Dopamine-1 receptor stimulation impairs intestinal oxygen utilization during critical hypoperfusion

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The splanchnic circulation is particularly susceptible to ischemia during shock (1, 17). This regional ischemia is thought to play an important role in the development of multiple-system organ failure by activation of a systemic inflammatory response (22, 35). In an effort to prevent or decrease gut ischemia, numerous gut-directed therapeutic approaches have been attempted with conflicting results (12). To date, clinical attempts to improve gut perfusion have focused mainly on the use of vasoactive drugs (16, 20, 21). However, the lack of splanchnic selectivity by these vasoactive agents could yield unwanted effects on gut oxygenation and desired outcomes. The most “gut-selective” vasoactive agent in common clinical use is dopamine given at relatively low doses. In animal models, low-dose dopamine infusions accelerate the onset of gut ischemia, impair gut oxygen extraction, and decrease gut VO₂ (9, 32). It is unclear from these data whether the adverse effects of low-dose dopamine are secondary to redistribution of flow within the gut or due to dopamine-induced alterations in gut metabolic rate.

Fenoldopam, a benzazepine derivative used clinically for treating systemic hypertension, is a relatively selective postsynaptic dopamine-1 (DA-1) receptor agonist with minimal α₂-receptor antagonistic activity, weak 5-HT₂ receptor agonist activity, and no significant affinity for α₁, β₁, or DA-2 receptors (3, 4, 23). Data from our laboratory have shown that DA-1 receptor stimulation increases portal blood flow and redistributes blood flow away from the intestinal serosa in favor of the mucosa during basal conditions and after hemorrhage. In addition, by augmenting the fraction of cardiac output directed to the gut, fenoldopam maintains splanchnic blood flow during systemic hypoperfusion and attenuates the splanchnic vasoconstrictive response to hemorrhage (15). However, the data used to assess the effects of fenoldopam on intestinal oxygen utilization are scarce and available results are conflicting (8, 31). Furthermore, because of the lack of methodological means, there have not been any attempts to investigate mucosal DO₂-VO₂ relationships.

The present study was conducted 1) to assess whether fenoldopam affects the relationship between oxygen transport and utilization in the systemic and splanchnic circulations and the level of DO₂ that marks the onset of supply dependency (DO₂crit), and 2) to describe the DO₂-VO₂ relationship at the level of the mucosa. Oxygen uptake relationships were studied in anesthetized dogs during sequential hemorrhage. Control (group 1) and experimental animals (group 2) were treated similarly except for the addition of fenoldopam (1.0 μg·kg⁻¹·min⁻¹) in group 2. Both groups had comparable systemic critical DO₂ (DO₂crit), but animals in group 2 had a higher gut DO₂crit (1.12 ± 1.13 vs. 0.80 ± 0.69 ml·kg⁻¹·min⁻¹, P < 0.05). At the mucosal level, a clear biphasic delivery-uptake relationship was not observed in group 1; thus oxygen consumption by the mucosa may be supply dependent under physiological conditions. Group 2 demonstrated higher peak mucosal blood flow and lack of supply dependency at higher mucosal DO₂ levels. Fenoldopam resulted in a more conspicuous biphasic relationship at the mucosa and a rightward shift of overall splanchnic DO₂crit despite increased splanchnic blood flow. These findings suggest that DA-1 receptor stimulation results in increased gut perfusion heterogeneity and redistribution of perfusion, resulting in increased susceptibility to ischemia.

oxygen supply dependency; splanchnic ischemia; vasodilators

AT A GIVEN LEVEL OF METABOLIC demand, systemic oxygen consumption is maintained constant despite moderate changes in systemic oxygen delivery (DO₂) (6, 14, 25, 30, 31). This is accomplished by changes in peripheral oxygen extraction, with a consequent decrease in mixed venous oxygen content. However, once DO₂ falls below a critical threshold, parallel decreases in oxygen uptake (VO₂) are observed. This “oxygen supply dependency” is accompanied by maximal tissue oxygen extraction, development of anaerobic metabolism, and venous hypercarbia (12, 14).

The splanchnic circulation is particularly susceptible to ischemia during shock (1, 17). This regional ischemia is thought to play an important role in the development of multiple-system organ failure by activation of a systemic inflammatory response (22, 35). In an effort to prevent or decrease gut ischemia, numerous gut-directed therapeutic approaches have been attempted with conflicting results (12). To date, clinical attempts to improve gut perfusion have focused mainly on the use of vasoactive drugs (16, 20, 21). However, the lack of splanchnic selectivity by these vasoactive agents could yield unwanted effects on gut oxygenation and desired outcomes. The most “gut-selective” vasoactive agent in common clinical use is dopamine given at relatively low doses. In animal models, low-dose dopamine infusions accelerate the onset of gut ischemia, impair gut oxygen extraction, and decrease gut VO₂ (9, 32). It is unclear from these data whether the adverse effects of low-dose dopamine are secondary to redistribution of flow within the gut or due to dopamine-induced alterations in gut metabolic rate.

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The present study was conducted 1) to assess whether fenoldopam affects the relationship between oxygen transport and utilization in the systemic and splanchnic circulations and the level of DO₂ that marks the onset of supply dependency (DO₂crit), and 2) to describe the DO₂-VO₂ relationship at the level of the mucosa.
intestinal mucosa during sequential reductions in $D\bar{O}_2$ by progressive hemorrhage.

METHODS

Surgical preparation. This protocol was approved by the Animal Investigation Committee of Wayne State University. Twelve mongrel dogs (15–30 kg) were fasted overnight, anesthetized with an intravenous injection of pentobarbital sodium (30 mg/kg), endotracheally intubated, and placed on mechanical ventilation (model MA-1; Puritan-Bennett; Carlsbad, CA) with a constant tidal volume (15 ml/kg). The respiratory rate was adjusted to achieve a baseline arterial partial pressure of CO$_2$ ($P_{ACO_2}$) of $\sim$40 Torr. A femoral vein and artery were exposed by surgical dissection and cannulated with vascular catheters for continuous intravenous infusions of pentobarbital sodium (0.06 mg·kg$^{-1}$·min$^{-1}$) and normal saline solution as well as for continuous monitoring of mean arterial blood pressure and intermittent blood sampling for blood gas and hemoglobin (Hb) analysis. A balloon-tipped, continuous thermodilution pulmonary artery catheter (model 746HFS; Baxter Healthcare; Irvine, CA) was advanced through the femoral vein and 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, an 8-mm ultrasonic flow probe (model 8RS; Transonic Systems; Ithaca, NY) was placed around the vessel and 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 palpation of the tip of the catheter through the wall of the portal vein. After a small ileostomy was performed, a laser-Doppler flow probe (type R; Transonic Systems) was sewn to the antimesenteric mucosal surface. Transonic Systems modified the probe so that it could be secured to the mucosa without compromising perfusion in the area of interest. After being calibrated with precision gas mixtures, a polarographic oxygen electrode (model 840, Novametrix Medical Systems; Wallingford, CT) was sutured to the antimesenteric surface of the ileum for mucosal $P_{O_2}$ measurement, and the ileostomy was closed. After hemostasis was assured, the laparotomy was closed and the animal allowed to stabilize for 45 min, when minute ventilation was readjusted if necessary to maintain $P_{ACO_2}$ at $\sim$40 Torr. The core temperature was monitored with the thermistor of the pulmonary artery catheter and maintained at $38.0 \pm 0.5^\circ$C with the use of heating pads and overhead infrared lamps.

Measurements and calculations. Systemic arterial, mixed venous, and portal venous blood samples were analyzed for $P_{O_2}$, $P_{CO_2}$, and pH with an automated blood gas analyzer (model 860; Bayer Diagnostics; Medfield, MA). Hb concentration and oxyHb saturation were assayed spectrophotometrically with a CO-oximeter calibrated for canine blood (model CO-oximeter, model MA-1; Puritan-Bennett; Carlsbad, CA) with a constant tidal volume (15 ml/kg). The respiratory rate was adjusted to achieve a baseline arterial partial pressure of CO$_2$ ($P_{ACO_2}$) of $\sim$40 Torr. A femoral vein and artery were exposed by surgical dissection and cannulated with vascular catheters for continuous intravenous infusions of pentobarbital sodium (0.06 mg·kg$^{-1}$·min$^{-1}$) and normal saline solution as well as for continuous monitoring of mean arterial blood pressure and intermittent blood sampling for blood gas and hemoglobin (Hb) analysis. A balloon-tipped, continuous thermodilution pulmonary artery catheter (model 746HFS; Baxter Healthcare; Irvine, CA) was advanced through the femoral vein and 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, an 8-mm ultrasonic flow probe (model 8RS; Transonic Systems; Ithaca, NY) was placed around the vessel and 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 palpation of the tip of the catheter through the wall of the portal vein. After a small ileostomy was performed, a laser-Doppler flow probe (type R; Transonic Systems) was sewn to the antimesenteric mucosal surface. Transonic Systems modified the probe so that it could be secured to the mucosa without compromising perfusion in the area of interest. After being calibrated with precision gas mixtures, a polarographic oxygen electrode (model 840, Novametrix Medical Systems; Wallingford, CT) was sutured to the antimesenteric surface of the ileum for mucosal $P_{O_2}$ measurement, and the ileostomy was closed. After hemostasis was assured, the laparotomy was closed and the animal allowed to stabilize for 45 min, when minute ventilation was readjusted if necessary to maintain $P_{ACO_2}$ at $\sim$40 Torr. The core temperature was monitored with the thermistor of the pulmonary artery catheter and maintained at $38.0 \pm 0.5^\circ$C with the use of heating pads and overhead infrared lamps.

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respectively; the onset of supply dependency. The lack of a plateau in the VO2-D02 relationship was accepted if the angle subtended by the two regression lines was within 15° of perfect linearity (i.e., ±165°). Critical gut mucosal PO2, mucosal blood flow, and portal venous PCO2 were determined by interpolation of the respective two points closest to the critical splanchnic D02. Student’s unpaired t-test was used to compare D02crit, interpolated values for other monitored variables at D02crit, and angles subtended by regression line pairs between study groups. Two-way repeated-measures analysis of variance was used to compare changes in intestinal mucosal blood flow between study groups during sequential bleeding episodes. Two-tailed P values ≤0.05 were considered statistically significant. Statistical calculations were performed with Excel (version 7.0; Microsoft; Redmond, WA) and SigmaStat (version 2.0; SPSS; Chicago, IL).

RESULTS

The two groups underwent a similar number of sequential bleeding episodes and had comparable volumes of blood withdrawn during the experiments (37.4 ± 2.5 vs. 40.4 ± 4.8 ml/kg for groups 1 and 2, respectively; P = not significant, NS). Table 1 shows the principal systemic and splanchnic hemodynamic and oxygen transport variables at baseline and at the end of hemorrhage. Systemic variables were comparable between groups at the beginning and at the end of experiments, despite the infusion of a selective DA-1 receptor agonist in group 2. On the other hand, group 2 had significantly higher values for baseline splanchnic D02 and portal blood flow compared with group 1. Values at the end of hemorrhage were comparable in both groups for all variables shown in Table 1. Baseline mucosal PO2 was somewhat higher among animals in group 2 (18.3 ± 1.9 vs. 13.8 ± 3.2 Torr); however, this difference was not statistically significant. By the end of the experiments, mucosal PO2 levels were undetectable in both groups.

Figure 1 shows pooled systemic and splanchnic D02 versus VO2 relationships. Systemic D02crit was similar in both groups (11.8 ± 2.6 and 12.0 ± 2.1 ml·kg⁻¹·min⁻¹ for groups 1 and 2, respectively; P = NS). Systemic oxygen extraction ratios at systemic D02crit were also comparable between study groups (0.50 ± 0.09 vs. 0.53 ± 0.10 for groups 1 and 2, respectively; P = NS). In contrast, the animals in group 2 had a significantly higher critical splanchnic D02 compared with controls. Portal venous PCO2 at splanchnic D02crit was significantly higher in animals that received fenoldopam (72.6 ± 4.2 compared with 57.5 ± 4.2 Torr in controls, P < 0.05), consistent with impaired splanchnic O2 utilization. Mucosal blood flow was observed to decrease steadily with each bleeding episode in the control group (Fig. 2). In animals receiving fenoldopam, mucosal blood flow was higher compared with controls during the first six bleeding episodes. Beyond that point, mean mucosal blood flows were essentially indistinguishable.

Table 1. Hemodynamic and oxygen transport-related variables during baseline and at end of hemorrhage in both groups

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>End of Hemorrhage</th>
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<tbody>
<tr>
<td>Heart rate, beats/min</td>
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<tr>
<td>Group 1</td>
<td>142 ± 10</td>
<td>188 ± 19</td>
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<tr>
<td>Group 2</td>
<td>151 ± 6</td>
<td>186 ± 9</td>
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<td>Mean arterial blood pressure, mmHg</td>
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<tr>
<td>Group 1</td>
<td>116 ± 5</td>
<td>23 ± 3</td>
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<tr>
<td>Group 2</td>
<td>116 ± 8</td>
<td>21 ± 4</td>
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<tr>
<td>Cardiac output, ml·kg⁻¹·min⁻¹</td>
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<tr>
<td>Group 1</td>
<td>140 ± 18</td>
<td>26 ± 7</td>
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<tr>
<td>Group 2</td>
<td>121 ± 12</td>
<td>20 ± 6</td>
</tr>
<tr>
<td>Portal blood flow, ml·kg⁻¹·min⁻¹</td>
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<tr>
<td>Group 1</td>
<td>17.4 ± 1.6</td>
<td>1.4 ± 0.5</td>
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<tr>
<td>Group 2</td>
<td>27.8 ± 4.5*</td>
<td>1.3 ± 0.4</td>
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<tr>
<td>Systemic oxygen delivery, ml·kg⁻¹·min⁻¹</td>
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<tr>
<td>Group 1</td>
<td>21.7 ± 2.1</td>
<td>3.3 ± 0.9</td>
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<tr>
<td>Group 2</td>
<td>21.6 ± 2.8</td>
<td>3.3 ± 0.9</td>
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<tr>
<td>Splanchnic oxygen delivery, ml·kg⁻¹·min⁻¹</td>
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<tr>
<td>Group 1</td>
<td>2.9 ± 0.5</td>
<td>0.27 ± 0.10</td>
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<tr>
<td>Group 2</td>
<td>4.7 ± 0.6*</td>
<td>0.21 ± 0.06</td>
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<tr>
<td>Systemic oxygen consumption, ml·kg⁻¹·min⁻¹</td>
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<tr>
<td>Group 1</td>
<td>5.6 ± 0.3</td>
<td>2.4 ± 0.6</td>
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<tr>
<td>Group 2</td>
<td>6.2 ± 0.4</td>
<td>2.8 ± 0.4</td>
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<tr>
<td>Splanchnic oxygen consumption, ml·kg⁻¹·min⁻¹</td>
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<tr>
<td>Group 1</td>
<td>0.54 ± 0.13</td>
<td>0.23 ± 0.08</td>
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<tr>
<td>Group 2</td>
<td>0.57 ± 0.21</td>
<td>0.16 ± 0.05</td>
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<tr>
<td>Systemic oxygen extraction</td>
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<tr>
<td>Group 1</td>
<td>0.24 ± 0.04</td>
<td>0.83 ± 0.06</td>
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<tr>
<td>Group 2</td>
<td>0.21 ± 0.04</td>
<td>0.80 ± 0.04</td>
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<tr>
<td>Splanchnic oxygen extraction</td>
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<tr>
<td>Group 1</td>
<td>0.18 ± 0.03</td>
<td>0.81 ± 0.04</td>
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<tr>
<td>Group 2</td>
<td>0.11 ± 0.04</td>
<td>0.78 ± 0.05</td>
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Values are means ± SE. Group 1, control; Group 2, fenoldopam. *P = 0.05 compared with group 1; †P < 0.05 compared with group 1.
between the two groups. Mucosal blood flow at gut
$D_{\text{O2crit}}$ was 5.8 ± 1.2 and 5.6 ± 0.5 TPU in groups 1
and 2, respectively ($P = \text{NS}$). Similarly, mucosal $P_{\text{O2}}$
at gut $D_{\text{O2crit}}$ was also comparable between groups
(6.2 ± 4.0 vs. 7.7 ± 3.2 Torr for groups 1 and 2,
respectively; $P = \text{NS}$).

Figure 3 shows individual graphs of mucosal $V_{\text{O2}}$
versus mucosal $D_{\text{O2}}$ for each animal in each group.
Supply dependency relationships are clearly seen over
the lower range of $D_{\text{O2}}$ values in all animals. At high
$D_{\text{O2}}$ levels, clear plateaus are not seen in the control
animals; however, they are more persuasively demon-
strated in the animals receiving fenoldopam. The mean
of group 1 slopes obtained by simple linear regression
(i.e., without dual regression analysis) was $0.80 ± 0.06$.
Application of dual regression analysis to each group
yielded mean supply dependency slopes of $0.89 ± 0.06$
and $0.85 ± 0.05$, respectively ($P = \text{NS}$). However, this
analysis generated signifi-
cantly higher $D_{\text{O2crit}}$ values
for group 2 compared with group 1 ($1.78 ± 0.22$ vs.
$1.12 ± 0.18 \text{ ml} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$, respectively; $P < 0.05$). The
slopes for the plateau portion of the relationship were
$0.43 ± 0.19$ in group 1 and $0.18 ± 0.09$ in group 2 ($P = \text{NS}$).
The mean angle subtended by the two regression
lines was 166.4° ± 3.5° versus 152.1° ± 1.9° for groups
1 and 2, respectively ($P < 0.01$). Peak mucosal $V_{\text{O2}}$ was
$1.74 ± 0.16$ versus $2.07 ± 0.36 \text{ ml} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$ ($P = \text{NS}$),
whereas peak mucosal $D_{\text{O2}}$ was $2.30 ± 0.30$ versus
$2.91 ± 0.47 \text{ ml} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$ ($P = \text{NS}$), for groups 1
and 2, respectively.

DISCUSSION

Examination of systemic $V_{\text{O2}}$ and $D_{\text{O2}}$ in our control
group showed the typical biphasic relationship re-
ported in many previous studies (6, 10, 24, 25, 29, 30).
This relationship indicates that systemic $V_{\text{O2}}$ is inde-
Fig. 3. Relationship between intestinal mucosal oxygen delivery ($\dot{D}i_{\dot{m}O_2}$) and intestinal mucosal oxygen consumption ($\dot{V}i_{\dot{m}O_2}$) in group 1 (A; ○) and group 2 (B; ●).
dependent of $D_{O_2}$ over a wide range of perfusion; however, below a certain critical delivery, $V_{O_2}$ demonstrates supply dependency. A similar, albeit somewhat less clear-cut, relationship was observed at the level of the overall splanchnic circulation, and this too has been shown previously (24--26, 29, 30).

At the dose administered, fenoldopam did not have significant effects on systemic hemodynamics or oxygen transport variables and did not affect systemic $D_{O_2}$crit. We (15) previously demonstrated that fenoldopam increases portal blood flow in a similar experimental model. The present study corroborates this effect and also demonstrates that this results in increased splanchnic $D_{O_2}$, which is expected from the augmentation in regional flow. We also found that fenoldopam increases splanchnic $D_{O_2}$crit, apparently reflecting an increased susceptibility of the gut to ischemia. Coupled with the lack of effect on systemic $D_{O_2}$crit, this finding corroborates and supplements what is known about the selective effects of fenoldopam on the splanchnic circulation.

The effects of fenoldopam on $D_{O_2}$crit have not been previously reported, but a limited number of other drugs with vasodilating properties have been shown to have this effect. For example, propofol, etomidate, and pentobarbital have all been shown to increase systemic $D_{O_2}$crit in a dose-dependent manner (37). On the other hand, prostaglandin E1 has been shown to decrease systemic $D_{O_2}$crit in anesthetized pigs (10). The nitric oxide synthase inhibitor Nω-nitro-L-arginine methyl ester, however, had no effect on either systemic or gut $D_{O_2}$crit (30). Vasodilators that increase $V_{O_2}$, such as dinitrophenol, would be expected to shift $D_{O_2}$crit to the right by increasing splanchnic oxidative metabolism (19). However, this is an unlikely explanation in the case of fenoldopam because, based on our findings, splanchnic $V_{O_2}$ was not significantly affected by the drug.

The overall increase in gut perfusion and $D_{O_2}$ induced by fenoldopam would seem to argue against the drug as a cause of splanchnic supply dependency, unless it also results in a maldistribution of perfusion. This could occur if there are changes in functional capillary density that increase perfusion heterogeneity and lead to a localized mismatch between $D_{O_2}$ and metabolic demand. Vasodilation could alter functional capillary density and increase flow to areas in which $D_{O_2}$ was previously matched to oxygen demand, resulting in superfluous perfusion in that area. At a given level of organ blood flow, this form of physiological shunting would simultaneously induce (or worsen) oxygen supply dependency in other areas that were previously matched (or already unmatched) with respect to oxygen supply and demand but are now robbed of needed perfusion. Thus development or worsening of supply dependency in only one region within the splanchnic territory could have the effect of shifting overall splanchnic $D_{O_2}$crit to the right. In an isolated, autoperfused jejunal segment model, fenoldopam has been shown to increase capillary filtration without altering capillary permeability (5). This finding suggests that fenoldopam can increase perfused capillary density.

As opposed to the systemic and overall splanchnic $V_{O_2}$ versus $D_{O_2}$ relationships, inspection of the $V_{O_2}$-$D_{O_2}$ curves limited to the splanchnic mucosa do not clearly show plateaus in the control group. This interpretation denotes that mucosal supply dependency prevailed in the control group throughout our experiments, a condition not observed in the relationships between $V_{O_2}$ and $D_{O_2}$ for the overall splanchnic or systemic circulations. If correct, this could signify that the mucosa experiences supply dependency under physiological conditions. Alternatively, it may have occurred under the baseline conditions of our study secondary to the effects of anesthesia and surgery, which could have induced a degree of mucosal flow limitation. Whereas the control animals have a paucity of points defining any clear-cut plateaus, most animals in the fenoldopam group show discernable plateaus. This might be expected if fenoldopam simply raised mucosal $D_{O_2}$ to a level above $D_{O_2}$crit. However, peak mucosal $D_{O_2}$ was not significantly augmented by fenoldopam in our experiments.

Lack of a plateau at the level of the mucosa under physiological conditions may be due to the anatomic configuration of the microcirculation within intestinal villi. As arteriolar blood courses toward the tip of the villus, there is transmural diffusion of oxygen directly to the venules and the venous side of the capillaries, decreasing the oxygen content of blood arriving at the tip (34). The countercurrent arrangement of arteriolar and venular capillaries augments the degree of shunting and causes the effect to be further pronounced during low-flow states (17). This base-to-apex $P_{O_2}$ gradient results in inefficiency of $D_{O_2}$ to the villous mucosa, particularly at the tips of the villi, and could be the basis for oxygen supply dependency in this region even under physiological conditions. We (13, 14) have shown that mucosal $P_{CO_2}$ is consistently higher than the $P_{CO_2}$ of portal venous blood in anesthetized dogs, an expected finding if the mucosa is normally in a state of supply dependency.

Analysis of our graphical data may argue against a typical biphasic relationship at the mucosal level, particularly among control animals, in which case dual regression analysis would not be applicable. However, to objectively evaluate the alternative hypothesis, we applied dual regression analysis to arrive at mucosal $D_{O_2}$crit points and obtain slopes for the regression lines in both the control and fenoldopam groups. Supply dependency slopes were similar for the two groups by this analysis, indicating similar maxima for $O_{2er}$ at the mucosal level. The slopes for the plateau portions of the control group graphs are well above zero, higher than those seen in the fenoldopam group, and higher than the plateaus of the systemic and overall splanchnic curves. In this analysis, the relatively steep slopes in the mucosal plateau regions of the control group are consistent with residual oxygen supply dependency; i.e., a partial or incomplete transition from supply independence to flow dependency. This implies that
independence of $\dot{V}O_2$ from delivery has not been fully reached, even at the highest mucosal $D\dot{O}_2$ levels found in our experiments. Thus both analyses point to same conclusion.

In a similar experimental model, we (15) showed that fenoldopam induces a redistribution of gut blood flow away from the serosa and favors the mucosa. Assuming that local perfusion is normally closely matched to local oxygen demands, this drug-induced redistribution could result in a less favorable perfusion heterogeneity and explains the increase in $D\dot{O}_{2crit}$ found for the overall splanchnic circulation. As noted previously, certain other splanchnic vasoconstrictors are known to increase gut oxygen demand. Arguing against this, peak mucosal $V\dot{O}_2$ did not increase significantly in our animals that received fenoldopam.

At gut $D\dot{O}_{2crit}$, portal venous $P_{CO_2}$ was significantly higher in the fenoldopam group. Portal venous $P_{CO_2}$ rises if splanchnic blood flow is decreased, reflecting slower removal of $CO_2$ produced by aerobic cellular metabolism and, therefore, accumulation of $CO_2$ in splanchnic tissue. At a given level of portal blood flow, portal hypercarbia will also result if aerobic metabolism is increased in the gut, resulting in increased generation of $CO_2$ by way of the tricarboxylic acid cycle. Finally, portal hypercarbia can occur during anaerobic metabolism due to augmented $CO_2$ production caused by increased mucosal oxygen demand. Arguing against this, peak mucosal $V\dot{O}_2$ did not increase significantly in our animals that received fenoldopam.

In summary, the biphasic relationship between $V\dot{O}_2$ and $D\dot{O}_2$ normally observed in the systemic and overall splanchnic circulation may not occur at the level of the intestinal mucosa under physiological conditions. This could be due to the unique microvascular architecture of the intestinal villus. Fenoldopam administration increases splanchnic blood flow, but despite this effect, it also causes a rightward shift of overall splanchnic $D\dot{O}_{2crit}$. This change in $D\dot{O}_{2crit}$ is likely caused by the vasoactive properties of the drug, leading to increased perfusion heterogeneity and a maldistribution of perfusion, resulting in increased susceptibility to ischemia and earlier appearance of anaerobic metabolism.

REFERENCES