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# Splanchnic hemodynamics and gut mucosal-arterial $P_{CO_2}$ gradient during systemic hypocapnia

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**Guzman, Jorge A., and James A. Kruse.** Splanchnic hemodynamics and gut mucosal-arterial $P_{CO_2}$ gradient during systemic hypocapnia. *J. Appl. Physiol.* 87(3): 1102–1106, 1999.—The effects of hypocapnia [arterial $P_{CO_2}$ ($Pa_{CO_2}$) 15 Torr] on splanchnic hemodynamics and gut mucosal-arterial $P_{CO_2}$ were studied in seven anesthetized ventilated dogs. Ileal mucosal and serosal blood flow were estimated by using laser Doppler flowmetry, mucosal $P_{CO_2}$ was measured continuously by using capnometric recirculating gas tonometry, and serosal surface $P_{O_2}$ 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 $Pa_{CO_2}$ 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 hypocapnia. Similarly, mucosal and serosal blood flow decreased by 15 ± 4 and by 34 ± 7%, respectively. Also, an increase in the mucosal-arterial $P_{CO_2}$ gradient of 10.7 Torr and a reduction in serosal $P_{O_2}$ of 30 Torr were observed with hypocapnia ($P < 0.01$ for both). Hypocapnia caused ileal mucosal and serosal hypoperfusion, with redistribution of flow favoring the mucosa, accompanied by increased $P_{CO_2}$ gradient and diminished serosal $P_{O_2}$.

hypocapnia; intramucosal carbon dioxide tension; carbon dioxide tension gradient; splanchnic blood flow; tonometry

VARIATIONS IN ARTERIAL $P_{CO_2}$ ($Pa_{CO_2}$) are frequently observed in response to a wide variety of clinical conditions seen in critically ill patients. Changes in $Pa_{CO_2}$ affect peripheral arterioles and lead to vasodilatation or constriction (3, 16). Hypocapnia causes both vasoconstriction and mild depression of myocardial contractility (21), and, in the splanchnic region, this results in reduction of both hepatic artery and portal vein blood flow (4, 11).

Monitoring gut intramucosal $P_{CO_2}$ ($Pi_{CO_2}$) by gastrointestinal tonometry has been increasingly advocated as the method of choice for assessing splanchnic perfusion clinically. Numerous studies have demonstrated its usefulness in various experimental and clinical settings (1, 5, 8, 13, 14). $Pi_{CO_2}$ varies in direct proportion to mucosal $CO_2$ production and $Pa_{CO_2}$, and inversely with splanchnic blood flow, variables that determine regional delivery and removal of $CO_2$ by way of the circulation. Alterations in $Pa_{CO_2}$ theoretically should lead to proportional changes in $Pi_{CO_2}$, more so if $CO_2$ production and blood flow remain constant.

Recently, the gradient between $Pi_{CO_2}$ and $Pa_{CO_2}$ ($Pi_{CO_2} - Pa_{CO_2}$, or $P_{CO_2}$ gap) has been proposed as a more specific marker of gut perfusion by accounting for the influence that $Pa_{CO_2}$ may have on $Pi_{CO_2}$ (17, 20). However, as previously noted, hypocapnia per se can induce changes in splanchnic blood flow, and these changes could alter $Pi_{CO_2}$. The $Pi_{CO_2} - Pa_{CO_2}$ 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 $Pi_{CO_2} - Pa_{CO_2}$ gradient and showed that during hyperventilation this gradient increased, suggesting that factors not yet clearly understood were responsible for the rise in the $Pi_{CO_2}$-$Pa_{CO_2}$ 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 $Pi_{CO_2} - Pa_{CO_2}$ 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 $P_{CO_2}$ by removal of this dead space once the experimental protocol was initiated. Respiratory rate was adjusted to achieve a baseline $Pa_{CO_2}$ 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 $mg \cdot kg^{-1} \cdot min^{-1}$ iv), cisatracurium besylate (0.2 mg/kg bolus followed by 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$), 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, thermodilution 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 8RS; 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 $P_{CO_2}$ 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 $ml \cdot min^{-1} \cdot 100\ g^{-1}$) 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 $P_{O_2}$ 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 $Pa_{CO_2}$ 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 $P_{O_2}$, $P_{CO_2}$, 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). $Pi_{CO_2}$ was monitored continuously, by use of the balloon-tipped ileal catheter, with the use of capnometric recirculating gas tonometry (6–8). End-tidal $P_{CO_2}$ ($P_{ET_{CO_2}}$) was monitored continuously by using a mainstream capnograph (model N6000; Nellcor Puritan Bennett, Pleasanton, CA).

Systemic arterial ($Ca_{O_2}$), mixed venous ($Cmv_{O_2}$), and portal venous ($Cpv_{O_2}$) blood $O_2$ contents; systemic and splanchnic $O_2$ delivery ($D_{O_2}$); $O_2$ consumption ($\dot{V}_{O_2}$); and $O_2$ extraction ratios ($O_{2er}$) were calculated from gas tensions (in Torr) and fractional oxyhemoglobin saturations of systemic arterial ($Pa_{O_2}$ and $Sa_{O_2}$, respectively), pulmonary arterial ($Pmv_{O_2}$ and $Smv_{O_2}$, respectively), and portal venous ($Ppv_{O_2}$ and $Spv_{O_2}$, respectively) blood, Hb concentration (in g/dl), portal vein blood flow (in $ml \cdot kg^{-1} \cdot min^{-1}$), and cardiac output (in $ml \cdot kg^{-1} \cdot min^{-1}$) according to

$$Ca_{O_2} = (Hb \times 1.39 \times Sa_{O_2}) + (Pa_{O_2} \times 0.0031)$$

$$Cmv_{O_2} = (Hb \times 1.39 \times Smv_{O_2}) + (Pmv_{O_2} \times 0.0031)$$

$$Cpv_{O_2} = (Hb \times 1.39 \times Spv_{O_2}) + (Ppv_{O_2} \times 0.0031)$$

$$\text{Systemic } O_{2er} = 100 \times (Ca_{O_2} - Cmv_{O_2})/Ca_{O_2}$$

$$\text{Splanchnic } O_{2er} = 100 \times (Ca_{O_2} - Cpv_{O_2})/Ca_{O_2}$$

$$\text{Systemic } D_{O_2} = Ca_{O_2} \times \text{cardiac output}/100$$

$$\text{Splanchnic } D_{O_2} = Ca_{O_2} \times \text{portal blood flow}/100$$

$$\text{Systemic } \dot{V}_{O_2} = (Ca_{O_2} - Cmv_{CO_2}) \times \text{cardiac output}/100$$

$$\text{Splanchnic } \dot{V}_{O_2} = (Ca_{O_2} - Cpv_{O_2}) \times \text{portal blood flow}/100$$

*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 $P_{ET_{CO_2}}$) and monitoring of $Pi_{CO_2}$ (measured continuously but reported at 15-min intervals) was commenced, dead space was incrementally removed to achieve hypocapnia (targeted $Pa_{CO_2}$ 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 $ml \cdot kg^{-1} \cdot h^{-1}$ 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 $Pa_{CO_2}$ (13.8 ± 1.3 Torr). $P_{ET_{CO_2}}$ 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.

$Pa_{O_2}$, $Pmv_{O_2}$, and $Ppv_{O_2}$ did not change significantly during the experiment. The changes in $Pa_{CO_2}$, $Pmv_{CO_2}$, and $Ppv_{CO_2}$ and in lactate concentration at baseline, after 45 min of hypocapnia, and 45 min after restoring eucapnia are shown in Fig. 1. $Pa_{CO_2}$ 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 $Pmv_{CO_2}$ and $Ppv_{CO_2}$. 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 $O_2$ transport variables during the experiment. Mucosal and serosal $D_{O_2}$ 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.

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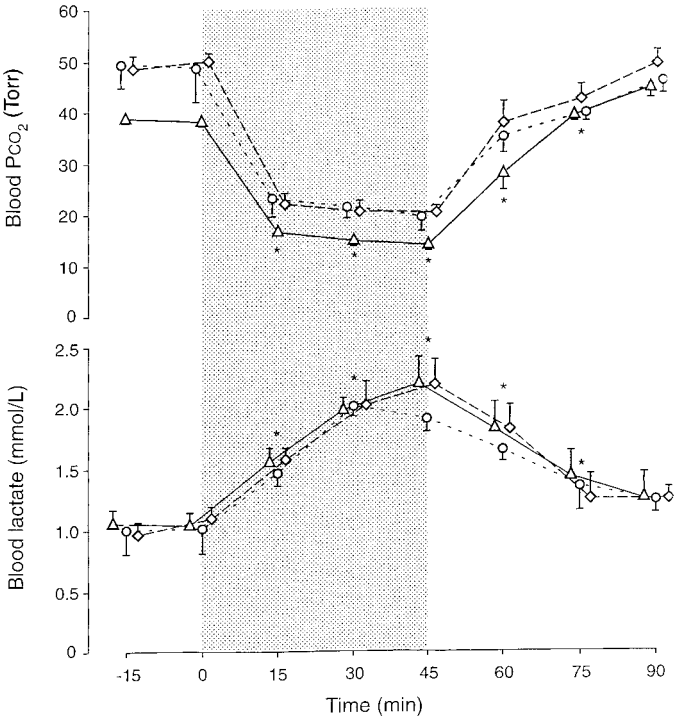


Fig. 1. Arterial $P_{CO_2}$ ($Pa_{CO_2}$; △), mixed venous $P_{CO_2}$ (○), and portal venous $P_{CO_2}$ (◇) (*top*) and lactate concentrations (*bottom*) at baseline, during hypocapnia (shaded area), and after restoring eucapnia. *Significant difference for all 3 variables at indicated time point compared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

Figure 2 shows the changes in gut-arterial $P_{CO_2}$ ($Pi_{CO_2} - Pa_{CO_2}$) gradient and mucosal and serosal blood flow during the experiment. $Pi_{CO_2} - Pa_{CO_2}$ increased from 24.4 ± 3.1 to 35.2 ± 4.8 Torr after hypocapnia and

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*

| Variable | Baseline | 45 min Posthypocapnia | 45 min Posteucapnia | *P* Value |
|---|---|---|---|---|
| Heart rate, beats/min | 128 ± 9 | 129 ± 7 | 116 ± 8* | <0.001 |
| Mean arterial blood pressure, mmHg | 96.9 ± 6.1 | 89.7 ± 9.0 | 101.1 ± 8.0 | NS |
| Cardiac output, ml·kg$^{-1}$·min$^{-1}$ | 175.6 ± 36.4 | 136.1 ± 28.36 | 137.0 ± 16.6 | <0.05 |
| Portal blood flow, ml·kg$^{-1}$·min$^{-1}$ | 20.3 ± 3.3 | 11.6 ± 1.8† | 14.7 ± 2.5† | <0.001 |
| Systemic $D_{O_2}$, ml·kg$^{-1}$·min$^{-1}$ | 21.6 ± 2.4 | 18.9 ± 5.3 | 19.5 ± 2.5 | NS |
| Splanchnic $D_{O_2}$, ml·kg$^{-1}$·min$^{-1}$ | 2.70 ± 0.5 | 1.50 ± 0.2† | 2.03 ± 0.3* | <0.001 |
| Systemic $\dot{V}_{O_2}$, ml·kg$^{-1}$·min$^{-1}$ | 4.73 ± 1.2 | 3.60 ± 0.8 | 4.23 ± 0.6 | NS |
| Splanchnic $\dot{V}_{O_2}$, ml·kg$^{-1}$·min$^{-1}$ | 0.43 ± 0.06 | 0.34 ± 0.08 | 0.41 ± 0.08 | NS |
| Systemic $O_2$ extraction, % | 23 ± 1 | 26 ± 2 | 25 ± 2 | NS |
| Splanchnic $O_2$ extraction, % | 17 ± 3 | 23 ± 4 | 22 ± 4 | NS |

Values are means ± SE; $n$ = 7 dogs. $D_{O_2}$, $O_2$ delivery; $\dot{V}_{O_2}$, $O_2$ uptake; NS, not significant. Significant difference from baseline by Dunnett's multiple comparisons: *$P < 0.05$; †$P < 0.01$.

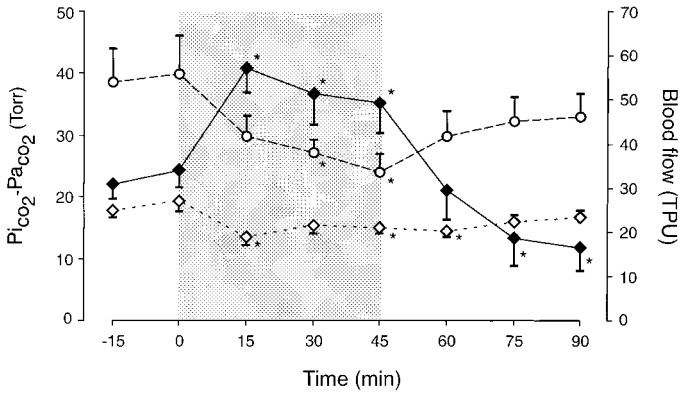


Fig. 2. Gut intramucosal $P_{CO_2}$ ($Pi_{CO_2}$) − $Pa_{CO_2}$ gradient (◆) and mucosal (◇) and serosal (○) blood flow changes during experiment. Shaded area reflects duration of hypocapnia. TPU, tissue perfusion units (estimated ml·min$^{-1}$·100 g$^{-1}$). *Significant difference compared with corresponding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

decreased to 11.9 ± 3.8 Torr at the end of eucapnia ($P < 0.001$ by ANOVA). Figure 3 shows the changes in raw $Pi_{CO_2}$ 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

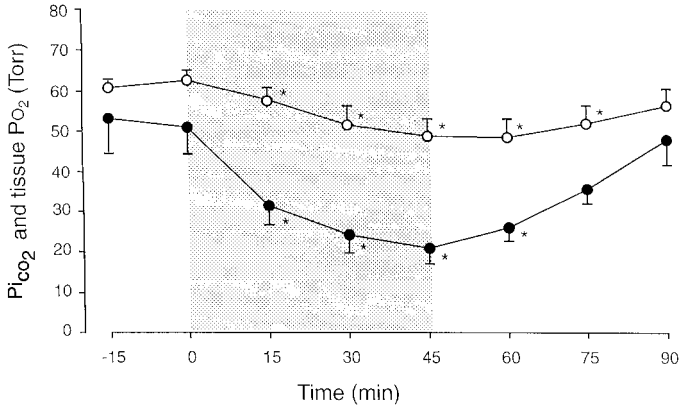


Fig. 3. Raw $Pi_{CO_2}$ (○) measured by capnometric recirculating gas tonometry and serosal surface $P_{O_2}$ (●) measured by polarographic electrode during experiment. Shaded area reflects duration of hypocapnia. *Significant difference compared with corresponding baseline measurement by Dunnett's multiple-comparison statistic, $P < 0.05$.

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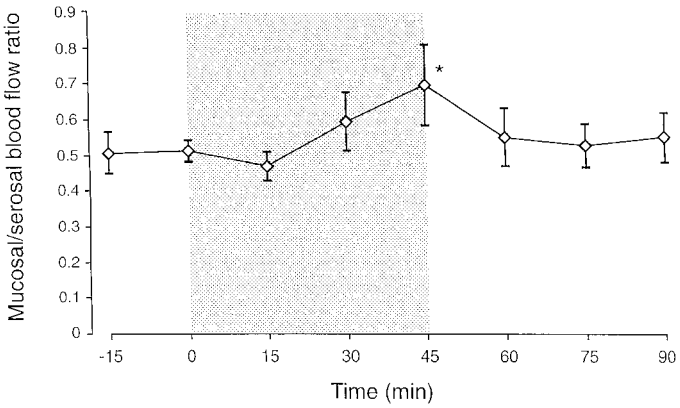


Fig. 4. Mucosal-to-serosal blood flow ratio during experiment. Shaded area reflects duration of hypocapnia. *Significant difference compared with corresponding baseline measurement by Dunnett's multiple-comparison statistic, $P < 0.05$.

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 $Pi_{CO_2}$ decreased after hypocapnia was induced, the reduction did not quantitatively parallel the decrease in $Pa_{CO_2}$, and, as a consequence, the $Pi_{CO_2} - Pa_{CO_2}$ 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 $Pa_{CO_2}$ 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 $P_{O_2}$ decreased. The decrease by more than one-half in the serosal surface $P_{O_2}$ 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 $O_{2er}$ in the face of reduced splanchnic $D_{O_2}$ (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 $Pi_{CO_2}$; i.e., is the major factor flow stagnation or anaerobic metabolism? In support of flow stagnation are the facts that, although splanchnic $O_2$ consumption decreased and splanchnic $O_{2er}$ increased compared with baseline, neither variable changed significantly, despite the significant reduction in splanchnic $D_{O_2}$. Moreover, the critical $D_{O_2}$ level, either systemic or splanchnic, at which $O_2$-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 $P_{CO_2}$ gradient immediately after induced hypocapnia is secondary only to the relatively long time constant of the tonometric techniques used to monitor $Pi_{CO_2}$. A slow response time to achieve tonometric $P_{CO_2}$ equilibration could potentially result in a transient artifactual widening of the $Pi_{CO_2} - Pa_{CO_2}$ 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 $P_{CO_2}$ 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 $P_{O_2}$ 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 $P_{CO_2}$ gradient was observed during hypocapnia. Our findings provide an explanation as to why the $P_{CO_2}$ gradient does not remain constant in the setting of induced systemic hypocapnia, and these findings strengthen the idea that the $Pi_{CO_2} - Pa_{CO_2}$ gradient is a useful clinical variable for assessing splanchnic perfusion.

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