Dopamine-1 receptor stimulation attenuates the vasoconstrictive response to gut ischemia

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Guzman, Jorge A., Ariosto E. Rosado, and James A. Kruse. Dopamine-1 receptor stimulation attenuates the vasoconstrictive response to gut ischemia. J Appl Physiol 91: 596–602, 2001.—The effects of fenoldopam, a dopamine-1 (DA-1) receptor agonist, were studied in two groups of anesthetized dogs before and after induction of splanchnic ischemia by way of hemorrhage. During the first portion of the experiment, both groups received fenoldopam (1.5 μg·kg⁻¹·min⁻¹) for 45 min followed by a 45-min washout. During the second portion, hemorrhage (10 ml/kg) was induced, followed by no intervention in group I (controls) and restarting of the fenoldopam infusion in group II. Prehemorrhage, fenoldopam increased composite portal blood flow by 33% (P < 0.01). After hemorrhage-induced splanchnic ischemia, fenoldopam restored portal vein blood flow to near baseline, maintained the splanchnic fraction of cardiac output, and attenuated the rise in gut mucosal PCO₂. DA-1 receptor stimulation increased portal blood flow and redistributed blood flow away from the serosal layer in favor of the mucosa during basal conditions and after hemorrhage, suggesting a more concentrated distribution of splanchnic DA-1 receptors within the mucosal layer vasculature. Fenoldopam maintained splanchnic blood flow during hypoperfusion and attenuated the splanchnic vasoconstrictive response to hemorrhage.

fenoldopam; hemorrhage; splanchnic perfusion

Although assessment of the adequacy of tissue oxygenation has been a major focus in the clinical management of critically ill patients, conventional hemodynamic and oxygen-derived physiological variables have been shown to be insensitive and may even be normal in early states of perfusion failure or shock (5, 8). Inadequate organ perfusion due to hemorrhage or other causes results in tissue hypercarbia and acidosis (10, 11, 20, 22, 24). Furthermore, a variety of pathological conditions commonly observed in intensive care units (e.g., hemorrhagic shock, sepsis, and trauma) are associated with poor outcome, usually attributable to refractory shock as an early or multiple organ system failure (MOSF) as a late feature of disease progression (3, 13). Although patients may exhibit a normal or even high cardiac output after fluid resuscitation, tissue hypoxia may still be present in certain regional tissues such as the gut and kidneys (15, 17). This apparent paradox has been rationalized by invoking the existence of an inflammation-induced maldistribution of perfusion at the microcirculatory level. Clinical use of vasoactive drugs to enhance blood flow to those vascular beds particularly at risk of hypoxia, such as the splanchnic and renal circulation, might be of therapeutic value in this setting (9, 16).

An attractive approach is the use of a selective vasodilating drug that increases blood flow to the splanchnic and renal territories. Dopamine affects all adrenergic receptor types. In low doses (typically <3 μg·kg⁻¹·min⁻¹), dopaminergic effects in combination with mild β-adrenergic effects may selectively increase blood flow in the splanchnic and renal territories, but, as the dose is increased, these vasodilatory effects are rapidly masked by α₁-adrenergic receptor stimulation resulting in vasoconstriction. Despite theoretical benefits, the effects of dopamine on the splanchnic circulation in either animal or human studies are conflicting (16, 18, 21, 27).

Fenoldopam, a benzazepine derivative used for treating systemic hypertension, is a selective postsynaptic dopamine-1 (DA-1) receptor agonist with minimal α₂-receptor antagonistic activity and no significant affinity for α₁, β₁, or DA-2 receptors (4). The effects of fenoldopam on the splanchnic circulation have not been extensively studied. In a porcine model, fenoldopam improved oxygenation of the jejunal mucosa in a dose-related manner (7). In a different study, fenoldopam did not increase oxygen delivery to the splanchnic region in a hyperdynamic ovine model of endotoxemia (26). However, the effects of fenoldopam on gut hemodynamics and oxygen metabolism during perfusion failure have not been examined previously. The present study was conducted 1) to assess the effects of fenoldopam on the splanchnic circulation and gut oxygenation and 2) to assess whether fenoldopam-induced mesenteric vasodilation exerts protective effects on perfusion during splanchnic ischemia modeled by systemic hemorrhage.

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MATERIAL AND METHODS

Surgical preparation. This protocol was approved by the Animal Investigation Committee of Wayne State University. Fourteen mongrel dogs (15–30 kg) were fasted overnight and then 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) using a constant tidal volume (15 ml/kg). Respiratory rate was adjusted to achieve a baseline arterial PCO\textsubscript{2} (P\textsubscript{ACO\textsubscript{2}}) 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\textsuperscript{-1}·min\textsuperscript{-1}) and normal saline solution, as well as for continuous monitoring of mean arterial blood pressure (MAP) and intermittent blood sampling for blood gas and hemoglobin analysis. A balloon-tipped, continuous thermodilution pulmonary artery catheter (746HF8; 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 the adjacent lymphatic tissue. A 7-Fr catheter was advanced through the splenic vein to the portal vein for blood sampling and pressure (PVP) recording. 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 continuous intramucosal PCO\textsubscript{2} (PiCO\textsubscript{2}) monitoring (measured continuously but indexed to body and estimated total gut weight (kg), respectively) blood and hemoglobin concentration (Hb, g/dl) according to

\[
\text{Ca}_{\text{O}_2} = (\text{Hb} \times 1.39 \times \text{Sa}_{\text{O}_2}) + (\text{PaO}_2 \times 0.0031) \quad (1)
\]

\[
\text{CmvO}_2 = (\text{Hb} \times 1.39 \times \text{Sv}_{\text{O}_2}) + (\text{PvO}_2 \times 0.0031) \quad (2)
\]

\[
\text{CvpO}_2 = (\text{Hb} \times 1.39 \times \text{SpvO}_2) + (\text{PpvO}_2 \times 0.0031) \quad (3)
\]

\[
\text{Systemic O}_2\text{ER} = \frac{(\text{CaO}_2 - \text{CmvO}_2)}{\text{CmvO}_2} \quad (4)
\]

\[
\text{Splanchnic O}_2\text{ER} = \frac{((\text{CaO}_2 - \text{CvpO}_2)/\text{CvpO}_2)}{\text{CvpO}_2} \quad (5)
\]

Systemic and mesenteric vascular resistances (SVR and MVR, respectively) were calculated according to the following formulas using MAP, central venous pressure (CVP), PVP (mmHg), and cardiac output and PBF (l·kg\textsuperscript{-1}·min\textsuperscript{-1}) indexed to body and estimated total gut weight (kg), respectively (19)

\[
\text{SVR} = (\text{MAP} - \text{CVP}) \times \text{weight} \times 80/\text{CO} \quad (6)
\]

\[
\text{MVR} = (\text{MAP} - \text{PVP}) \times \text{estimated gut weight} \times 80/\text{PBF} \quad (7)
\]

Experimental procedure. After baseline measurements (vital signs; arterial, mixed venous, and portal blood gas; acid-base and lactate values; portal, mesenteric, and splanchnic blood flow; intestinal surface P\textsubscript{O}_2; and cardiac output) were obtained and P\textsubscript{ACO\textsubscript{2}} monitoring (measured continuously but reported at 5 min intervals) was started, animals were divided into a control (group I) and an experimental group (group II). The study protocol consisted of two parts. During the first part (identical for both groups), a continuous intravenous infusion of fenoldopam (1.5 μg·kg\textsuperscript{-1}·min\textsuperscript{-1}) (7) was started and maintained for 45 min, during which time measurements were obtained at 15-min intervals. After the fenoldopam infusion was discontinued, a washout period of 45 min was allowed to reverse the systemic and splanchnic hemodynamic changes induced by the drug (elimination half-life of ~5 min) (4). During this washout period, a set of measurements was obtained at 30 and 45 min after drug discontinuation. During the second part, the animals were subjected to hemorrhage (aimed to achieve an initial 20% drop in PBF, i.e., to 80% of the last washout value) by allowing blood to flow from the arterial catheter over ~5 min. An intravenous infusion of normal saline solution was maintained at a constant rate of 7 ml·kg\textsuperscript{-1}·min\textsuperscript{-1} throughout the first part of the experiment and discontinued at the time of initiating hemorrhage. Twenty minutes after hemorrhage, animals in group II had fenoldopam restarted at a rate of 1.5 μg·kg\textsuperscript{-1}·min\textsuperscript{-1} and measurements obtained at 15-min intervals for the next 45 min. Animals in group I were followed for a similar period of time and measurements obtained at similar intervals, but they did not receive fenoldopam posthemorrhage.

Statistical analysis. Summary values are expressed as means ± SE. Because the two groups underwent identical interventions in the first part of the experiment, one-factor repeated-measures ANOVA was used to compare sequential composite measurements for each tested variable obtained.
between baseline and the end of the washout period and between the end of washout period and 20 min posthemorrhage. 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 and the last measurement obtained at the end of the washout period. The same analysis was applied separately for each group from the 20-min posthemorrhage time point through the end of the experiment. The control value for Dunnett’s test in these analyses was designated as the last posthemorrhage value before restarting fenoldopam in group II or the corresponding time point in group I. Two-factor (one factorial, one repeated-measures) ANOVA was used to compare the two groups with respect to sequential measurements over the last four experimental time points (20 min after inducing hemorrhage and then at 15-min intervals during the last 45 min). Probability values (two-tailed) of <0.05 were considered statistically significant. Statistical calculations were performed using Excel (version 7.0; Microsoft, Redmond, WA) and SigmaStat (version 1.0; Jandel, San Rafael, CA) software.

RESULTS

Fourteen animals were studied (7 per group). Systemic hemodynamic variables and arterial lactate concentrations over the course of the experiment are shown in Table 1 for both animal groups. The mean blood volume removed during hemorrhage was similar in both groups (9.5 ± 0.5 and 11.0 ± 1.0 ml/kg for groups I and II, respectively; P = not significant). Posthemorrhage, animals receiving fenoldopam were more tachycardic compared with controls (P < 0.01), but this effect was not seen in the prehemorrhage period while on fenoldopam. MAP mildly decreased in both groups after fenoldopam infusion and hemorrhage. Albeit more pronounced in group II, these changes were not statistically different from the changes observed in group I. Cardiac output remained essentially constant during the fenoldopam infusion and decreased during washout, suggesting rebound vasoconstriction. A further drop in cardiac output was evident in both groups after hemorrhage, with a composite change of −25 ± 4% (P < 0.01). Composite PBF for both groups increased from an initial baseline of 15.4 ± 2.2 to 20.1 ± 2.9 ml·kg⁻¹·min⁻¹ after administering fenoldopam for 15 min (P < 0.05 by Dunnett’s multiple comparisons statistic) and remained essentially constant during the subsequent 30 min of the infusion (Fig. 1). Composite PBF returned to near-baseline value (14.0 ± 2.0 ml·kg⁻¹·min⁻¹, P = not significant) at 30 min after the fenoldopam infusion and remained unchanged 15 min later. Twenty minutes after hemorrhage was initiated, the composite PBF decreased to 66% of the prehemorrhage value. PBF continued to fall slightly in the control animals, whereas it returned to near-baseline levels in the animals receiving fenoldopam (P < 0.01 by 2-way ANOVA). Fenoldopam had little effect on the fraction of cardiac output comprising PBF during the prehemorrhage period (Fig. 2). Inducing splanchnic ischemia by way of hemorrhage sharply decreased PBF/cardiac output (38%) by the end of the experiment in group I. However, in animals receiving fenoldopam, this fractional perfusion was maintained above prehemorrhage levels (P < 0.001, 2-way ANOVA).

As shown in Fig. 3, the initial fenoldopam infusion lowered systemic and mesenteric resistance (composite changes = −7% and −25%, respectively). This was

**Table 1. Systemic hemodynamic variables and arterial lactate concentration at major experimental timepoints**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>End of Fenoldopam</th>
<th>End of Washout</th>
<th>20 min Posthemorrhage</th>
<th>End of Experiment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group I</td>
<td>Group II</td>
<td>Group I</td>
<td>Group II</td>
<td>Group I</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>143 ± 10</td>
<td>146 ± 7</td>
<td>141 ± 14</td>
<td>148 ± 7</td>
<td>133 ± 11</td>
</tr>
<tr>
<td>MAP, mmHg*</td>
<td>102 ± 5</td>
<td>102 ± 4</td>
<td>93 ± 6</td>
<td>93 ± 6</td>
<td>116 ± 7</td>
</tr>
<tr>
<td>Cardiac output, ml·kg⁻¹·min⁻¹</td>
<td>149 ± 17</td>
<td>140 ± 12</td>
<td>153 ± 22</td>
<td>142 ± 10</td>
<td>129 ± 16</td>
</tr>
<tr>
<td>Arterial lactate, mmol/l</td>
<td>2.1 ± 0.4</td>
<td>1.8 ± 0.2</td>
<td>1.9 ± 0.3</td>
<td>1.7 ± 0.2</td>
<td>2.0 ± 0.3</td>
</tr>
</tbody>
</table>

Values are means ± SE. MAP, mean arterial blood pressure. No statistically significant differences were observed for any temporally related values between groups. *P < 0.05 by one-factor repeated-measures ANOVA for both groups.

Fig. 1. Portal blood flow (PBF) for groups I (○) and II (●) during experiments. Vertical arrow represents initiation of hemorrhage. †P < 0.05 for times 15 through 90 min for both groups combined compared with baseline. ‡P < 0.05 for times 100 and 110 min for both groups combined compared with 90 min. §P < 0.05 for times 125 through 155 min for each group separately compared with 110 min. $\$P < 0.001 between groups for times 110 through 155 min.
followed by a rebound increase in vascular resistance after discontinuing fenoldopam. Posthemorrhage, but before restarting fenoldopam in group II animals, SVR and MVR increased by 52% and 42%, respectively, for both groups combined compared with prehemorrhage values. Vascular resistance continued to climb markedly in the control animals but decreased in animals restarted on fenoldopam. Mean MVR at the end of the experiment was essentially at the original baseline level (~2% of baseline) in group II but increased by ~160% above baseline in group I.

During the first half of the experiment, fenoldopam had a minimal effect on mucosal blood flow (Fig. 4). On the other hand, serosal blood flow decreased by 23% \((P < 0.05)\). After hemorrhage, both serosal and mucosal blood flow dropped sharply, as expected. However, fenoldopam administered posthemorrhage markedly improved mucosal blood flow compared with control animals, whereas serosal perfusion was unaffected. Changes in serosal \(\text{PO}_2\) roughly paralleled these changes in serosal blood flow. Baseline composite serosal \(\text{PO}_2\) was 40.7 ± 8.1 Torr, decreased by 22% 45 min after fenoldopam was initially started \((P < 0.05)\), and returned to near baseline at the end of washout. A
second drop was observed after hemorrhage, and, although not statistically significant, serosal Po2 increased to near baseline 45 min after restarting fenoldopam in group II (39.7 ± 7 vs. 34.8 ± 10.1 Torr).

Systemic O2ER increased in both groups during the washout period. As expected, a pronounced increase in O2ER was observed after hemorrhage in both groups; however, a subsequent drop in O2ER was observed posthemorrhage in animals of group II once fenoldopam was restarted. Although the difference in systemic O2ER between groups at the end of the experiment appears substantial, the overall difference did not reach statistical significance. Changes in mesenteric O2ER after bleeding were concordant with the preceding except that the separation between groups was statistically significant (Fig. 5). PiCO2 rose sharply in both groups after hemorrhage was induced (Fig. 6). This increase continued unabated in group I but plateaued in group II following administration of fenoldopam.

DISCUSSION

The circulatory response to shock involves a pattern of selective vasoconstriction and vasodilation, which renders a distribution of the diminished cardiac output away from certain regions such as the kidneys and splanchnic organs (14, 25) and initiates an inflammatory reaction that potentially can lead to MOSF. Our data support the hypothesis that stimulation of mesenteric DA-1 receptors increases splanchnic blood flow, maintains gut mucosal perfusion, and modulates regional vasomotor tone during basal and ischemic conditions.

Effects of fenoldopam in the absence of mesenteric ischemia. Fenoldopam induced a significant increase in PBF followed by a return to near-baseline values after discontinuation of the infusion. Concomitantly, mesenteric vascular resistance decreased by ~25%, whereas mucosal blood flow was essentially unchanged and serosal blood flow decreased by ~20%. Serosal Po2 decreased during fenoldopam infusion and did not return to baseline immediately after discontinuation. At the level of the systemic circulation, MAP decreased slightly with the DA-1 agonist infusion, and a rebound increase was seen after drug discontinuation. Cardiac output fluctuations during infusion and washout were not statistically significant. Interestingly, SVR mildly decreased during fenoldopam infusion, but a rebound increase of about 35% was observed at the end of the washout period.

The decrease in arterial blood pressure and the chronotropic response to fenoldopam have been characterized previously (4, 7, 12). Our findings are in agreement with these previous reports and provide additional information on the hemodynamic response to DA-1 receptor stimulation by this drug. An increase in SVR following discontinuation of fenoldopam has not been described previously, and its cause is unclear. It may be postulated that mild α2-adrenergic receptor antagonism exerted by fenoldopam persists beyond that of the DA-1 receptor activity resulting in rebound vasoconstriction after discontinuation of the drug.

Fig. 5. Change in systemic and mesenteric oxygen extraction ratios (O2ER) for groups I (○) and II ( ●). Vertical arrow represents initiation of hemorrhage. *P < 0.05 for times 15 through 90 min for both groups combined compared with baseline. †P < 0.05 for times 100 and 110 min for both groups combined compared with 90 min. §P < 0.001 between groups for times 110 through 155 min.

Fig. 6. Change in intestinal mucosal Pco2 (PiCO2) for groups I (○) and II ( ●) during experiment. Vertical arrow represents initiation of hemorrhage. *P < 0.05 for times 15 through 90 min for both groups combined compared with baseline. †P < 0.05 for times 100 and 110 min for both groups combined compared with 90 min. §P < 0.05 for times 125 through 155 min for each group separately compared with 110 min.
The impairment in serosal oxygenation also has not been described previously. Germann et al. (7) evaluated the effects of fenoldopam on porcine jejunal mucosal and serosal oxygenation using multiwire Clark electrodes. They found an increase in jejunal mucosal PO₂ but no change in serosal PO₂ regardless of the dose used. On the other hand, although we did not evaluate mucosal oxygenation, we observed a decrease in serosal PO₂. The discrepancy might be explained by interspecies variability or methodological differences in determining tissue PO₂, although a decrease would be expected in light of diminished serosal blood flow. To our knowledge, the effects of fenoldopam on gut mucosal and serosal blood flow have not been described previously. DA-1 receptor stimulation induced a redistribution of flow in favor of the mucosal layer. The exact distribution of DA-1 receptors across the splanchnic territory has not been clearly elucidated, but our findings suggest a more selective distribution of postsynaptic DA-1 receptors on the rich intestinal mucosal vasculature.

Effects of fenoldopam in the presence of induced mesenteric ischemia. The hemodynamic changes induced by hemorrhage were partially or, for some variables, completely reversed by fenoldopam. PBF decreased similarly in both groups after hemorrhage and returned to prehemorrhage levels after fenoldopam was restarted despite the diminished cardiac output. In contrast to animals in the control group, those who received fenoldopam after hemorrhage had an increase in mucosal blood flow to almost prehemorrhage levels, consistent with a distribution of splanchnic DA-1 receptors localized more within the mucosal vasculature. The drop in SVR during fenoldopam is explained by its vasodilatory effect. In contrast to animals in group I, MVR remained almost constant in group II during the posthemorrhage period. This finding, along with the blunted change in mesenteric O₂ER, may be explained by altered vasomotor tone in the mesenteric vasculature with relaxation of precapillary sphincters and increased splanchnic perfusion as evidenced by the rise in portal blood flow.

Fenoldopam infusion altered the normal splanchnic vasconstrictor response to ischemia (14), in this case induced by hemorrhage, and maintained the splanchnic fraction of cardiac output almost constant. This could have important clinical implications because redistribution of blood flow away from the gut during otherwise compensated global hypoperfusion is thought to be one of the initiating events leading to an exaggerated inflammatory response and subsequent development of MOSF (1, 2, 28).

It could be argued that the tendency toward a lower MAP in group II could counter the potentially beneficial effects of fenoldopam-induced vasodilation by worsening tissue perfusion. However, stable arterial lactate levels in both groups, as well as the tendency for PICO₂ to decrease after hemorrhage in group II, suggest otherwise. Maintaining splanchnic perfusion might confer gut protective effects despite the mild decrease in arterial pressure.

In summary, our data show that DA-1 receptor stimulation increases PBF and redistributes blood flow away from the serosal layer in favor of the mucosa during basal conditions and after inducing gut ischemia modeled by hemorrhage. These findings suggest a distribution of splanchnic DA-1 receptors that is more concentrated in the mucosal layer vasculature. After inducing mesenteric ischemia, fenoldopam maintained splanchnic blood flow and attenuated the splanchnic vasoconstrictive response despite a diminished cardiac output. The potential effects of DA-1 receptor stimulation on gut permeability, bacterial translocation, and MOSF remain to be studied.

REFERENCES


