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

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INTRAMUCOSAL-ARTERIAL PCO$_2$ GRADIENT DOES NOT REFLECT INTESTINAL DYSOXIA IN ANEMIC HYPOXIA
ABSTRACT

Background: An increase in intramucosal-arterial PCO$_2$ gradient (ΔPCO$_2$) might be caused by tissue hypoxia or by diminished blood flow. Our hypothesis was that ΔPCO$_2$ should not be altered in anemic hypoxia with preserved blood flow.

Methods: In 18 anesthetized, mechanically ventilated sheep, oxygen transport was stepwise reduced by hemorrhage (hypovolemia, n = 9) or by hemorrhage and simultaneous dextran infusion (hemodilution, n = 9).

Results: Hypovolemia and hemodilution produced comparable decreases in systemic and intestinal oxygen transport and uptake. However, mixed venoarterial and mesenteric venoarterial PCO$_2$ gradients and ΔPCO$_2$ were significantly higher in hypovolemia than in hemodilution (25 ± 5 vs. 10 ± 2 mm Hg; 21 ± 6 vs. 10 ± 5 mm Hg; and 41 ± 18 vs. 14 ± 9 mm Hg, respectively; p < 0.01).

Conclusion: ΔPCO$_2$ did not reflect intestinal dysoxia during VO$_2$/DO$_2$ dependency attributable to hemodilution. Blood flow seems to be the main determinant of ΔPCO$_2$.

Keywords. Carbon dioxide - Oxygen consumption – Mesenteric perfusion - Dysoxia - Ischemia

Arnaldo Dubin¹, Elisa Estenssoro¹, Gastón Murias¹, Mario O. Pozo¹, Pablo Sottile¹, Marcelo Barán¹, Enrique Piacentini¹, Héctor S. Canales¹ and Graciela Etcheverry¹

¹Cátedra de Farmacología, Facultad de Ciencias Médicas, Universidad Nacional de La Plata, La Plata, Argentina

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INTRODUCTION

Tonometry is one of the few clinical tools available for monitoring tissue oxygenation. A decrease in gastrointestinal intramucosal pH has usually been considered as a marker of tissue dysxia [1–5] which occurs when oxygen supply is unable to meet tissue demands. More recently, the intramucosal-arterial PCO₂ gradient (ΔPCO₂) has been identified as better indicator of gastrointestinal mucosal oxygenation [6]. Luminal intestinal PCO₂ can rise by two mechanisms [7]: first, by bicarbonate buffering of protons generated in the hydrolysis of high-energy phosphate compounds, or of anaerobically produced acids as lactate. In this case, an increase of luminal PCO₂ could represent tissue dysxia. Alternatively, an increase of luminal PCO₂ could denote hypoperfusion and diminished carbon dioxide removal. In this last situation, aerobic metabolism could be preserved. If ΔPCO₂ increases reflected only blood flow reductions, this gradient should not be altered in the face of tissue dysxia with high or normal cardiac output. We have previously shown that ΔPCO₂ remains unaltered when oxygen uptake falls because of systemic hypoxemia [8]. However, Nevière et al. found an increase of ΔPCO₂ in the same state, though smaller than in hypovolemia [9]. To further explore the relationship of ΔPCO₂ to blood flow, we performed this experimental study to test the hypothesis that, in extreme hemodilution with high blood flow, ΔPCO₂ does not reflect the presence of tissue dysxia.

MATERIALS AND METHODS

Surgical preparation

Eighteen sheep were anesthetized with 30 mg/kg of sodium pentobarbital, intubated, and mechanically ventilated (Harvard Apparatus Dual Phase Control Respirator Pump Ventilator, Southnatick, MA) with a tidal volume of 15 mL/kg, an FIO₂ of 0.21, a respiratory rate of 12 breaths/min, and positive end-expiratory pressure adjusted to maintain oxygen arterial saturation greater than 90%. This ventilatory pattern was kept constant during the experiment. Additional pentobarbital boluses (1 mg/kg/h) were administered as required. Neuromuscular blockade was performed with intravenous pancuronium bromide (0.06 mg/kg). Catheters were advanced through the left femoral vein to administer fluids and drugs and through the left femoral artery to measure blood pressure, to obtain blood gases, and to perform hemorrhage. A thermodilution pulmonary artery catheter was inserted through the right external jugular vein. Then, a midline laparotomy, a gastrotomy and drainage of gastric contents, and a splenectomy were performed.

An electromagnetic flow probe was placed around the superior mesenteric artery to measure intestinal blood flow. A catheter was placed in the mesenteric vein through a small vein proximal to the gut to draw blood gases. A tonometer
was inserted through a small ileotomy to measure intramucosal PCO$_2$. Lastly, after careful hemostasis, the abdominal wall incision was closed.

**Measurements and derived calculations**

Cardiac output was measured in triplicate by thermodilution, with 5 mL of 0°C saline solution (HP Omni Care Model 24 A 10, Hewlett Packard, Andover, MA) and was referred to body weight (Q). Intestinal blood flow was measured by the electromagnetic method (Spectramed Blood Flowmeter model SP 2202 B, Spectramed, Inc., Oxnard, CA) with in vitro calibrated transducers 5 to 7 mm in diameter (Blood Flowmeter Transducer, Spectramed). Occlusive zero was controlled before and after each experiment. Nonocclusive zero was corrected before each measurement. Superior mesenteric blood flow was referred to gut weight ($Q_{\text{intestinal}}$).

Arterial, mixed venous and mesenteric venous $PO_2$, $PCO_2$, pH, hemoglobin, and oxygen saturation were measured with a blood gas analyzer and a co-oximeter (ABL 5 and OSM 3, Radiometer, Copenhagen, Denmark). Systemic and intestinal $DO_2$ and $VO_2$ were calculated by standard formulae.

Intramucosal PCO$_2$ was measured with a tonometer [10] (TRIP Sigmoid Catheter, Tonometrics, Inc., Worcester, MA) filled with 2.5 mL of saline solution; 1.0 mL was discarded after an equilibration period of 30 minutes, and PCO$_2$ was measured in the remaining 1.5 mL. Its value was corrected for the corresponding equilibration period and used to calculate $\Delta PCO_2$.

Mixed venous arterial and mesenteric venous arterial $PCO_2$ differences were also calculated. Arterial, mixed venous, and mesenteric venous carbon dioxide contents ($CCO_2$) and their differences were calculated using Giovannini’s algorithm [11], to assess the changes in CO$_2$ dissociation curve. Global blood capacity for transporting CO$_2$ was evaluated with the ratio between venoarterial $CCO_2$ and $PCO_2$ differences (Ra-v). This index has been used to evaluate the amount of CO$_2$ transported by the blood in relation to the venoarterial gradient of PCO$_2$ [12]. Systemic and intestinal CO$_2$ production ($VCO_2$ and $VCO_2i$, respectively) were calculated as follows: $VCO_2 \times Q \times \text{mixed venoarterial } CCO_2 \text{ difference and } VCO_2i \times Q_{\text{intestinal}} \times \text{mesenteric venoarterial } CCO_2 \text{ difference.}$

**Experimental procedure**

Basal measurements were taken after a stabilization period of no less than 30 minutes. The animals were then assigned to hemodilution ($n = 9$) or hypovolemia ($n = 9$). In the hemodilution group, blood was replaced by dextran 40. The amount of blood exchanged to reach desired levels of hematocrits of approximately 0.15, 0.10, 0.07, and 0.05 in each step was estimated as previously mentioned [13]. In the hypovolemia group, consecutive bleedings of 5 to 10 mL/kg were performed. Similar values of systemic and intestinal $DO_2$ were pursued in each stage in both groups. Measurements were obtained at 30-minute intervals for
120 minutes. Blood temperature was kept constant throughout the study with a heating lamp.

At the end of the experiment, the animals were killed with an additional dose of pentobarbital and a KCl bolus. A catheter was inserted into the superior mesenteric artery and India ink was instilled through it. Dyed intestinal segments were dissected, washed, and weighed to calculate gut indexes.

This study was approved by the local animal care committee. Animals were cared for in accordance with National Institutes of Health guidelines.

Statistical analysis
Data were assessed for normality and expressed as mean ± SD. They were analyzed with two-way analysis of variance and t test with Bonferroni correction for post hoc comparisons [14].

RESULTS
Arterial, mixed-venous, and mesenteric venous blood gas values in basal conditions and during hemodilution and hypovolemia are shown in Tables 1 through 3. Systemic and intestinal VO₂/DO₂ dependency was comparable in both groups (Fig. 1). In hemodilution, this was because of a progressive reduction of arterial hemoglobin (from 9.9 ± 1.5 g/dL to 1.7 ± 0.2 g/dL, p < 0.0001), notwithstanding the increase of Q and Q_interstitial (0.099 ± 0.016 L/min/kg to 0.166 ± 0.047 L/min/kg and 0.625 ± 0.112 L/min/kg to 0.958 ± 0.341 L/min/kg, p < 0.01 for both). In hypovolemia, VO₂/DO₂ dependency was caused by stepwise decreases of Q and Q_interstitial (0.102 ± 0.028 L/min/kg to 0.047 ± 0.007 L/min/kg and 0.610 ± 0.203 L/min/kg to 0.222 ± 0.085 L/min/kg, p < 0.0001 for both). Changes in VO₂ and changes in base deficit were linearly related (Fig. 2).

From early stages, CO₂ gradients behaved differently in both groups (Figs. 3 and 4). In hemodilution, there were no significant changes in ΔPCO₂ or mesenteric venoarterial PCO₂ and CCO₂ differences. Mixed venoarterial PCO₂ difference had a small but significant increase, together with a reduction of CCO₂ difference. In hypovolemia, all gradients were enlarged.

Mixed and mesenteric venoarterial Ra-V decreased in hemodilution (0.61 ± 0.14 mL/dL/mm Hg vs. 0.23 ± 0.09 mL/dL/mm Hg, p < 0.0001; and 0.59 ± 0.17 mL/dL/mm Hg vs. 0.29 ± 0.12 mL/dL/mm Hg; p < 0.01, respectively). However, they remained unchanged in hypovolemia (0.54 ± 0.21 mL/dL/mm Hg vs. 0.55 ± 0.22 mL/dL/mm Hg; and 0.53 ± 0.13 mL/dL/mm Hg vs. 0.51 ± 0.22 mL/dL/mm Hg; p < not significant for both). After 120 minutes, there were no significant changes in systemic VCO₂ in hemodilution and in hypovolemia (3.9 ± mL/min/kg vs. 3.8 ± 1.7 mL/min/kg, and 4.5 ± 1.9 mL/min/kg vs. 6.2 ± 2.1 mL/min/kg, respectively), or in intestinal VCO₂ (25.1 ± 9.5 mL/min/kg vs. 24.1 ± 7.4 mL/ min/kg and 26.8 ± 7.5 mL/min/kg vs. 21.5 ± 10.9 mL/min/ kg). Consequently, systemic respiratory
### Table 1. Arterial blood gases in basal conditions and during hemodilution and hypovolemia.

<table>
<thead>
<tr>
<th>GROUP</th>
<th>BASAL</th>
<th>30 minutes</th>
<th>60 minutes</th>
<th>90 minutes</th>
<th>120 minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial pH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hemodilution</td>
<td>7.40 ± 0.05</td>
<td>7.40 ± 0.07</td>
<td>7.39 ± 0.07</td>
<td>7.36 ± 0.06</td>
<td>7.30 ± 0.06†</td>
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<td>hypovolemia</td>
<td>7.35 ± 0.06</td>
<td>7.34 ± 0.07</td>
<td>7.32 ± 0.08</td>
<td>7.28 ± 0.10</td>
<td>7.23 ± 0.10†</td>
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<tr>
<td>Arterial PCO₂ (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hemodilution</td>
<td>32 ± 4</td>
<td>33 ± 6</td>
<td>32 ± 5</td>
<td>30 ± 5</td>
<td>29 ± 4*</td>
</tr>
<tr>
<td>hypovolemia</td>
<td>33 ± 3</td>
<td>31 ± 3†</td>
<td>31 ± 4†</td>
<td>29 ± 3‡</td>
<td>26 ± 4‡</td>
</tr>
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<td>Arterial PO₂ (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hemodilution</td>
<td>81 ± 15</td>
<td>78 ± 17</td>
<td>86 ± 14</td>
<td>100 ± 22</td>
<td>108 ± 18*</td>
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<tr>
<td>hypovolemia</td>
<td>76 ± 10</td>
<td>78 ± 11</td>
<td>77 ± 11</td>
<td>78 ± 12</td>
<td>84 ± 13**</td>
</tr>
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<td>Arterial HCO₃ (mmol/l)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hemodilution</td>
<td>19 ± 2</td>
<td>19 ± 2</td>
<td>19 ± 2</td>
<td>16 ± 2†</td>
<td>14 ± 2‡</td>
</tr>
<tr>
<td>hypovolemia</td>
<td>18 ± 3</td>
<td>17 ± 3</td>
<td>16 ± 3†</td>
<td>14 ± 3‡</td>
<td>11 ± 3§</td>
</tr>
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<td>Arterial base excess (mmol/l)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hemodilution</td>
<td>-4 ± 2</td>
<td>-4±2</td>
<td>-5 ± 2</td>
<td>-7 ± 2*</td>
<td>-11 ± 2†</td>
</tr>
<tr>
<td>hypovolemia</td>
<td>-6 ± 4</td>
<td>-7 ± 4</td>
<td>-9 ± 5†</td>
<td>-11 ± 5†</td>
<td>-15 ± 5‡</td>
</tr>
</tbody>
</table>

Data are shown as mean ± SD. * p < 0.05 vs. basal. † p < 0.01 vs. basal. ‡ p < 0.001 vs. basal. § p < 0.0001 vs. basal. ** p < 0.05 hypovolemia vs. hemodilution.

### Table 2. Mixed venous blood gases in basal conditions and during hemodilution and hypovolemia.

<table>
<thead>
<tr>
<th>GROUP</th>
<th>BASAL</th>
<th>30 minutes</th>
<th>60 minutes</th>
<th>90 minutes</th>
<th>120 minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixed-venous pH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>hemodilution</td>
<td>7.36 ± 0.04</td>
<td>7.35 ± 0.06</td>
<td>7.33 ± 0.06</td>
<td>7.27 ± 0.05†</td>
<td>7.19 ± 0.07‡</td>
</tr>
<tr>
<td>hypovolemia</td>
<td>7.29 ± 0.06</td>
<td>7.27 ± 0.07</td>
<td>7.23 ± 0.09†</td>
<td>7.17 ± 0.10†</td>
<td>7.08 ± 0.11‡</td>
</tr>
<tr>
<td>Mixed-venous PCO₂ (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hemodilution</td>
<td>38 ± 4</td>
<td>39 ± 6</td>
<td>39 ± 5</td>
<td>40 ± 5</td>
<td>40 ± 6</td>
</tr>
<tr>
<td>hypovolemia</td>
<td>42 ± 3</td>
<td>44 ± 3</td>
<td>46 ± 3†**</td>
<td>48 ± 4†**</td>
<td>51 ± 7**††</td>
</tr>
<tr>
<td>Mixed-venous PO₂ (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hemodilution</td>
<td>37 ± 3</td>
<td>35 ± 4</td>
<td>29 ± 4†</td>
<td>24 ± 3§</td>
<td>25 ± 4§</td>
</tr>
<tr>
<td>hypovolemia</td>
<td>33 ± 3</td>
<td>26 ± 5§††</td>
<td>24 ± 4§</td>
<td>21 ± 7§</td>
<td>17 ± 4§††</td>
</tr>
<tr>
<td>Mixed-venous HCO₃ (mmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hemodilution</td>
<td>21 ± 2</td>
<td>21 ± 2</td>
<td>21 ± 2</td>
<td>18 ± 2†</td>
<td>15 ± 2§</td>
</tr>
<tr>
<td>hypovolemia</td>
<td>20 ± 3</td>
<td>20 ± 3</td>
<td>20 ± 3</td>
<td>19 ± 4*</td>
<td>16 ± 4‡</td>
</tr>
<tr>
<td>Mixed-venous base excess (mmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hemodilution</td>
<td>-3 ± 2</td>
<td>-3 ± 2</td>
<td>-4 ± 2</td>
<td>-7 ± 2†</td>
<td>-11 ± 2‡</td>
</tr>
<tr>
<td>hypovolemia</td>
<td>-6 ± 5</td>
<td>-7 ± 5</td>
<td>-8 ± 5</td>
<td>-10 ± 6†</td>
<td>-12 ± 6‡</td>
</tr>
</tbody>
</table>

Data are shown as mean ± SD. † p < 0.01 vs. basal. ‡ p < 0.001 vs. basal. § p < 0.0001 vs. basal. ** p < 0.05 hypovolemia vs. hemodilution. †† p < 0.01 hypovolemia vs. hemodilution.

...quotient increased in both groups (0.79 ± 0.17 vs. 1.30 ± 0.30 in hemodilution, and 0.78 ± 0.30 in hemodilution vs. 1.61 ± 0.53 mL/min/kg in hypovolemia, p < 0.05 for both). Intestinal respiratory quotient also rose (0.99 ± 0.37 vs. 1.67 ± 0.69 in hemodilution, and 0.99 ± 0.26 vs. 1.32 ± 0.31 in hypovolemia, p <0.05 for both).
Table 3. Mesenteric venous blood gases in basal conditions and during hemodilution and hypovolemia.

<table>
<thead>
<tr>
<th>GROUP</th>
<th>BASAL</th>
<th>30 minutes</th>
<th>60 minutes</th>
<th>90 minutes</th>
<th>120 minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>hemodilution</td>
<td>7.35 ± 0.06</td>
<td>7.34 ± 0.07</td>
<td>7.33 ± 0.07</td>
<td>7.27 ± 0.06*</td>
</tr>
<tr>
<td></td>
<td>hypovolemia</td>
<td>7.28 ± 0.08</td>
<td>7.26 ± 0.09*</td>
<td>7.23 ± 0.09†</td>
<td>7.19 ± 0.11†</td>
</tr>
<tr>
<td>Mesenteric venous pH (mm Hg)</td>
<td>hemodilution</td>
<td>40 ± 5</td>
<td>39 ± 7</td>
<td>39 ± 6</td>
<td>40 ± 7</td>
</tr>
<tr>
<td></td>
<td>hypovolemia</td>
<td>42 ± 4</td>
<td>44 ± 4</td>
<td>45 ± 5</td>
<td>46 ± 5*</td>
</tr>
<tr>
<td>Mesenteric venous PCO₂ (mm Hg)</td>
<td>hemodilution</td>
<td>40 ± 4</td>
<td>38 ± 2</td>
<td>34 ± 4†</td>
<td>29 ± 5‡</td>
</tr>
<tr>
<td></td>
<td>hypovolemia</td>
<td>38 ± 6</td>
<td>31 ± 5§††</td>
<td>31 ± 4§</td>
<td>27 ± 4§</td>
</tr>
<tr>
<td>Mesenteric venous PO₂ (mm Hg)</td>
<td>hemodilution</td>
<td>22 ± 2</td>
<td>21 ± 2†</td>
<td>20 ± 2†</td>
<td>18 ± 2†</td>
</tr>
<tr>
<td></td>
<td>hypovolemia</td>
<td>20 ± 3</td>
<td>20 ± 3</td>
<td>19 ± 3</td>
<td>18 ± 3†</td>
</tr>
<tr>
<td>Mesenteric venous HCO₃ (mmol/l)</td>
<td>hemodilution</td>
<td>-2 ± 2</td>
<td>-3 ± 2</td>
<td>-4 ± 2</td>
<td>-7 ± 2†</td>
</tr>
<tr>
<td></td>
<td>hypovolemia</td>
<td>-6 ± 4</td>
<td>-7 ± 5</td>
<td>-8 ± 5†</td>
<td>-10 ± 5‡</td>
</tr>
</tbody>
</table>

Data are shown as mean ± SD. * p < 0.05 vs. basal. † p < 0.01 vs. basal. ‡ p < 0.001 vs. basal. § p < 0.0001 vs. basal.

Fig. 1. Dependency of oxygen consumption on oxygen transport in hypovolemia and hemodilution at the systemic level (A) and at the intestinal level (B). Data are shown as mean ± SEM. *p < 0.05 versus basal; †p < 0.01 versus basal.
Fig. 2. Correlation of changes in systemic oxygen consumption and base deficit in hypovolemia (A) and hemodilution (B).

DISCUSSION

The main finding of this study was the failure of the ΔPCO₂ to reflect tissue dysoxia during the dependency of VO₂ on DO₂ caused by hemodilution. In contrast to this state of tissue dysoxia with high blood flow, similar reductions in DO₂ produced by hypoperfusion generated large increases of CO₂ gradients.

Experimental model of tissue dysoxia

Tissue dysoxia appears when DO₂ can no longer sustain VO₂ and aerobic metabolism [15]. In this study, we sought to discriminate between tissue dysoxia and low blood flow as causes of the increased CO₂ concentration. Progressive hemorrhage was compared with progressive hemodilution in two groups of animals, with comparable reductions in systemic and intestinal DO₂ and VO₂. Tissue dysoxia was identified by the start of VO₂/DO₂ dependency [16]. In
hemodilution, lowering hemoglobin concentration induced state of tissue dyoxia with high blood flow. Metabolic acidosis, evidenced as reduced bicarbonate and base excess levels, also developed in both groups. Although lactate or lactate/pyruvate levels were not measured, several experimental studies have shown that lactate has no advantage over base deficit to reflect oxygen debt [17-19]. Recently, Siegel et al. have shown that base deficit and lactate adequately estimate oxygen debt in an experimental model of hemorrhagic shock and resuscitation [20]. Confirming these results, we found a linear relationship between changes in base deficit and changes in oxygen consumption in hemodilution and hypovolemia, with similar $r^2$, slopes, and ranges of data. Respiratory quotient, another marker of anaerobic metabolism, increased in both groups [21-23]. Because the extent of

Fig. 3. Changes in systemic and intestinal CO$_2$ gradients in hemodilution and hypovolemia: mixed venoarterial CO$_2$ (A), mixed venoarterial CO$_2$ content (B), mesenteric venoarterial CO$_2$ (C), and mesenteric venoarterial CO$_2$ content (D). Data are shown as mean ± SEM. *p < 0.05 versus basal; †p < 0.01 versus basal; ‡p < 0.001 versus basal; §p < 0.0001 versus basal; p < 0.001 hypovolemia versus hemodilution; p < 0.0001 hypovolemia versus hemodilution.
dysoxia in hemodilution and hypovolemia was similar, greater oxygen debt could be discarded as the cause of CO$_2$ accumulation in ischemia.

Significance of $\Delta$PCO$_2$

An increase of VCO$_2$ caused by anaerobic metabolism or diminished washout of aerobically produced CO$_2$ might elevate $\Delta$PCO$_2$. Venous PCO$_2$ increases in shock have been explained by the last mechanism, in analogy to “mixed respiratory acidosis” described during cardiopulmonary resuscitation [24-26]. However, Schlichtig and Bowles [7] applied the Dill nomogram to demonstrate that increments in mucosal PCO$_2$ below critical DO$_2$ are caused by anaerobic production. Notwithstanding this, diminishing flow to induce critical DO$_2$ might be potential confounding factor [27]. We used model of hemodilution to carefully discriminate between effects of tissue dysoxia and changes in blood flow, because it was kept elevated throughout the experiment.

Changes in $\Delta$PCO$_2$

Although having reached comparable extent of dysoxia, hypovolemia and hemodilution behaved differently in this study. In hemodilution, $\Delta$PCO$_2$ was not modified significantly. Small but clinically irrelevant increases in venoarterial PCO$_2$ gradients (approximately 4 mm Hg) were observed, together with decreased differences in CO$_2$ content. On the contrary, during VO$_2$/DO$_2$ dependency induced by hemorrhage, $\Delta$PCO$_2$ and venoarterial PCO$_2$ gradients increased to 40 and 20 mm Hg, respectively. Venoarterial gradients of CO$_2$ contents paralleled these changes. Besides, these changes anteceded VO$_2$ decreases, as has been described [28]. PCO$_2$ and CO$_2$ content gradients were significantly different in both groups from the initial stages of hemorrhage and hemodilution. These
results suggest that, at least in our experimental model, tissue perfusion seems to be the major determinant of \( \Delta \text{PCO}_2 \) increase.

Nevière et al. assessed a similar hypothesis in pigs, comparing the effects of reduced FIO\(^2\) and decreased blood flow measured with laser Doppler [9]. In hypovolemia, \( \Delta \text{PCO}_2 \) increased to 60 mm Hg. In systemic hypoxemia, in which mucosal blood flow was maintained constant, only the lowest FIO\(^2\) (0.06) made \( \Delta \text{PCO}_2 \) increase to 30 mm Hg. The authors concluded that intramucosal PCO\(_2\) elevation denoted local CO\(_2\) generation. However, in the two preceding steps of FIO\(^2\) reductions, VO\(_2\)/DO\(_2\) dependency had been reached and \( \Delta \text{PCO}_2 \) remained unchanged.

In previous study of acute lung injury in sheep caused by hydrochloric acid aspiration and preserved blood flow, we found that systemic hypoxemia caused VO\(_2\)/DO\(_2\) dependency [8]. However, \( \Delta \text{PCO}_2 \) did not increase. The data of Nevière’s et al. and ours could disagree because of different animal species (and thus distinct microvascular features) involved or because of differing extent of hypoxemia. Besides, some flow heterogeneity could have been present in their experiments that was not assessed by laser Doppler, method that only tracks global microvascular changes. Despite this, both studies illustrate that \( \Delta \text{PCO}_2 \) can fail to reflect dysoxia in systemic hypoxemia.

Measurement of superior mesenteric blood flow certainly does not allow evaluating mucosal perfusion. However, if subtle hypoperfusion occurred, it was unable to change \( \Delta \text{PCO}_2 \).

Similar to our results, Vallet et al. showed that blood flow is the key determinant of venoarterial PCO\(_2\) difference in ischemic and hypoxic dysoxia in the muscle [23]. This gradient increases in ischemia and is maintained in hypoxia.

Venous and tissue PCO\(_2\) in anemia have not been extensively analyzed. Deem et al. described constancy of venoarterial PCO\(_2\) differences in hemodilution, until hematocrit of 12 was reached [29]. Morimoto et al. showed stability of brain PCO\(_2\) with hemoglobin of 2.4 g/dL, although tissue PO\(_2\) and brain VO\(_2\) were reduced [30]. Bacher et al. found that intramucosal pH was better preserved in normovolemic hemodilution than in controls during cardiac surgery [31]. In hemorrhagic shock, Diebel et al. demonstrated normalization of intramucosal PCO\(_2\) and pH after resuscitation, notwithstanding hematocrit of 18 2% [32]. Finally, Layland et al. showed that intramucosal pH was maintained during normovolemic hemodilution, despite reaching hemoglobin of 8.2 ± 1.4 g/dL [33]. However, no previous study has specifically addressed the issue of \( \Delta \text{PCO}_2 \) behavior in supply dependency-induced hemodilution.

**Physiologic determinants of PCO\(_2\) gradients**

Venoarterial and intramucosal-arterial PCO\(_2\) gradients are the result of interactions in aerobic and anaerobic CO\(_2\) production, CO\(_2\) dissociation curve, and blood flow to tissues. During VO\(_2\)/DO\(_2\) dependency, opposite changes in
aerobic and anaerobic CO$_2$ production occur; CO$_2$ aerobic production decreases as consequence of the fall in aerobic metabolism, but at the same time, CO$_2$ anaerobic production starts because of bicarbonate buffering of protons derived from fixed acids. Total CO$_2$ production might not increase, as in our experiments. However, as VO$_2$ falls, there is an increase in the respiratory quotient [21-24]. The relative increment of VCO$_2$ with respect to VO$_2$ can only cause venous and tissue hypercarbia in low-flow states, in which CO$_2$ removal is reduced. Other conditions in which intramucosal acidosis could rise, with preserved global blood flow, are reperfusion injury [34] and cytopathic hypoxia in endotoxemia [35], with cell injury and metabolic alterations as underlying causes. However, even in this condition, significant changes in microcirculation have been found [36]. Thus, failure of blood flow to clear CO$_2$ remains the main factor responsible for its accumulation.

Lastly, we found decrease in global blood capacity for transporting CO$_2$ in anemic hypoxia, which was evaluated with the Ra-v ratio. This index assesses the amount of blood transported CO$_2$ in relation to the venoarterial PCO$_2$ gradient [12]. This effect occurred despite the large reduction in hemoglobin saturation and might be ascribed to acidosis and diminished concentrations of hemoglobin. We found small increase of venoarterial PCO$_2$ gradient that goes with diminished venoarterial CO$_2$ content gradient. Because blood flow was elevated in the face of stable CO$_2$ production, reduction in blood CO$_2$ transport capacity remains as the only explanation for the elevated venoarterial PCO$_2$ gradient.

In summary, to our knowledge, this is the first study that shows that ΔPCO$_2$ is unable to reflect intestinal dysoxia in anemic hypoxia. Our results also suggest that blood flow is the main ΔPCO$_2$ determinant. Tonometry seems to be useful method for monitoring perfusion, but it has limited value when blood flow is preserved. Additional studies are needed to reinforce these conclusions.
REFERENCES


