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

JORGE A. GUZMAN, ARIOSTO E. ROSADO, AND JAMES A. KRUSE
Division of Pulmonary, Critical Care, and Sleep Medicine, Wayne State University School of Medicine, Detroit, Michigan 48201
Submitted 22 July 2002; accepted in final form 7 October 2002

Guzman, Jorge A., Ariosto E. Rosado, and James A. Kruse. Dopamine-1 receptor stimulation impairs intestinal oxygen utilization during critical hypoperfusion. Am J Physiol Heart Circ Physiol 284: H668–H675, 2003; 10.1152/ajpheart.00636.2002.—Effects of a dopamine-1 (DA-1) receptor agonist on systemic and intestinal oxygen delivery (D˙O2)–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 D˙O2 (D˙O2crit), but animals in group 2 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 D˙O2–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 D˙O2 that marks the onset of supply dependency (D˙O2crit), and 2) to describe the D˙O2–VO2 relationship at the level of the 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 (D˙O2) (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 D˙O2 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
intestinal mucosa during sequential reductions in $D_2O$ 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$_{aco2}$) of ~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 thermocoupling 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 R8S; 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 inserted to the antimesenteric surface of the ileum for mucosal $O_2$ 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$_{aco2}$ at ~40 Torr. The core temperature was monitored with the thermistor of the pulmonary artery catheter and maintained at 38.0 ± 0.5°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 $P_{o2}$, $P_{aco2}$, 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 OSM-3, Radiometer; Westlake, OH). Systemic VO$_2$ was continuously monitored by expired gas analysis (Deltatrac; SensorMedics; Yorba Linda, CA). The instrument was calibrated before each experiment with the use of a precision gas mixture of known component concentrations. The VO$_2$ value (in ml·kg$^{-1}$·min$^{-1}$) used for each experimental time point was designated as the average of the preceding five measurements taken at 1-min intervals. Cardiac output was measured by continuous thermodilution (Vigilance; Baxter Healthcare). Hemodynamic pressures were measured by electronic transduction and integration (Transpac; Abbott Laboratories; North Chicago, IL). Portal vein blood flow was measured ultrasonically (model T206; Transonic Systems). Ileal mucosal blood flow was measured continuously by laser-Doppler velocimetry (model BLF21; Transonic Systems) and reported in tissue perfusion units (TPU), which represent estimates of absolute flow (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 as a reliable means of estimating relative changes in mucosal perfusion (27). Systemic arterial blood O$_2$ content (CaO$_2$), mixed venous blood O$_2$ content (CmvO$_2$), portal venous blood O$_2$ content (CpvO$_2$), and intestinal mucosal venous blood O$_2$ content (CimO$_2$); systemic and splanchnic oxygen extraction ratios (O$_2$er); systemic, splanchic, and intestinal mucosal $D_2O$, and splanchic and mucosal VO$_2$ were calculated from gas tensions (Torr) and fractional oxyhemoglobin saturations of systemic arterial (P$_{aco2}$ and SaO$_2$, respectively), pulmonary arterial (PmvO$_2$ and SmvO$_2$, respectively), portal venous (PpvO$_2$ and SpvO$_2$, respectively), and intestinal mucosal (PimO$_2$ and SimO$_2$, respectively); cardiac output (ml·kg$^{-1}$·min$^{-1}$), portal blood flow (ml·kg$^{-1}$·min$^{-1}$), mucosal blood flow (TPU) and Hb concentration (g/dl) according to methods described by sequentially shifting data points with 0.0031; CmvO$_2$ = (Hb × 1.39 × SmvO$_2$) + (PpvO$_2$ × 0.0031); CpvO$_2$ = (Hb × 1.39 × SpvO$_2$) + (PpvO$_2$ × 0.0031); CimO$_2$ = (Hb × 1.39 × SimO$_2$) + (PimO$_2$ × 0.0031); systemic oxygen extraction (O$_2$er) = (CaO$_2$ - CmvO$_2$)/CaO$_2$; splanchic oxygen extraction (O$_2$er) = (CaO$_2$ - CpvO$_2$)/CpvO$_2$; systemic $D_2O = CaO_2$ - cardiac output/100; splanchic $D_2O = CaO_2$ - portal blood flow/100; intestinal mucosal $D_2O = CaO_2$ - intestinal mucosal blood flow/100; splanchic VO$_2$ = (CaO$_2$ - CpvO$_2$) × portal blood flow/100; and intestinal mucosal VO$_2 = (CaO$_2$ - CimO$_2$) × intestinal mucosal blood flow/100.

PimO$_2$ was equated to ileal mucosal tissue PO$_2$. SimO$_2$ was derived from ileal mucosal tissue PO$_2$ using a polynomial mathematical model of the oxyhemoglobin dissociation curve (18).

**Experimental procedure.** The animals were divided into two groups of equal number: control (group 1) and experimental animals (group 2). Both groups were treated similarly except for the addition of a continuous intravenous infusion of fenoldopam (1.0 μg·kg$^{-1}$·min$^{-1}$) (15) in group 2, which was started after surgical preparation was completed and hemodynamic stability achieved and continued to the end of the experiment. Baseline measurements (vital signs; arterial, mixed venous, and portal blood gases; systemic, portal, and mucosal blood flow; and mucosal $P_{aco2}$) were subsequently obtained, and all animals were then subjected to stepwise hemorrhage of 5 ml/kg to reduce $D_2O$ in stages. Approximately 15 min were allowed between each bleeding episode to allow hemodynamic equilibration between measurements. Stepwise hemorrhage was continued until the animals could no longer maintain a stable blood pressure or developed cardiac arrest.

**Statistical analysis.** Summary values are expressed as means ± SE. The onset of supply dependency was determined for systemic, splanchic, and intestinal mucosal circulations for each animal with the use of dual regression analysis as follows. Corresponding VO$_2$ and $D_2O$ data points were divided into low- and high-$D_2O$ groups; the low group initially comprising points associated with the two lowest $D_2O$ values, and the high group comprising the remaining points. Separate regression lines were constructed for each group by the least-squares method of linear regression (27) using sequentially shifting data points with successively higher $D_2O$ values from the high-$D_2O$ group to the low-$D_2O$ group, all possible regression line pairs were examined (27). The line pair associated with a low-$D_2O$ slope having the lowest residual sum of squares was selected. The intersection of the selected regression line pair defined...
the critical $\text{DO}_2$; i.e., the onset of supply dependency. The lack of a plateau in the $\text{VO}_2$-$\text{DO}_2$ relationship was accepted if the angle subtended by the two regression lines was within 15° of perfect linearity (i.e., $\pm 165^\circ$). Critical gut mucosal $\text{PO}_2$, mucosal blood flow, and portal venous $\text{PCO}_2$ were determined by interpolation of the respective two points closest to the critical splanchnic $\text{DO}_2$. Student’s unpaired t-test was used to compare $\text{DO}_{2\text{crit}}$, interpolated values for other monitored variables at $\text{DO}_{2\text{crit}}$, 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 $\leq 0.05$ 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 $\text{DO}_2$ 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 $\text{PO}_2$ 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 $\text{PO}_2$ levels were undetectable in both groups.

Figure 1 shows pooled systemic and splanchnic $\text{DO}_2$ versus $\text{VO}_2$ relationships. Systemic $\text{DO}_{2\text{crit}}$ was similar in both groups ($11.8 \pm 2.6$ and $12.0 \pm 2.1$ ml·kg$^{-1}$·min$^{-1}$ for groups 1 and 2, respectively; $P = $ NS). Systemic oxygen extraction ratios at systemic $\text{DO}_{2\text{crit}}$ were also comparable between study groups ($0.50 \pm 0.09$ vs. $0.53 \pm 0.10$ for groups 1 and 2, respectively; $P = $ NS). In contrast, the animals in group 2 had a significantly higher critical splanchnic $\text{DO}_2$ compared with controls. Portal venous $\text{PCO}_2$ at splanchnic $\text{DO}_{2\text{crit}}$ 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 $\text{O}_2$ 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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<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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<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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<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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<td>Group 2</td>
<td>27.8 ± 4.5*</td>
<td>1.3 ± 0.4</td>
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<td>Systemic oxygen delivery, ml·kg$^{-1}$·min$^{-1}$</td>
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<td>Group 1</td>
<td>21.7 ± 2.1</td>
<td>3.3 ± 0.9</td>
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<td>Group 2</td>
<td>21.6 ± 2.8</td>
<td>3.3 ± 0.9</td>
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<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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<td>Group 2</td>
<td>4.7 ± 0.6†</td>
<td>0.21 ± 0.06</td>
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<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>
<td></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 ḊO2crit was 5.8 ± 1.2 and 5.6 ± 0.5 TPU in groups 1 and 2, respectively (P = NS). Similarly, mucosal Po2 at gut ḊO2crit was also comparable between groups (6.2 ± 4.0 vs. 7.7 ± 3.2 Torr for groups 1 and 2, respectively; P = NS).

Figure 3 shows individual graphs of mucosal V̇O2 versus mucosal ḊO2 for each animal in each group. Supply dependency relationships are clearly seen over the lower range of ḊO2 values in all animals. At high ḊO2 levels, clear plateaus are not seen in the control animals; however, they are more persuasively demonstrated 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 = NS). However, this analysis generated significantly higher ḊO2crit values for group 2 compared with group 1 (1.78 ± 0.22 vs. 1.12 ± 0.18 ml·min⁻¹·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 = 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 V̇O2 was 1.74 ± 0.16 versus 2.07 ± 0.36 ml·min⁻¹·100 g⁻¹ (P = NS), whereas peak mucosal ḊO2 was 2.30 ± 0.30 versus 2.91 ± 0.47 ml·min⁻¹·100 g⁻¹ (P = NS), for groups 1 and 2, respectively.

DISCUSSION

Examination of systemic V̇O2 and ḊO2 in our control group showed the typical biphasic relationship reported in many previous studies (6, 10, 24, 29, 30). This relationship indicates that systemic V̇O2 is inde-
Fig. 3. Relationship between intestinal mucosal oxygen delivery (\(\dot{D}i\text{mO}_2\)) and intestinal mucosal oxygen consumption (\(\dot{V}\text{mO}_2\)) in group 1 (A; \(\triangle\)) and group 2 (B; \(\bullet\)).
dependent of $\dot{D}O_2$ over a wide range of perfusion; however, below a certain critical delivery, $\dot{V}O_2$ 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 $\dot{D}O_{2crit}$. 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 $\dot{D}O_2$, which is expected from the augmentation in regional flow. We also found that fenoldopam increases splanchnic $\dot{D}O_{2crit}$, apparently reflecting an increased susceptibility of the gut to ischemia. Coupled with the lack of effect on systemic $\dot{D}O_{2crit}$, this finding corroborates and supplements what is known about the selective effects of fenoldopam on the splanchnic circulation.

The effects of fenoldopam on $\dot{D}O_{2crit}$ 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 $\dot{D}O_{2crit}$ in a dose-dependent manner (37). On the other hand, prostaglandin E$_1$ has been shown to decrease systemic $\dot{D}O_{2crit}$ in anesthetized pigs (10). The nitric oxide synthase inhibitor N$^\omega$-nitro-l-arginine methyl ester, however, had no effect on either systemic or gut $\dot{D}O_{2crit}$ (30). Vasodilators that increase $\dot{V}O_2$, such as dinitrophenol, would be expected to shift $\dot{D}O_{2crit}$ 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 $\dot{V}O_2$ was not significantly affected by the drug.

The overall increase in gut perfusion and $\dot{D}O_2$ 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 $\dot{D}O_2$ and metabolic demand. Vasodilation could alter functional capillary density and increase flow to areas in which $\dot{D}O_2$ 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 $\dot{D}O_{2crit}$ 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 $\dot{V}O_2$ versus $\dot{D}O_2$ relationships, inspection of the $\dot{V}O_2$-$\dot{D}O_2$ 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 $\dot{V}O_2$ and $\dot{D}O_2$ 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 $\dot{D}O_2$ to a level above $\dot{D}O_{2crit}$. However, peak mucosal $\dot{D}O_2$ 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 $\dot{D}O_2$ 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 $\dot{D}O_{2crit}$ 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 $D_O_2$ 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 $D_O_2crit$ found for the overall splanchnic circulation. As noted previously, certain other splanchnic vasodilators are known to increase gut oxygen demand (19). Hence, another explanation is that fenoldopam simply increased mucosal oxygen demand. Arguing against this, peak mucosal $V_O_2$ did not increase significantly in our animals that received fenoldopam.

At gut $D_O_2crit$, 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 buffering of hydrogen ions generated during glycolysis. The higher portal venous $P_CO_2$ in our fenoldopam group cannot be explained simply by flow stagnation because portal flow and splanchnic $D_O_2$ were higher in this group compared with the control group. Neither is it explained by increased aerobic metabolism because the mean values of splanchnic $V_O_2$ were identical for the two groups. These findings therefore implicate increased anaerobic metabolism induced by fenoldopam. The rightward shift in gut $D_O_2crit$ also supports the notion that this effect of the drug is mediated by changes in the distribution of perfusion (38).

Although the Fick principle allows assessment of $V_O_2$ in whole organs or discrete territories, such as a limb, it is not readily accomplishable for a particular tissue type or histological layer within an organ. Splanchnic $V_O_2$ can thus be derived from portal blood flow and systemic arterial and portal vein oximetry. However, deriving intestinal mucosal $V_O_2$ by the Fick method would require measurement of mucosal blood flow and sampling of mucosal venous effluent for oximetric analysis. Furthermore, the flow measurement would need to represent either the entire or a defined portion of the mucosal microcirculation, and the sampled venous blood would need to represent mixed regional effluent from either the entire or the same defined portion of the mucosal microcirculation. Surface laser-Doppler velocimetry allows only microvascular perfusion measurements over a limited area and does not provide flow measurements in absolute terms. Nevertheless, the method has been previously validated as a reliable means of estimating relative changes in mucosal perfusion (27). Cannulation of veins specifically draining the mucosa was not possible in our experiments. This lack of access to mucosal mixed venous effluent necessitated an alternative to direct measurements of local venous $P_O_2$ and oxyhemoglobin saturation to determine mucosal $V_O_2$. Thus mucosal tissue $P_O_2$ was substituted for mucosal venous $P_O_2$, and the corresponding saturation was derived by the use of the standard oxyhemoglobin dissociation relationship (18). We were able to adjust this relationship to the prevailing portal blood pH and $P_CO_2$, but these values may not accurately reflect those at the mucosal level.

While not without precedent, the assumption that venous effluent $P_O_2$ can be approximated from tissue $P_O_2$ is another limitation of our method for determining mucosal $V_O_2$ (36). Although the two tensions have been shown in previous studies (7, 11) to be closely correlated in some in vivo models, the gradient has been shown in mathematical models to potentially vary to some degree and in either direction as other parameters are varied over their physiological range (11, 33, 34). This poses an inherent constraint for in vivo studies examining mucosal tissue $V_O_2$ and necessitated equating mucosal venous $P_O_2$ with mucosal tissue $P_O_2$ in our experiments.

In summary, the biphasic relationship between $V_O_2$ and $D_O_2$ 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 $D_O_2crit$. This change in $D_O_2crit$ 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