Splanchnic hemodynamics and gut mucosal-arterial \( \text{PCO}_2 \) gradient during systemic hypocapnia

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Guzman, Jorge A., and James A. Kruse. Splanchnic hemodynamics and gut mucosal-arterial PCO\(_2\) gradient during systemic hypocapnia. J. Appl. Physiol. 87(3): 1102–1106, 1999.—The effects of hypocapnia [arterial PCO\(_2\) (PaCO\(_2\)] of 15 Torr] on splanchnic hemodynamics and gut mucosal-arterial PCO\(_2\) were studied in seven anesthetized ventilated dogs. Ileal mucosal and serosal blood flow were estimated by using laser Doppler flowmetry, mucosal PCO\(_2\) was measured continuously by using capnometric recirculating gas tonometry, and serosal surface PO\(_2\) 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 PaCO\(_2\) 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 hypopcapnia. Similarly, mucosal and serosal blood flow decreased by 15 ± 4 and by 34 ± 7%, respectively. Also, an increase in the mucosal-arterial PCO\(_2\) gradient of 10.7 Torr and a reduction in serosal PO\(_2\) 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 PCO\(_2\) gradient and diminished serosal PO\(_2\).

Recently, the gradient between PiCO\(_2\) and PaCO\(_2\) (PiCO\(_2\) – PaCO\(_2\), or PCO\(_2\) gap) has been proposed as a more specific marker of gut perfusion by accounting for the influence that PaCO\(_2\) may have on PiCO\(_2\) (17, 20). However, as previously noted, hypocapnia per se can induce changes in splanchnic blood flow, and these changes could alter PiCO\(_2\). The PiCO\(_2\) – PaCO\(_2\) gradient could therefore increase as a consequence of induced hyperventilation, and these effects may need to be accounted for when assessing gut perfusion in the setting of hypocapnic alkalosis. Furthermore, we recently described the effects of systemic hypo- and hypercapnia induced by changes in minute ventilation on the PiCO\(_2\) – PaCO\(_2\) gradient and showed that during hyperventilation this gradient increased, suggesting that factors not yet clearly understood were responsible for the rise in the PiCO\(_2\) – PaCO\(_2\) gradient (7). We conducted the present study to better understand the effects of systemic hypocapnia on the splanchnic circulation and to elucidate the influence that respiratory alkalosis has on the PiCO\(_2\) – PaCO\(_2\) 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 PCO\(_2\) by removal of this dead space once the experimental protocol was initiated. Respiratory rate was adjusted to achieve a baseline PaCO\(_2\) 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, thermistlated 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 done, the duodenum and small intestine were displaced to expose the portal vein. After careful dissection was performed, an 8-mm ultrasonic flow probe (model BRS; 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
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 (modelABL-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) was monitored continuously by using a mainstream capnograph (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) was monitored continuously by using a mainstream capnograph (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) was monitored continuously by using a mainstream capnograph (model T206; Transonic Systems).

Systemic arterial (CaO2), mixed venous (CmvO2), and portal venous (CpvO2) blood O2 contents; systemic and splanchnic O2 delivery (DO2); O2 consumption (VO2); and O2 extraction ratios (O2ER) were calculated from gas tensions (in Torr) and fractional oxyhemoglobin saturations of systemic arterial (PaO2 and SaO2, respectively), pulmonary arterial (PmvO2 and SmvO2, respectively), and portal venous (PpvO2 and SpvO2, respectively) blood, Hb concentration (in g/dl), portal vein blood flow (in ml/kg·min⁻¹), and cardiac output (in ml/kg·min⁻¹) according to

\[ CaO_2 = (Hb \times 1.39 \times SaO_2) \right) + (PaO_2 \times 0.0031) \]

\[ CmvO_2 = (Hb \times 1.39 \times SmvO_2) + (PmvO_2 \times 0.0031) \]

\[ CpvO_2 = (Hb \times 1.39 \times SpvO_2) + (PpvO_2 \times 0.0031) \]

Systemic \( O_2ER = 100 \times (CaO_2 - CmvO_2) / CaO_2 \)

Splanchnic \( O_2ER = 100 \times (CaO_2 - CpvO_2) / CaO_2 \)

Systemic \( DO_2 = CaO_2 \times cardiac \ output / 100 \)

Splanchnic \( DO_2 = CaO_2 \times portal \ blood \ flow / 100 \)

Systemic \( VO_2 = (CaO_2 - CmvO_2) \times cardiac \ output / 100 \)

Splanchnic \( VO_2 = (CaO_2 - CpvO_2) \times portal \ blood \ flow / 100 \)

Experimental procedure. After baseline measurements were obtained (vital signs; arterial, mixed venous, and portal vein blood-gas measurements; lactate and acid-base values; portal, mucosal, and serosal blood flow; cardiac output; and 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 hypocapnic 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 $P_{CO_2}$ gradient and mucosal and serosal blood flow during the experiment. $P_{CO_2}$ 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 $P_{CO_2}$ and serosal surface $P_{O_2}$ during the experiment. The ratio between mucosal and serosal blood flow remained almost unchanged for 15 min after induction of hypocapnia, but this was followed by a progressive increase in the ratio that favored the mucosal layer and reached statistical significance by the end of the hypocapnic period, before it returned nearly to baseline value after restoration of eucapnia (Fig. 4).

**DISCUSSION**

This study provides further evidence that hypocapnia alters systemic and, more importantly, splanchnic hemodynamics. To avoid potential modification of splanchnic hemodynamics by variations in airway and intrathoracic pressure attributable to changes in tidal volume or respiratory frequency, we induced systemic hypocapnia by manipulating respiratory dead space volume. To ensure adequate fluid replacement and to avoid negative fluctuations in intravascular volume status, we maintained a constant but generous rate of fluid infusion.

**Table 1.** Hemodynamic and $O_2$ 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>&lt;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>&lt;0.001</td>
</tr>
<tr>
<td>Systemic $D_O_2$, 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 $D_O_2$, 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>&lt;0.001</td>
</tr>
<tr>
<td>Systemic $V_O_2$, 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 $V_O_2$, 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 $O_2$ extraction, %</td>
<td>23 ± 1</td>
<td>26 ± 2</td>
<td>25 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>Splanchnic $O_2$ 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. $D_O_2$, $O_2$ delivery; $V_O_2$, $O_2$ uptake; NS, not significant. Significant difference from baseline by Dunnett's multiple comparisons: *$P < 0.05$; †$P < 0.01$. 

Fig. 2. Gut intramucosal $P_{CO_2}$ ($P_{iCO_2}$) – $P_{aCO_2}$ gradient (●) and mucosal (○) and serosal (○) blood flow changes during experiment. Shaded area reflects duration of hypocapnia. TPU, tissue perfusion units (estimated ml·min⁻¹·100 g⁻¹). *Significant difference compared with corresponding baseline measurement by Dunnett's multiple-comparison statistic, $P < 0.05$. 

Fig. 3. Raw $P_{iCO_2}$ (●) measured by capnometric recirculating gas tonometry and serosal surface $P_{O_2}$ (○) measured by polarographic electrode during experiment. Shaded area reflects duration of hypocapnia. *Significant difference compared with corresponding baseline measurement by Dunnett's multiple-comparison statistic, $P < 0.05$. 

Fig. 1. Arterial $P_{CO_2}$ ($PaCO_2$; △), mixed venous $P_{CO_2}$ (○), and portal venous $P_{CO_2}$ (○) (top) and lactate concentrations (bottom) at baseline, during hypocapnia (shaded area), and after restoring eucapnia. *Significant difference for all 3 variables at indicated time point compared with corresponding baseline measurement by Dunnett's multiple-comparison statistic, $P < 0.05$. 

Fig. 4. Blood lactate and $P_{CO_2}$ changes during experiment. Shaded area reflects duration of hypocapnia.
PaCO2 gap increased significantly in the face of hypodecrease in PaCO2, and, as a consequence, the PiCO2 produced, the reduction did not quantitatively parallel the critical reductions in blood flow that would otherwise attempt to protect more vulnerable tissue layers from redistribution of flow in favor of the mucosal bed. This occurred at the serosal layer, thus clearly revealing necessary to confirm or reject this hypothesis. 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 splanchnic, 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 splanchnic 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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HYPOCAPNIA-INDUCED SPLANCHNIC HYPOPERFUSION


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