Effects of Short-term Fenoldopam Infusion on Gastric Mucosal Blood Flow in Septic Shock

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Background: Inadequate splanchnic perfusion in septic shock is associated with increased morbidity and mortality. As result of splanchnic ischemia, mucosal permeability increases. Considering the implication of improved mucosal perfusion in terms of maintenance of mucosal barrier integrity, dopamine-1 receptor stimulation could be helpful in septic shock. The goal of the current study was to determine the effects of fenoldopam on systemic hemodynamic parameters and gastric mucosal perfusion in patients with septic shock. Furthermore, the authors tested the hypothesis that the addition of fenoldopam (0.1 μg · kg⁻¹ · min⁻¹) to a combination of norepinephrine and dobutamine (5 μg · kg⁻¹ · min⁻¹) may improve gastric mucosal perfusion in septic shock.

Methods: Patients with septic shock were randomized to a double-blind 2-h infusion of fenoldopam (n = 20) or placebo (n = 20). Each group received dobutamine (5 μg · kg⁻¹ · min⁻¹), and the dosage of norepinephrine was adjusted to achieve a mean arterial pressure between 70 and 80 mmHg. A laser-Doppler probe and tonometer were introduced into the gastrointestinal lumen.

Results: A significant increase in gastric mucosal perfusion, detected by laser-Doppler flowmetry, was observed in the group treated with fenoldopam (P < 0.05). In addition, this increase in microcirculatory flow occurred despite the fact that systemic flow remained unchanged. Differences in gastrointestinal partial pressure of carbon dioxide values were not statistically significant in the fenoldopam and placebo groups.

Conclusions: The study showed that, for the same mean arterial pressure, short-term fenoldopam infusion increased gastric mucosal perfusion in patients with septic shock.

SEPTIC shock is characterized by decreased peripheral vascular resistance, impaired distribution of blood flow, and oxygen extraction with normal or improved oxygen delivery. Altered peripheral resistance in septic shock results in redistribution of cardiac output (CO) with hypoperfusion of splanchnic organs. The gut mucosa has been identified as one of the most important targets of injury during septic shock. An alteration of blood flow within the gut wall may be one contributing factor to gut mucosal injury. Gut mucosal hypoxia may play a key role in the pathogenesis of multiple organ dysfunction.1,2 The combination of vasodilatation and pronounced vascular hyporeactivity often necessitates a treatment with high-dose norepinephrine to maintain blood pressure and to increase oxygen delivery in septic shock. However, the administration of high-dose norepinephrine may cause or at least worsen splanchnic hypoperfusion.3-4 To prevent gut ischemia and to improve gut perfusion, numerous gut-directed therapeutic approaches have been attempted by administration of vasoactive drugs.5-7 Unfortunately, the lack of splanchnic selectivity by these vasoactive agents could yield adverse effects on gut perfusion and oxygenation. Fenoldopam is a relatively selective postsynaptic dopamine (DA)-1 receptor agonist, with weak 5-hydroxytryptamine-2 receptor agonist activity and no significant affinity for α, β, or DA-2 receptors.8 As shown in the studies by Guzman et al.,9,10 during hemorrhage, fenoldopam restored portal vein flow to near baseline, maintained fractional splanchnic blood flow, and mitigated the increase in ileal mucosal partial pressure of carbon dioxide (PCO₂). In addition, fenoldopam redistributed blood flow away from the serosal to the mucosal layer, both at baseline and during hemorrhage.

Considering that few validated techniques to measure gastric perfusion can be applied to humans, available data on the effects of fenoldopam on gut circulation in patients with septic shock are limited. The goal of this study is to evaluate the effects of low-dose fenoldopam infusion (0.1 μg · kg⁻¹ · min⁻¹) on gastric mucosal perfusion (GMP) using laser-Doppler flowmetry and on intramucosal pH using gastric tonometry in patients with septic shock treated with a combination of norepinephrine (perfused at rates achieving mean arterial pressure [MAP] between 70 and 80 mmHg) and dobutamine (5 μg · kg⁻¹ · min⁻¹).

Materials and Methods

Patients

The study protocol was approved by the local institutional ethics committee (University of Rome “La Sapienza,” Rome, Italy). Informed written consent was obtained from the closest relative of each patient.

The study was performed in two different multidisciplinary intensive care units (ICUs) in a university hospital. Forty critically ill patients were enrolled in the study.
FENOLDOPAM AND GASTRIC MUCOSAL PERFUSION IN SEPSIS

Table 1. Comparison of Baseline Data, Mortality Data, and Hospital Stay between Fenoldopam and Placebo Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fenoldopam Group (n = 20)</th>
<th>Placebo Group (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>62.86 ± 6.3</td>
<td>63.5 ± 5.0</td>
</tr>
<tr>
<td>Female, %</td>
<td>28</td>
<td>31</td>
</tr>
<tr>
<td>APACHE II (admission to ICU)</td>
<td>26.2 ± 1.8</td>
<td>25.8 ± 1.9</td>
</tr>
<tr>
<td>APACHE II (admission to the study)</td>
<td>23.2 ± 2.1</td>
<td>24.1 ± 1.6</td>
</tr>
<tr>
<td>Norepinephrine at baseline, μg·kg⁻¹·min⁻¹</td>
<td>0.117 ± 0.021</td>
<td>0.109 ± 0.016</td>
</tr>
<tr>
<td>Gram-positive cultures, %</td>
<td>57.1</td>
<td>71.4</td>
</tr>
<tr>
<td>Gram-negative cultures, %</td>
<td>42.8</td>
<td>28.5</td>
</tr>
<tr>
<td>Site of infection, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>64.3</td>
<td>50.0</td>
</tr>
<tr>
<td>Abdomen</td>
<td>21.4</td>
<td>35.7</td>
</tr>
<tr>
<td>Other</td>
<td>14.3</td>
<td>14.3</td>
</tr>
<tr>
<td>ICU mortality, %</td>
<td>43.3</td>
<td>45.1</td>
</tr>
<tr>
<td>Hospital mortality, %</td>
<td>52.1</td>
<td>53.2</td>
</tr>
<tr>
<td>30-Day mortality, %</td>
<td>50.3</td>
<td>52.8</td>
</tr>
<tr>
<td>Duration of ICU stay, days</td>
<td>13.5 ± 3.2</td>
<td>14.2 ± 2.1</td>
</tr>
<tr>
<td>Duration of hospital stay, days</td>
<td>56.4 ± 4.6</td>
<td>58.1 ± 2.6</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD or percentage. No statistically significant differences were observed in any of these variables between groups.

APACHE II = Acute Physiology and Chronic Health Evaluation II (score); ICU = intensive care unit.

(age, 63.1 ± 6 yr; 29% female). All patients had clinical and laboratory parameters that fulfilled the criteria of septic shock. The etiology of septic shock was documented infection in all patients. The Acute Physiology and Chronic Health Evaluation II scores were 26 ± 4 after the first 24 h in the ICU and 23 ± 2 before study entry. We included only patients with septic shock whose hypotension failed to respond to 20 μg·kg⁻¹·min⁻¹ dopamine associated with volume resuscitation (pulmonary artery occlusion pressure, 14 mmHg). The clinical characteristics of the study groups are summarized in Table 1. Each patient was mechanically ventilated and sedated with continuous intravenous sufentanil and midazolam. Exclusion criteria were pregnancy and present or suspected acute coronary artery disease.

Parameters Investigated

Systemic Hemodynamic and Oxygenation Parameters. Routine clinical monitoring of the patients included a pulmonary artery catheter (7.5 French; Arrow International Inc., Reading, PA) and a radial artery catheter. MAP, right atrial pressure, mean pulmonary arterial pressure, and pulmonary artery occlusion pressure (Solar M8000; Marquette Hellige Medical Systems, Milwaukee, WI) were measured at end-expiration. Heart rate was analyzed from a continuous recording of the electrocardiogram with ST segments monitored. CO was measured by means of thermodilution (Solar M8000) from the average of four injections of 10 ml ice-cold saline solution randomly spread over the respiratory cycle. Systemic vascular resistance index was calculated as mean systemic arterial pressure minus right atrial pressure divided by cardiac index (CI). Arterial and mixed venous blood samples were drawn for the measurement of PaO₂ and PaCO₂. Arterial oxygen delivery index, oxygen consumption index, and oxygen extraction ratio were calculated from standard formulas.

Gastric Mucosal Parameters. Gastric mucosal perfusion was evaluated by means of a laser-Doppler technique flowmeter (Periflux System 5000; Perimed, Stockholm, Sweden), using a gastric probe for the measurement of GMP described below, and by means of a tonometer (Tonometrics, Worcester, MA), enabling measurement of gastric mucosal PCO₂.

The laser-Doppler flowmeter consists of a 780-nm laser diode (1 mW) that has a relevant penetration depth, a fiberoptic probe, and a photodetector with a signal-processing unit. The laser light is conducted to tissue by a flexible fiberoptic guide. The gastric probe (P 424; Perimed) is intended for GMP measurement, and the measuring area of the probe has multiple probe tips. Each of the probe tips has transmitting and receiving fibers. The distance between transmitting and receiving fibers influences the penetration depth. The measuring volume increases with greater fiber separation. Values from each probe tip are optically integrated into one value. This method enables measurement over a larger area, especially in tissues with spatial variations in blood perfusion. The signal-processing unit consists of a photodetector and an analog circuit to analyze the frequency spectrum of the back-reflected scattered light. By determining the instantaneous mean Doppler frequency and the fraction of the scattered light that is Doppler shifted, the signal-processing unit provides a continuous output proportional to the number of erythrocytes moving in the measured volume and the mean velocity of these cells. Erythrocyte flux measurements were performed with a bandwidth of 12 kHz and a time constant of 0.2 s. This setting makes it possible to single out the flow signal from possible artifacts due to inappropriate contact of the probe against the gastric wall, recognizable as sharp spikes or erratic waves. The flow value was expressed in units of relative flux (perfusion units). The gastric probe was inserted via nasogastric or orogastric route. The correct position of the gastric probe in the lumen of the stomach was confirmed by radiography. Because the probe is at the tip of a nasogastric tube, we fixed the probe to the mucosa, generating a negative pressure through a 4-mm hole at 20 mm from the reading surface of the probe. When the laser-Doppler signal was satisfactory, aspiration via the probe held the tip of the probe against the gastric wall at the site of measurement. The degree of aspiration (40 mmHg) has been determined to produce adequate adhesion without affecting the laser-Doppler signal.

The laser-Doppler flowmetry signal was considered...
reliable when pulse waves and respiratory-synchronous fluctuation could be identified and were free of motion artifacts. The output signal from the flowmeter, i.e., GMP, was continuously monitored on a personal computer using the Perisoft® software (Perimed). The software enabled the performance of continuous monitoring as well as the acquisition and processing of the laser-Doppler signal for the whole duration of the study, with a period of 240 s at each set of measurements to average the laser-Doppler flowmetry values over this period.

Because the data of GMP were measured in arbitrary units (perfusion units), the results were expressed as a percentage of change between the reference value, defined as the value at the baseline, and each measurement. This was calculated according to the following formula: GMP = (measured value - baseline value / baseline value). In addition, we calculated the ratio between the absolute value of GMP (an index of local oxygen delivery) and systemic oxygen delivery, which may be considered to reflect the fraction of total erythrocyte flux perfusing gastric mucosa.12

We measured gastric mucosal $\text{PCO}_2$ using a nasogastric tonometer. The tonometer was inserted via the nasogastric route, and its position in the stomach was confirmed by radiography. The tonometer balloon was filled with 2.5 ml normal saline solution at room temperature 60 min before measurement. After this 60-min equilibration time, the saline sample was removed from the tonometer. The first 1 ml was discarded as catheter dead space, and blood gas analysis (IL-482; Radiometer, Copenhagen, Denmark) was performed on the remainder. $\text{PCO}_2$ measurements were temperature corrected to 37°C. The body temperature of the patients did not change during the course of the study. The gradient between gastric mucosal and arterial $\text{PCO}_2$ ($\Delta \text{P}_{g-a\text{CO}_2}$) was calculated as gastric mucosal $\text{PCO}_2$ minus arterial $\text{PCO}_2$. The intramucosal pH was calculated using the Henderson-Hasselbalch equation. Enteral feeding was discontinued during the study, and vacuity was ensured by gastric aspiration. Histamine receptor antagonists were not routinely used.13

**Experimental Protocol**

An initial set of measurements was taken. Patients were then randomized, using a computer-based procedure, to receive an infusion of 0.1 $\mu$g · kg$^{-1}$ · min$^{-1}$ fenoldopam or placebo in a double-blind fashion for 2 h. The dose of 0.1 $\mu$g · kg$^{-1}$ · min$^{-1}$ fenoldopam has been determined to achieve an increase in splanchic blood flow without modifications of systemic perfusion and cardiac function.14

During the study, the vasopressor agent (norepinephrine) was titrated to maintain MAP constant between 70 and 80 mmHg. A continuous intravenous fluid infusion (6% hydroxyethyl starch) at starting dose of 70 ml/h was performed to maintain the pulmonary artery occlusion pressure constant during the study. All other medications were held constant, the dobutamine infusion (5 $\mu$g · kg$^{-1}$ · min$^{-1}$) was not adjusted, and mechanical ventilator settings and positive end-expiratory pressure were not changed. If the patient’s condition deteriorated at any time during administration of the study drug, unblinding of the study drug infusion was allowed.

Measurements of systemic hemodynamics and GMP were performed at baseline and at the end of the 2 h infusion of fenoldopam. At the end of study period, 1 h after the discontinuation of fenoldopam infusion, a final set of measurements was obtained to complete the study. Schematic representation of the study is shown in figure 1.

Patients were followed up for 30 days after admission to the ICU or until discharge from the hospital, whichever was longer. The following data were collected: ICU, hospital, and 30-day mortalities; and durations of ICU and hospital stays.

**Statistical Analysis**

A prospective power calculation indicated that 30 patients would be needed to achieve a 90% power to detect modification in GMP (expressed as a percentage of change between the value at baseline at each measurement) at 2 h. The measured variables showed skewed distributions. Therefore, we used a nonparametric statistical analysis. We tested for differences in baseline characteristics between the experimental groups.
using a Mann–Whitney test, and we tested for changes from baseline to 2 h and 3 h in variables between the two study groups using the Kruskal-Wallis analysis of variance. All $P$ values are two tailed, and a $P$ value of less than 0.05 was considered significant. We used the statistical software SPSS (version 9; SPSS, Chicago, IL).

Results

Neither complications nor side effects were associated with either the administration of fenoldopam or the use of the laser-Doppler flowmeter and the gastric tonometer. No loss of contact between the laser-Doppler probe and the gastric mucosa or artifacts was observed in any patient during the study period. No patients were unblinded during the study period. Hemodynamic and gastric mucosal values are summarized in tables 2 and 3 and shown in figures 2 and 3. Patient groups were well matched so that there was no significant difference between the fenoldopam and placebo groups at the pre-study baseline. There were no significant differences in ICU mortality, hospital mortality, and 30-day mortality. Similarly, there was no significant difference in the duration of ICU stay or hospital stay between the two study groups. Values are summarized in table 1. As shown in table 2, during the fenoldopam and placebo infusions, for the same MAP, no statistical differences were found for the amount of fluid perfused, right atrial pressure, mean pulmonary arterial pressure, pulmonary artery occlusion pressure, $P_{a02}$, $P_{aco2}$, and hemoglobin concentration. This suggested that volume status and ventilatory support were maintained constant. Similarly, there was no significant difference in CI, heart rate, systemic vascular resistance index, or pulmonary vascular resistance index in the fenoldopam and placebo groups at each set of measurements. At the baseline measurement set, the ratio of GMP to systemic oxygen delivery was significantly lower in the fenoldopam group as compared to the placebo group.

Table 2. Hemodynamic Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fenoldopam</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>2 h</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>73.3 ± 2.9</td>
<td>73.3 ± 1.8</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>112.7 ± 10</td>
<td>113.8 ± 6.6</td>
</tr>
<tr>
<td>RAP, mmHg</td>
<td>12.7 ± 0.8</td>
<td>12.5 ± 0.6</td>
</tr>
<tr>
<td>MPAP, mmHg</td>
<td>14.1 ± 0.7</td>
<td>14.2 ± 0.6</td>
</tr>
<tr>
<td>GMP, %</td>
<td>26.6 ± 1.4</td>
<td>25.5 ± 1.4</td>
</tr>
<tr>
<td>CI, l·min⁻¹·m⁻²</td>
<td>4.5 ± 0.5</td>
<td>4.4 ± 0.4</td>
</tr>
<tr>
<td>SVRI, dyn·s·cm⁻⁵·m⁻²</td>
<td>1,125.1 ± 151.1</td>
<td>1,115.8 ± 130.6</td>
</tr>
<tr>
<td>PVRI, dyn·s·cm⁻⁵·m⁻²</td>
<td>225.5 ± 35.8</td>
<td>222.6 ± 31.4</td>
</tr>
<tr>
<td>Do2, ml·min⁻¹·m⁻²</td>
<td>720 ± 80.6</td>
<td>719.5 ± 72.1</td>
</tr>
<tr>
<td>Vo2, ml·min⁻¹·m⁻²</td>
<td>232.2 ± 29.1</td>
<td>229.1 ± 25.7</td>
</tr>
<tr>
<td>Svo2, %</td>
<td>67.2 ± 2.6</td>
<td>68.1 ± 1.9</td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>8.3 ± 0.8</td>
<td>8.6 ± 0.7</td>
</tr>
<tr>
<td>Fluid infusion, ml/h</td>
<td>78 ± 9</td>
<td>72 ± 11</td>
</tr>
<tr>
<td>Norepinephrine, μg·kg⁻¹·min⁻¹</td>
<td>0.117 ± 0.021</td>
<td>0.117 ± 0.015</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD. No statistically significant differences were observed in any of these variables between groups or over time.

CI = cardiac index; Do2 = oxygen delivery; HR = heart rate; MAP = mean arterial pressure; MPAP = mean pulmonary arterial pressure; PAOP = pulmonary artery occlusion pressure; PVRI = pulmonary vascular resistance index; RAP = right atrial pressure; Svo2 = mixed venous oxygen saturation; SVRI = systemic vascular resistance index; Vo2 = oxygen consumption.

Table 3. Gastric Mucosal Parameters

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fenoldopam</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>2 h</td>
</tr>
<tr>
<td>GMP, PU</td>
<td>214.8 ± 50.4</td>
<td>462.7 ± 52.8</td>
</tr>
<tr>
<td>GMP/Do2</td>
<td>0.3 ± 0.08</td>
<td>0.64 ± 0.081</td>
</tr>
<tr>
<td>GMP, %</td>
<td>—</td>
<td>125.0 ± 52.4</td>
</tr>
<tr>
<td>pH</td>
<td>7.33 ± 0.01</td>
<td>7.33 ± 0.0</td>
</tr>
<tr>
<td>pHi</td>
<td>7.23 ± 0.009</td>
<td>7.24 ± 0.012</td>
</tr>
<tr>
<td>ΔPaco2, mmHg</td>
<td>13.2 ± 1.1</td>
<td>13.1 ± 0.66</td>
</tr>
<tr>
<td>Paco2, mmHg</td>
<td>49.8 ± 1.9</td>
<td>50.1 ± 2</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD.

* $P < 0.05$ vs. placebo. † $P < 0.001$ vs. baseline. ‡ $P < 0.001$ vs. 3 h. § $P < 0.001$ vs. placebo.

GMP, % = gastric mucosal perfusion expressed as a percentage of change between the value at baseline and each measurement, calculated according to the following formula: GMP, % = [measured value – baseline value/baseline value] * 100; GMP/Do2 = ratio between gastric mucosal perfusion and systemic oxygen delivery; GMP, PU = gastric mucosal laser-Doppler perfusion arbitrary perfusion units; ΔPaco2 = gastric partial pressure of carbon dioxide minus arterial partial pressure of carbon dioxide; $P_{aco2}$ = gastric partial pressure of carbon dioxide; $pHi$ = gastric mucosal pH.
Compared with the placebo group. This finding might be related to the severity of our patients’ illness. However, as compared with placebo infusion, laser-Doppler GMP was significantly increased during fenoldopam infusion ($P < 0.05$). Gastric-arterial $\text{PCO}_2$ gradient and intramucosal pH values did not change significantly in the fenoldopam and placebo groups, and no statistical differences were found between the two study groups at each set of measurements. In the fenoldopam group, at the end of the study, gastric mucosal parameters did not show statistical differences as compared with prestudy baseline values. No statistical differences were found in norepinephrine infusion rate between the two study groups. The concordance of prestudy and end-study norepinephrine infusion rates in both the fenoldopam and placebo groups further demonstrates constant hemodynamic support and status during the whole study period. Data are presented in table 2. Fenoldopam administration did not alter the position of ST segment on the monitor electrocardiogram and did not produce arrhythmia.

**Discussion**

In the current study, we demonstrated that, for the same MAP, the addition of low-dose fenoldopam (0.1 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) to a combination of norepinephrine and dobutamine (5 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) increased GMP as assessed by laser-Doppler flowmetry in patients with septic shock.

**Methodologic Consideration**

Laser-Doppler flowmetry has been closely correlated with other flow-measuring techniques, such as radioactive microspheres, $133\text{Xe}$ clearance, or ultrasonic flow probes. However, with reference to data interpretation, it is important to consider the limitations of laser-Doppler flowmetry. First, the laser-Doppler measurements were recorded from a tissue area of only a few square millimeters (2–4 mm$^2$) and at a 1-mm$^3$ penetration depth (tissue volume) using a 780-nm laser diode with 250 $\mu\text{m}$ of separation between optical fibers. A second limitation is the difficulty to maintain optical coupling between the laser-Doppler probe and the gastric mucosa. This is particularly important because for each set of measurements, it is necessary to guarantee the study of the same tissue volume. However, considering its technical features, and as observed by others authors, the P 424 probe detects perfusion of gastric mucosa. Furthermore, the weight and the dimension of the tip of the P 424 probe and the degree of aspiration make it possible to maintain the probe in a stable position in the gastric lumen for the whole duration of the study. Continuous monitoring of the laser-Doppler signal on a personal computer using the Perisoft$^{18}$ software in the 40 patients in the study showed no loss of contact between the tip of the probe and the gastric mucosa. Taking into account the complexity of physiopathologic mechanisms and the heterogeneous character of splanchnic microcirculation modifications in patients with septic shock, we measured flow modifications without comparing them to any reference value. Furthermore, the high intraindividual variability due to clinical conditions and the flow measurement expressed in perfusion arbitrary units make it difficult to single out a reference value that can be defined as a normal laser-Doppler perfusion value.

**Systemic Hemodynamic and Gastric Mucosal Parameters**

Inadequate splanchnic perfusion in septic shock is associated with increased morbidity and mortality. Although bacterial translocation is clearly shown only in experimental models, as result of splanchnic ischemia,
mucosal permeability increases and endotoxin and other bacterial products can pass through the gut wall into the blood vessels. Considering the implication of improved mucosal perfusion in terms of maintenance of mucosal barrier integrity, DA-1 receptor stimulation could be helpful in septic shock. Dopamine is the most common gut vasoactive agent in clinical use. However, in experimental settings, low-dose dopamine accelerates the onset of gut ischemia and impairs oxygen extraction. Jakob et al. showed a decrease in splanchnic oxygen consumption during dopamine infusion despite an increase in regional perfusion. Previous findings suggest that DA-1 receptor stimulation by fenoldopam increases portal blood flow away from the serosa in favor of the mucosa after hemorrhage. In addition, augmenting the fraction of CO directed to the gut, fenoldopam maintains splanchnic blood flow during systemic hypoperfusion and mitigates the splanchnic vasoconstrictive response to hemorrhage. Guzman et al. showed that fenoldopam administration increased perfusion heterogeneity and maldistribution of perfusion, resulting in increased susceptibility to ischemia and earlier appearance of anaerobic metabolism. Whether fenoldopam improves splanchnic perfusion in patients with low systemic blood flow originating from conditions other than hemorrhage has not been demonstrated. Moreover, the data used to assess the effects of fenoldopam on gut perfusion and oxygen use are scarce and conflicting, so it is unclear whether fenoldopam administration is harmful to the splanchnic macrocirculation and microcirculation in septic shock. Taking into account the possible risk of increased perfusion heterogeneity on the gut, we added fenoldopam to a well-known effect combination of dobutamine and norepinephrine in septic shock. Duranteau et al. showed an increase in GMP when 5 µg·kg⁻¹·min⁻¹ dobutamine was added to norepinephrine. Because this finding was not associated with an increase in CI, this suggests a redistribution effect of dobutamine toward gastric mucosa. On the contrary, Vincent et al. reported a significant increase in CI and oxygen delivery after infusion of 5 µg·kg⁻¹·min⁻¹ dobutamine in septic patients. These differences could be explained with several individual factors, including the degree of myocardial depression and the β-receptor down-regulation. The goal of norepinephrine infusion is to increase MAP as a result of increased vascular resistance; for this reason, splanchnic blood flow could be at risk. In a recent trial, titrating norepinephrine to a MAP between 65 and 85 mmHg did not affect splanchnic blood flow in patients with septic shock, whereas CO increased by 15–20%. Therefore, norepinephrine at doses sufficient to achieve arterial blood pressure of 65–80 mmHg does not seem to impair total hepatosplanchnic blood flow. During the study, for the same MAP and at each set of measurements, the norepinephrine infusion rate was similar in the fenoldopam and placebo groups. It is conceivable that the constraining effects on intestinal microvessels by an α-adrenergic mechanism were similar in the two groups. The main finding of our study was, for the same MAP, the significant increase in GMP, without increase in CO or decrease in systemic vascular resistance, observed when fenoldopam was added to a combination of dobutamine and norepinephrine. The lack of significant increase in CI suggests a redistribution phenomenon of blood flow toward gastric circulation induced by fenoldopam or, more specifically, a redistribution of blood flow within the gastric wall layers toward the mucosa. The most likely explanation of our result could be the occurrence of a redistribution phenomenon of blood flow toward the mucosa induced by the DA-1 receptor stimulation to be added to the β-adrenergic effects of dobutamine. Combined action of DA-1 and β₂-receptor stimulation could limit the risk of increased perfusion heterogeneity and maldistribution of perfusion observed during fenoldopam administration without the addition of dobutamine. However, this aspect is speculative and open to conjecture; additional studies are required to know whether fenoldopam creates a hyperemic situation or restores flow back to normal and to determine the risk of impaired intestinal oxygen use during fenoldopam administration in patients with septic shock.

In our study, no significant differences in intramucosal pH and ΔPₘₐₗ₃CO₂ values were found between the two study groups at each set of measurements. The lack of significant changes in mucosal hypercarbia, despite the observed rapid changes in GMP, might be related to either the design of our protocol (short treatment phase of 2-h infusion) or the severity of our patients’ illness. In addition, during gastric mucosal hypoxia states, modification of ΔPₘₐₗ₃CO₂ and gastric mucosal blood flow could not be present at the same time. An increase in mucosal oxygen availability should induce a decrease in anaerobic carbon dioxide production, an increase in mucosal venous carbon dioxide washout, and a reduction of aerobic metabolism, and this could limit the magnitude of the decrease in mucosal hypercarbia. Hence, the initial ΔPₘₐₗ₃CO₂ response to a rapid increase in mucosal blood perfusion could be limited if compared with GMP evaluated by laser-Doppler technique. Although the assumption is made that carbon dioxide is of mucosal origin and this is supported by the presence of histologic damage to the mucosa in patients experiencing shock, it is also possible that carbon dioxide could be derived from the serosa or muscular layers of the gastrointestinal tract. Moreover, in our study, we used manual saline tonometry. This technique has the following limitations: samples must be collected and processed manually; it requires long equilibration times; and it could show errors associated with measurements by blood gas analysis. However, the semicontinuous air tonometry (spectrophotometry to measure carbon dioxide) has the advantage that Pₐₗ₃CO₂ in the intragastric bal-
loon equilibrates more rapidly with PCO2 in the stomach, and accurate readings are available within 30 min after the beginning of monitoring.

Finally, previous findings suggest that sepsis can directly impair cellular metabolism independently of oxygen supply.23 This could explain why a significant decrease of ΔP = CO2 was not observed in the fenoldopam group in our study.

This study has a number of limitations. The first is the lack of a nonseptic control group that would have offered the possibility to compare the tonometry and laser-Doppler data to values obtained in healthy patients. Moreover, such a control group would have also allowed distinguishing if fenoldopam treatment restored blood flow or caused a luxury perfusion in the gut mucosa. This aspect should be addressed in further studies. Second, the study duration was brief because we chose to focus on indexes of hemodynamic stability and measures of organ perfusion. Therefore, these data do not address the issue of whether fenoldopam increases survival of septic shock compared to conventional catecholamine therapy. Our sample size was limited to 40 patients. We chose this sample size to adequately address the current physiologic hypotheses. A much larger sample size is required to demonstrate a survival benefit.

In conclusion, our study showed that, for the same MAP, the addition of fenoldopam to a combination of norepinephrine and dobutamine increased GMP as assessed by laser-Doppler flowmetry in patients with septic shock. This result could be explained by a greater vasodilating effect of the combined action of DA-1 and β2 on gastric mucosal microcirculation, resulting in an increase of blood flow toward the mucosa. A properly powered, randomized, controlled trial with survival as the primary endpoint is required.

References

5. Duranteau J, Sitbon P, Teboul JL, Vicaut E, Anguel N, Richard C, Samii K: Effects of epinephrine and dopamine on hepatosplanchnic blood flow or caused a luxury perfusion in the gut mucosa. A properly powered, randomized, controlled trial with survival as the primary endpoint is required.

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