo Dubin, Bernardo Maskin, Gastón Murias, Mario Pozo, Juan Sottile, Marcelo Barán, Vanina Kanoore Edul, Héctor Canales, Elisa Estenssoro: Effects of levosimendan in normodynamic endotoxaemia: a controlled experimental study. *Resuscitation* 69, 277-286 (2006)
39. Arnaldo Dubin, Gastón Murias, Juan Sottile; Mario Pozo, Marcelo Barán, Vanina Kanoore Edul, Héctor Canales, Graciela Etcheverry, Bernardo Maskin, Elisa Estenssoro: Effects of levosimendan and dobutamine in experimental acute endotoxemia: A preliminary controlled study. *Intensive Care Medicine* 33:485-494 (2007)
40. Arnaldo Dubin, Gastón Murias, Elisa Estenssoro, Héctor Canales, Pablo Sottile, Julio Badie, Marcel Baran, Silvio Rossi, Mercedes Laporte, Fernando Palizas, Jorge Giampieri, Diego Mediavilla, Ernesto Vacca, Diego Botta: End-tidal CO₂ pressure determinants during hemorrhagic shock. *Intensive Care Med* 26, 1619-1623 (2000)

Mechanisms of tissue hypercarbia in sepsis

Abbreviations: $[\text{HCO}_3^-]$: arterial bicarbonate concentration; pHi: intramucosal pH; ΔPCO_2 : intramucosal-arterial PCO_2 difference; DO_2 : O_2 delivery; VO_2 : O_2 uptake; $\%\text{HbO}_{2v}$: measured venous oxyhemoglobin; $\%\text{HbO}_{2v}^{\text{DILL}}$: calculated venous oxyhemoglobin

Key Words: Shock, Dysoxia, Hypercarbia, Tonometry, Blood flow, Microcirculation, Review

Send correspondence to: Dr Arnaldo Dubin, Calle 42 No. 577, (1900) La Plata, Argentina, Tel: 54-221-4220507, Fax:54-221-4216932,E-mail: arnaldodubin@speedy.com.ar

<http://www.bioscience.org/current/vol13.htm>