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Splanchnic hemodynamics and gut mucosal-arterial 
PCO₂ gradient during systemic hypocapnia

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Guzman, Jorge A., and James A. Kruse. Splanchnic hemodynamics and gut mucosal-arterial PCO₂ gradient during systemic hypocapnia. J. Appl. Physiol. 87(3): 1102–1106, 1999.—The effects of hypocapnia [arterial PCO₂ (PaCO₂) 15 Torr] on splanchnic hemodynamics and gut mucosal-arterial PCO₂ were studied in seven anesthetized ventilated dogs. Ileal mucosal and serosal blood flow were estimated by using laser Doppler flowmetry, mucosal PCO₂ was measured continuously by using capnometric recirculating gas tonometry, and serosal surface PO₂ was assessed by using a polarographic electrode. Hypocapnia was induced by removal of dead space and was maintained for 45 min, followed by 45 min of eucapnia. Mean PaCO₂ at baseline was 38.1 ± 1.1 (SE) Torr and decreased to 13.8 ± 1.3 Torr after removal of dead space. Cardiac output and portal blood flow decreased significantly with hypocapnia. Similarly, mucosal and serosal blood flow decreased by 15 ± 4 and by 34 ± 7%, respectively. Also, an increase in the mucosal-arterial PCO₂ gradient of 10.7 Torr and a reduction in serosal PO₂ of 30 Torr were observed with hypocapnia (P < 0.01 for both). Hypocapnia caused ileal mucosal and serosal hyperperfusion, with redistribution of flow favoring the mucosa, accompanied by increased PCO₂ gradient and diminished serosal PO₂. VARIATIONS IN ARTERIAL PCO₂ (PaCO₂) are frequently observed in response to a wide variety of clinical conditions seen in critically ill patients. Changes in PaCO₂ affect peripheral arterioles and lead to vasodilation or constriction (3, 16). Hypocapnia causes both vasoconstriction and mild depression of myocardial contractility (21), and, in the splanchnic region, this relaxation this gradient increased, suggesting that factors not yet clearly understood were responsible for the rise in the PI CO₂–PaCO₂ gradient (7). We conducted the present study to better understand the effects of systemic hypocapnic alkalosis on the splanchnic circulation and to elucidate the influence that respiratory alkalosis has on the PI CO₂–PaCO₂ gradient.

MATERIALS AND METHODS

Surgical preparation. This protocol was approved by the Animal Investigation Committee of Wayne State University. Seven mongrel dogs (weight, 19–31 kg) were fasted overnight; they were then anesthetized with an injection of pentobarbital sodium (30 mg/kg iv), endotracheally intubated, and placed on mechanical ventilation (model MA-1; Puritan-Bennett, Carlsbad, CA) with a constant tidal volume (15 ml/kg). Excess ventilator-circuit tubing was employed at baseline to later achieve the targeted PCO₂ by removal of this dead space once the experimental protocol was initiated. Respiratory rate was adjusted to achieve a baseline PaCO₂ of ~40 Torr. A femoral vein and artery were exposed by surgical dissection and were cannulated with vascular catheters for continuous infusions of pentobarbital sodium (0.06 mg·kg⁻¹·min⁻¹ iv), cisatracurium besylate (0.2 mg/kg bolus followed by 5 µg·kg⁻¹·min⁻¹), and normal saline solution, as well as for continuous blood pressure monitoring (Transpac; Abbott Laboratories, North Chicago, IL) and intermittent blood sampling for blood gas, Hb, and lactate analysis. A balloon-tipped, thermocouple pulmonary artery catheter (Opticath; Abbott Laboratories) was advanced through the femoral vein and was guided into the pulmonary artery by pressure waveform analysis. After a midline laparotomy was performed, the duodenum and small intestine were displaced to expose the portal vein. After careful dissection was performed, an 8-mm ultrasonic flow probe (model BR5; Transonic Systems, Ithaca, NY) was placed around the vessel and was secured with sutures to the adjacent lymphatic tissue. A 7-Fr catheter was advanced through the splenic vein to the portal vein for blood sampling. Its position was confirmed by palpating the tip of the catheter through the wall of the portal vein. A double-lumen, silicone balloon-tipped catheter for continu-

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ous intramucosal PCO₂ measurements was positioned inside the ileum through a small antimesenteric enterostomy and was secured by a purse-string suture. Ileal mucosal and serosal blood flow were measured continuously by laser Doppler flowmetry and were reported in units of tissue perfusion, which represent estimates of absolute flow (in ml·min⁻¹·100 g⁻¹) made in accordance with algorithms derived by Bonner and colleagues (2). Although this methodology does not provide measurements of microvascular perfusion in absolute terms, it has been validated previously as a reliable means of estimating relative changes in mucosal perfusion (18, 24). After a small ileostomy was performed, a laser Doppler flow probe (type R; Transonic Systems) was sewn to the antimesenteric mucosal surface, and the ileostomy was closed. Similarly, a second laser-Doppler probe was sewn to the antimesenteric border of the ileal serosa. Both probes were modified by the manufacturer so that they could be secured to the mucosa or serosa without compromising perfusion in the area of interest. Finally, a surface tissue PO₂ electrode (model 860; Novametrix Medical Systems, Wallingford, CT) was attached to the antimesenteric surface of the ileal serosa and was kept in place with a tissue adhesive. After hemostasis was ensured, the laparotomy was closed, and the animal allowed to stabilize for 45 min, during which time minute ventilation was readjusted, if necessary, to maintain PaCO₂, at ~40 Torr. Core temperature was monitored by using the thermistor of the pulmonary artery catheter and was maintained at 37.0 ± 1.0°C by using heating pads and overhead lamps.

Measurements and calculations. Systemic arterial, mixed venous, and portal venous blood samples were analyzed for PO₂, PCO₂, and pH by using an automated blood-gas analyzer (model ABL-300; Radiometer, Westlake, OH). Hb concentration and oxyhemoglobin saturation were assayed spectrophotometrically by using a CO-oximeter calibrated for canine blood (OSM-3; Radiometer). Cardiac output was measured by thermodilution and was reported as the average of at least three repeated measurements. Portal vein blood flow was measured ultrasonically (model T206; Transonic Systems). PiCO₂ was monitored continuously, by use of the balloon-tipped ileal catheter, with the use of capnometric recirculating gas tonometry (6–8). End-tidal PCO₂ (PETCO₂) and monitoring of PiCO₂ (measured continuously but reported at 15-min intervals) was commenced, dead space was incrementally removed to achieve hypocapnia (targeted PaCO₂ of ~15 Torr) for 45 min, after which the removed dead space was added back to the respiratory circuit to restore eucapnia, and the experiments continued for another 45 min. A set of measurements was obtained every 15 min during the experimental protocol. Infusion of normal saline was maintained at a constant rate of 10 ml·kg⁻¹·h⁻¹ iv once the experiment started.

Statistical analysis. Summary values are expressed as means ± SE. One-way repeated measures ANOVA was used to compare sequential measurements for each tested variable obtained between baseline and the end of the restored eucapnia period. Dunnett’s test was used to make further comparisons if ANOVA revealed significant differences. The control value for Dunnett’s test was designated as the last measurement obtained at the end of the baseline period (time 0). Probability values (two-tailed) of <0.05 were considered statistically significant. Statistical calculations were performed by using Excel (version 7.0; Microsoft; Redmond, WA) and SigmaStat (version 1.0; Jandel; San Rafael, CA) software.

RESULTS

At the end of the baseline period, an average of 18.5 ± 2.1 ml/kg of dead space were removed to attain the targeted PaCO₂ (13.8 ± 1.3 Torr). PETCO₂ was 47.9 ± 3.5 Torr at the end of baseline, decreased to 14.6 ± 0.9 Torr (P < 0.001) after 45 min of hypocapnia, and then returned to near baseline value after 45 min of eucapnia. Arterial blood pH at the end of baseline was 7.30 ± 0.01 and increased up to 7.59 ± 0.02 (P < 0.001) after 45 min of hypocapnia.

PaO₂, PmvO₂, and PpvO₂ did not change significantly during the experiment. The changes in PaCO₂, PmvCO₂, and PpvCO₂, and in lactate concentration at baseline, after 45 min of hypocapnia, and 45 min after restoring eucapnia are shown in Fig. 1. PaCO₂ effectively decreased after removal of dead space and then remained almost constant during the 45 min of hypoxic alkalosis. A similar trend was observed with PmvCO₂ and PpvCO₂. After 45 min of hypocapnia, blood lactate values nearly doubled and then decreased to near baseline levels at the end of the restored eucapnia period. There was no net exchange of lactate over the pulmonary territory, and, although nonsignificant, a trend toward release was observed at the end of hypocapnia in the splanchnic vascular bed.

Table 1 shows the changes in hemodynamic and O₂ transport variables during the experiment. Mucosal and serosal Do₂ decreased by 19 ± 9 and 32 ± 14%, respectively (P < 0.05 for both), at the end of hypocapnia, and both returned to near baseline by the end of the experiment.
Figure 2 shows the changes in gut-arterial $\text{PCO}_2$ ($\text{PaCO}_2$) gradient and mucosal and serosal blood flow during the experiment. $\text{PiCO}_2 - \text{PaCO}_2$ increased from 24.4 ± 3.1 to 35.2 ± 4.8 Torr after hypocapnia and decreased to 11.9 ± 3.8 Torr at the end of eucapnia ($P < 0.001$ by ANOVA). Figure 3 shows the changes in raw $\text{PiCO}_2$ and serosal surface $\text{PO}_2$ during the experiment.

Table 1. Hemodynamic and $\text{O}_2$ transport variables at end of baseline, 45 min after induction of systemic hypocapnia, and 45 min after restoration of eucapnia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>45 min Posthypocapnia</th>
<th>45 min Posteucapnia</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, beats/min</td>
<td>128 ± 9</td>
<td>129 ± 7</td>
<td>116 ± 8*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean arterial blood pressure, mmHg</td>
<td>96.9 ± 6.1</td>
<td>89.7 ± 9.0</td>
<td>101.1 ± 8.0</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac output, ml·kg⁻¹·min⁻¹</td>
<td>175.6 ± 36.4</td>
<td>136.1 ± 28.36</td>
<td>137.0 ± 16.6</td>
<td>-0.05</td>
</tr>
<tr>
<td>Portal blood flow, ml·kg⁻¹·min⁻¹</td>
<td>20.3 ± 3.3</td>
<td>11.6 ± 1.8†</td>
<td>14.7 ± 2.5†</td>
<td>0.001</td>
</tr>
<tr>
<td>Systemic DO₂, ml·kg⁻¹·min⁻¹</td>
<td>21.6 ± 2.4</td>
<td>18.9 ± 5.3</td>
<td>19.5 ± 2.5</td>
<td>NS</td>
</tr>
<tr>
<td>Splanchnic DO₂, ml·kg⁻¹·min⁻¹</td>
<td>2.70 ± 0.5</td>
<td>1.50 ± 0.2†</td>
<td>2.03 ± 0.3*</td>
<td>0.001</td>
</tr>
<tr>
<td>Systemic VO₂, ml·kg⁻¹·min⁻¹</td>
<td>4.73 ± 1.2</td>
<td>3.60 ± 0.8</td>
<td>4.23 ± 0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Splanchnic VO₂, ml·kg⁻¹·min⁻¹</td>
<td>0.43 ± 0.06</td>
<td>0.34 ± 0.08</td>
<td>0.41 ± 0.08</td>
<td>NS</td>
</tr>
<tr>
<td>Systemic $\text{O}_2$ extraction, %</td>
<td>23 ± 1</td>
<td>26 ± 2</td>
<td>25 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>Splanchnic $\text{O}_2$ extraction, %</td>
<td>17 ± 3</td>
<td>23 ± 4</td>
<td>22 ± 4</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 7 dogs. DO₂, O₂ delivery; VO₂, O₂ uptake; NS, not significant. Significant difference from baseline by Dunnett’s multiple comparisons: *P < 0.05; †P < 0.01.
intravenous fluid replacement throughout the experiment.

Consistent with previous studies (10–12, 23, 26), cardiac output decreased by 22% after induction of respiratory alkalosis in the present experiments. The fact that cardiac output remained below baseline values at the end of the experiment could be explained by the effects of hypocapnia-induced vasoconstriction and impaired myocardial contractility (21). Portal blood flow also decreased significantly (43%) after hypocapnia. The portal fraction of cardiac output decreased from 12 to 9%. Although this change did not reach statistical significance, it suggests redistribution of flow away from the mesenteric region and more pronounced vasoconstriction within the splanchnic bed.

Although PiCO2 decreased after hypocapnia was induced, the reduction did not quantitatively parallel the decrease in PaCO2, and as a consequence, the PiCO2 – PaCO2 gap increased significantly in the face of hypocapnia. This observation can be explained mainly by two major findings. 1) Decreased blood flow to the ileal mucosal and serosal layers was induced by hypocapnia. A reduction in blood flow was observed almost immediately after PaCO2 was altered. Although mucosal flow decreased significantly, a more substantial reduction occurred at the serosal layer, thus clearly revealing redistribution of flow in favor of the mucosal bed. This can be construed teleologically as a compensatory attempt to protect more vulnerable tissue layers from critical reductions in blood flow that would otherwise lead to anaerobic metabolism and its deleterious consequences. 2) Serosal surface Po2 decreased. The decrease by more than one-half in the serosal surface Po2 is likely secondary to marked serosal vasoconstriction, microvascular shunting, and decreased functional capillary surface area. Furthermore, this hypothesis is supported by the relatively unchanged splanchnic O2er in the face of reduced splanchnic DO2 (9, 22). Similarly, it is likely that some degree of hypoxia occurred in the mucosal layer, because mucosal perfusion was diminished by hypocapnia despite blood flow redistribution from the serosa. However, further investigation is necessary to confirm or reject this hypothesis.

Although we know that mucosal and serosal hypoperfusion effectively occurred and that serosal hypoxia concomitantly developed during hypocapnia, the question remains as to which mechanism is mainly responsible for the relative increase in PiCO2; i.e., is the major factor flow stagnation or anaerobic metabolism? In support of flow stagnation are the facts that, although splanchnic O2 consumption decreased and splanchnic O2er increased compared with baseline, neither variable changed significantly, despite the significant reduction in splanchnic DO2. Moreover, the critical DO2 level, either systemic or splanchic, at which O2-supply dependency occurs has been reported to be much lower than the levels observed in the present study (8, 15, 19). Although blood lactate concentrations increased with hypocapnia, this phenomenon is well described during hypocapnia and is attributable to mechanisms other than tissue hypoxia (11, 25). In addition, we did not observe significant net lactate release from the splanchnic territory during hypocapnia; this fact argues against the presence of anaerobic metabolism.

Before this study, it could have been argued that widening of the PCO2 gradient immediately after induced hypocapnia is secondary only to the relatively long time constant of the tonometric techniques used to monitor PiCO2. A slow response time to achieve tonometric PiCO2 equilibration could potentially result in a transient artifactual widening of the PiCO2 – PaCO2 gradient. Although the possibility remains that this could be a factor, previous studies (6) that examined equilibration times for capnometric recirculating gas tonometry (of ~20 min) and our present findings of intestinal hypoperfusion and hypoxia oppose this being the major contributing factor that leads to the widened Pco2 gradient.

In summary, hypocapnia mediates splanchic as well as systemic reductions in blood flow. A clear redistribution in blood flow from the serosal to the mucosal layer was observed after inducing hypocapnia. Serosal surface Po2 decreased concomitantly with the reductions in splanchnic blood flow. However, despite redistribution of flow to the mucosa, a net reduction in mucosal flow occurred, and a widening of the Pco2 gradient was observed during hypocapnia. Our findings provide an explanation as to why the Pco2 gradient does not remain constant in the setting of induced systemic hypocapnia, and these findings strengthen the idea that the PiCO2 – PaCO2 gradient is a useful clinical variable for assessing splanchnic perfusion.

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