Increasing Splanchnic Blood Flow in the Critically Ill*

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Study objective: To assess the effect of low dose dopexamine and dopamine on splanchnic blood flow as measured by gastric intramucosal pH, hepatic metabolism of lidocaine (lidocaine) to monoethylglycinexylidide (MEGX), and plasma disappearance rate of indocyanine green (ICG).

Design: Single-blind randomization of patients with a gastric intramucosal acidosis to receive dopexamine (ten patients), dopamine (ten patients), or saline solution (five control patients) for 2 h.

Setting: All 25 patients were in the ICU of Guys’ Hospital.

Patients: All patients met the criteria for the diagnosis of the systemic inflammatory response syndrome, were mechanically ventilated, and had pulmonary artery catheters placed. All had a low gastric intramucosal pH and had a median first 24-h acute physiology and chronic health evaluation (II) score of 22 (range, 7 to 40).

Measurements and interventions: Baseline measurements of gastric intramucosal pH, MEGX formation from lidocaine, ICG plasma disappearance rate, heart rate, mean arterial pressure, pulmonary artery occlusion pressure, cardiac index, oxygen delivery index, oxygen uptake index, systemic vascular resistance, and arterial pH were taken. Dopexamine (1 mg·kg⁻¹·min⁻¹), dopamine (2.5 mg·kg⁻¹·min⁻¹), or 0.9% saline solution was then infused for 2 h, after which a repeated set of the measurements was taken.

Results: Dopexamine at a low dose had no effect on any of the systemic measurements. The median intramucosal pH rose from 7.23 to 7.35 (p<0.005), the median ICG plasma disappearance rate from 7.6 to 11.3%-min⁻¹ (p<0.02), and the median MEGX concentration from 4 to 10.2 ng·mL⁻¹ (p<0.005). Dopamine had no effect on any of the measured variables. There were no changes in the control group.

Conclusions: Low-dose dopexamine increases splanchnic blood flow as measured by gastric intramucosal pH, MEGX formation from lidocaine, and ICG clearance. The lack of any change in the systemic measurements suggests that these effects are the result of a selective vasodilatation of the splanchnic vessels. At the dose used in this study, dopamine had no effect on splanchnic blood flow. Dopexamine may be useful in the management of splanchnic ischemia in the critically ill.

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Key words: critical illness; dopaminergic agents; indocyanine green; lidocaine—diagnostic test; liver—physiology; splanchnic circulation—physiology

Multiple organ failure (MOF) continues to be a major cause of death in the critically ill.¹⁻³ Treatment of the underlying condition and supportive measures have been the mainstay of management, but figures for MOF have not changed since the APACHE II study in 1985.⁵

More recently, evidence has accumulated that the gut and the liver may be pivotal in the development of MOF. It has been suggested that a GI mucosal ischemia may lead to the translocation of endotoxin and microorganisms into the portal circulation.⁶,⁷ In association with an inadequacy of liver blood flow in relation to its metabolic demands, the resultant hepatocyte and Kupffer cell dysfunction⁸,⁹ leads to the systemic release of various cytokines (interleukin 1, tumor necrosis factor, interleukin 6, interleukin 8), which is thought to initiate a sequence of events that culminates in the clinical picture of sepsis and MOF.¹⁰⁻¹²

Both the GI tract and the liver can be inadequately perfused despite the presence of normal systemic measures of the adequacy of tissue oxygenation.¹³,¹⁴

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The development of gastric tonometry\(^7\) (to measure gastric intramuscosal pH) and the monoethylglycinexylidide (MEGX) test\(^15\) (to measure hepatic metabolism of lidocaine [lignocaine] as a dynamic assessment of hepatic blood flow and function) has permitted the detection, in those patients who appear adequately resuscitated by conventional criteria, of a significant splanchnic ischemia that may well contribute to morbidity and mortality.

Dopamine and selective dopamine receptor agonists have been shown previously to cause increases in blood flow to various organs.\(^16\,17\) Peripheral dopamine receptors are classified into two groups—dopamine 1 and dopamine 2—and it is thought that this effect is due to dopamine 1 receptor-mediated regional vasodilatation. The effects of dopamine on enhancing renal blood flow are well described,\(^18\,19\) but dopamine and doxepamine (a dopamine analogue developed for IV use in the treatment of heart failure and low cardiac output states\(^20\)) have both been demonstrated to enhance splanchnic blood flow.\(^21\,25\) This study was designed to assess the effects of dopamine and dopamine at low doses (1 mg·kg\(^{-1}\)·min\(^{-1}\) and 2.5 mg·kg\(^{-1}\)·min\(^{-1}\), respectively) on splanchnic blood flow in a group of critically ill patients by measuring changes in gastric intramuscosal pH, lidocaine metabolism to MEGX, and indocyanine green (ICG) clearance before and after infusion of the two drugs.

**Methods**

**Study Population**

Twenty-five critically ill patients admitted to the ICU of Guy’s Hospital were studied (Table 1). They all met the criteria for the diagnosis of the “systemic inflammatory response syndrome”\(^9\) and required both mechanical ventilation for acute respiratory failure and pulmonary artery catheterization for adequate hemodynamic management. They were sedated with a continuous infusion of narcotic (papaveretum or fentanyl) in combination with a benzodiazepine (midazolam) and were fully resuscitated by conventional criteria (cardiac filling pressures and output, measurements of oxygen transport) at the time of study. They all had a low intramuscosal pH (<7.32) and no patient was receiving any other vasoactive drugs. No patient received H2-receptor antagonists.

The study was approved by Guy’s Hospital Ethics Committee, and informed consent was obtained from the next of kin of each patient.

**Study Protocol**

The 25 patients were randomized (single blind) either to receive low-dose doxepamine (1 mg·kg\(^{-1}\)·min\(^{-1}\)—ten patients) or dopamine (2.5 mg·kg\(^{-1}\)·min\(^{-1}\)—ten patients), or to be controls (five patients). After ensuring the patient was in stable condition, gastric intramuscosal pH, MEGX formation from lidocaine, ICG clearance, and hemodynamic and oxygen transport variables were measured. The appropriate drug was then infused for 2 h, and at the end of this period, the measurements were repeated. Control subjects received an isovolumetric infusion of 0.9% saline solution.

**Measurements of Systemic Hemodynamics and Oxygen Transport**

All patients had a pulmonary artery flotation catheter (Oximetrics; Abbott Laboratories; North Chicago, Ill) and a radial arterial cannula inserted immediately following admission to the ICU. These were used for the measurement of intravascular pressures (central venous pressure [CVP]; pulmonary artery occlusion pressure [PAOP]; systemic mean arterial pressure [MAP], mm Hg; Hewlett-Packard M1166A; Andover, Mass). The ECG and heart rate were monitored continuously. Cardiac index (CI) was measured by thermodilution in triplicate (ice cold 10-mL boluses of 5% dextrose given at end expiration). Arterial and mixed venous blood was withdrawn anaerobically and used for the measurement of carbon dioxide tensions (Instrumentation Laboratory 1312 Blood Gas Analyzer; Warrington, England), oxygen saturation (%), arterial pH, and hemoglobin concentration (Instrumentation Laboratory 282 Co-oximeter). Arterial and mixed venous oxygen contents were then calculated from the standard formula 1, where CaO\(_2\) is the arterial oxygen content and CvO\(_2\) is the mixed venous oxygen content:

\[
(1) \quad \text{CaO}_2 \text{ or } \text{CvO}_2 = ([\text{Hb}] \times 1.34 \times \% \text{ saturation}) + (\text{PO}_2 \times 0.2325)
\]

Arterial oxygen delivery index (DO\(_2\)I, mL O\(_2\)·min\(^{-1}\)·m\(^{-2}\)) and oxygen uptake index (Q\(_{O2}\)I, mL O\(_2\)·min\(^{-1}\)·m\(^{-2}\)) were calculated from the standard formulas 2 and 3:

\[
(2) \quad \text{DO}_2\text{I} = \text{CI} \times \text{CaO}_2
\]

\[
(3) \quad \text{O}_2\text{U} = \text{CI} \times \text{C(\text{a-v})O}_2
\]

Systemic vascular resistance (SVR, dyne·s·cm\(^{-5}\)) was calculated from the standard formula 4:

\[
(4) \quad \frac{\text{MAP} - \text{CVP}}{\text{CO}} \times 79.9
\]

where CO is the cardiac output and 79.9 is the conversion factor used to convert Wood units to dyne·s·cm\(^{-5}\).

**Gastric Intramuscosal pH**

Gastric intramuscosal pH was measured using a gastric tonometer ("TRIP" TGS Catheter; Tonometrics Inc, Bethesda, Md) as described previously.\(^14\) Following nasogastric insertion, the tonometer was placed so that the balloon was located in the lumen of the stomach, and the position was confirmed by radiograph. For each measurement of gastric intramuscosal pH, 2.5 mL of 0.9% saline solution was placed in the silicone balloon via an external sampling port. After sufficient time for equilibration of Pco\(_2\) between the saline solution and the gastric lumen (30 min in all cases), the balloon saline solution was sampled anaerobically, simultaneously with an anaerobic sample of arterial blood. Tonometric Pco\(_2\) (kPa) and arterial bicarbonate concentration were measured using a standard blood gas analyzer (Instrumentation Laboratory 1312 Blood Gas Analyzer). A steady-state Pco\(_2\) was calculated using a correction factor (determined by in vitro studies) depending on the equilibration period, and used with the arterial bicarbonate concentration to represent the intramuscosal values in the Henderson-Hasselbalch equation, formula 5, for determination of the intramuscosal pH:

\[
(5) \quad \text{pH} = 6.1 + \log \left( \frac{[\text{HCO}_3^-]}{0.225 \times \text{Pco}_2} \right)
\]

(where 0.225 represents the solubility of CO\(_2\) in plasma and 6.1 the pK of carbonic acid).

**Systemic ICG Clearance**

This was measured using a well-established technique.\(^27\) Fifty milligrams of ICG (Cardio-Green; Becton Dickinson) was dissolved
in an aqueous solvent to produce a concentration of 5 mg·mL⁻¹. After withdrawal of 6 mL of arterial blood for plasma blank and standard curve construction, a bolus of ICG (0.5 mg·kg⁻¹·body weight) was rapidly injected into the superior vena cava. Blood was sampled from the radial arterial catheter at 5, 10, 15, and 20 min following the injection and collected into heparinized plastic tubes before being centrifuged to produce plasma. The preinjection plasma and dilutions of the original injectate were used to prepare standard concentrations of ICG in plasma of 5 mg·L⁻¹, 0.5 mg·L⁻¹, and 0 mg·L⁻¹. Standards and samples were analyzed by spectrophotometry (750 nm) for absorbance against the patient’s plasma blank. A regression line was drawn of concentration of standards against their absorbances, and the intercept and slope were used to calculate the concentrations of the samples from their measured absorbances. A spreadsheet was used to calculate ICG half-life and plasma disappearance rate using standard formulas.

**MEGX Formation From Lidocaine**

A subtherapeutic dose of lidocaine (1 mg/kg) was administered IV over 1 min and blood sampled from the radial arterial catheter at carefully timed intervals (0 and 15 min following the injection). This was collected into heparinized plastic tubes before being centrifuged to produce plasma. MEGX concentration was determined in plasma by a fluorescence polarization immunoassay (TDx system; Abbott Laboratories; Irving, Tex). The concentration at 0 min was subtracted from that at 15 min and this value was used as the amount of MEGX that has been produced in 15 min following the administration of lidocaine at the stated dose.

**Data Analysis**

All statistical analysis was carried out using a commercially available statistics software package (CSTAT; Cherwell Scientific, Oxford, United Kingdom). Data were nonparametric, and for this reason they are given as medians and ranges. Paired data were compared using the Wilcoxon signed rank paired differences test. Correlations were performed using the Spearman rank correlation test. A p value of 0.05 or less has been considered to be significant.

**RESULTS**

The demographic characteristics of the patients studied are shown in Table 1. Median age was 57 years (range 19 to 78 years) and median first 24-h APACHE II score was 22 (range 7 to 40). The ICU mortality rate for the 25 patients was 40%, and the standardized mortality ratio (actual hospital mortality: expected mortality) was 1.08. Both dopexamine and dopamine were well tolerated and there were no deleterious effects associated with administration of lidocaine or ICG. The three groups were homogeneous, there being no significant differences in baseline data among groups except for MEGX values (significantly lower in the dopexamine group).

**Table 1—Study Population***

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General surgery</td>
<td>12 (48)</td>
</tr>
<tr>
<td>Trauma</td>
<td>4 (16)</td>
</tr>
<tr>
<td>Cardiotoracic</td>
<td>6 (24)</td>
</tr>
<tr>
<td>Medical</td>
<td>3 (12)</td>
</tr>
</tbody>
</table>

*Twenty-five patients; median age, 57 years (range, 19 to 78 years). The median 24-h APACHE II score was 22 (range, 7 to 40). ICU mortality was 40%. The standardized mortality ratio was 1.08.

**Table 2—Effects of Dopexamine (1 mg/kg/min) (n=10)***

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>After Dopexamine</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>113 (62-131)</td>
<td>115 (74-137)</td>
<td>NS</td>
</tr>
<tr>
<td>MAP</td>
<td>88 (82-110)</td>
<td>90 (80-101)</td>
<td>NS</td>
</tr>
<tr>
<td>PAOP</td>
<td>15 (11-18)</td>
<td>14 (10-21)</td>
<td>NS</td>
</tr>
<tr>
<td>CI</td>
<td>3.9 (2.9-6.7)</td>
<td>4.1 (3.1-6.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Do2I</td>
<td>644 (440-1,007)</td>
<td>635 (501-990)</td>
<td>NS</td>
</tr>
<tr>
<td>O2UI</td>
<td>146 (109-174)</td>
<td>143 (55-181)</td>
<td>NS</td>
</tr>
<tr>
<td>SVR</td>
<td>823 (447-1,149)</td>
<td>861 (522-1,131)</td>
<td>NS</td>
</tr>
<tr>
<td>pHart</td>
<td>7.39 (7.34-7.45)</td>
<td>7.40 (7.35-7.44)</td>
<td>NS</td>
</tr>
<tr>
<td>pHim</td>
<td>7.23 (7.12-7.29)</td>
<td>7.35 (7.17-7.40)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>ICG PDR</td>
<td>7.6 (2.9-11.0)</td>
<td>11.3 (3.2-19.0)</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>MEGX</td>
<td>4.0 (1.0-18.3)</td>
<td>10.2 (5.0-36.9)</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

*HR=heart rate (beats-min⁻¹); MAP=mean arterial pressure (mm Hg); PAOP=pulmonary artery occlusion pressure (mm Hg); CI=cardiac index (L·min⁻¹·m⁻²); Do2I=oxygen delivery index (mL·min⁻¹·m⁻²); O2UI=oxygen uptake index (consumption index) (mL·min⁻¹·m⁻²); SVR=systemic vascular resistance (dyne·s·cm⁻⁵); pHart=arterial pH; pHim=gastric intramucosal pH; ICG PDR=plasma disappearance rate of indocyanine green (%·min⁻¹); MEGX=MEGX concentration (ng·mL⁻¹). Values are medians with ranges. p values refer to the significance of any difference between predopexamine and postdopexamine.

**Dopexamine Group**

Dopexamine at a low dose had no effect on heart rate, MAP, PAOP, CI, oxygen delivery index, oxygen uptake index, SVR, or arterial pH (Table 2). The median intramucosal pH rose from 7.23 to 7.35 (p<0.005; Fig 1), the median ICG plasma disappearance rate from 7.6 to 11.3·min⁻¹ (p<0.02; Fig 2), and the median MEGX concentration from 4 to 10.2 ng·mL⁻¹.
Figure 2: Effects of dopexamine (bottom) and dopamine (top) on ICG plasma disappearance rate. Each line represents data for individual patients.

Figure 3: Effects of dopexamine (bottom) and dopamine (top) on lidocaine metabolism to MEGX. Each line represents data for individual patients.

Table 3—Effects of Dopamine (2.5 mg/kg/min) (n=10)*

<table>
<thead>
<tr>
<th>HR</th>
<th>Baseline</th>
<th>After Dopamine</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP</td>
<td>110 (87-129)</td>
<td>112 (80-123)</td>
<td>NS</td>
</tr>
<tr>
<td>PAOP</td>
<td>84 (80-98)</td>
<td>83 (76-100)</td>
<td>NS</td>
</tr>
<tr>
<td>CI</td>
<td>13 (8-18)</td>
<td>15 (10-18)</td>
<td>NS</td>
</tr>
<tr>
<td>Dtex</td>
<td>4.2 (2.9-6.3)</td>
<td>4.0 (2.4-6.7)</td>
<td>NS</td>
</tr>
<tr>
<td>O2UI</td>
<td>744 (441-910)</td>
<td>664 (340-1,007)</td>
<td>NS</td>
</tr>
<tr>
<td>SVR</td>
<td>135 (124-203)</td>
<td>134 (121-172)</td>
<td>NS</td>
</tr>
<tr>
<td>pHart</td>
<td>7.38 (7.34-7.43)</td>
<td>7.39 (7.36-7.42)</td>
<td>NS</td>
</tr>
<tr>
<td>pHim</td>
<td>7.27 (7.06-7.33)</td>
<td>7.28 (7.06-7.50)</td>
<td>NS</td>
</tr>
<tr>
<td>ICG PDR</td>
<td>7.05 (3.2-8.5)</td>
<td>6.7 (3.4-15)</td>
<td>NS</td>
</tr>
<tr>
<td>MEGX</td>
<td>13.05 (4.0-21.0)</td>
<td>13.35 (4-27)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*See Table 2 footnotes for expansion of abbreviations and units of measure. Values are medians with ranges. The p values refer to the significance of any difference between nondopamine and postdopamine.

Dopamine Group and Control Subjects

Dopamine (Table 3) had no effect on any of the measured variables (Figs 1 through 3). There were no changes in the control group (Table 4).

DISCUSSION

Splanchnic ischemia (affecting both the GI tract and liver) seems to be a major factor determining outcome in critically ill patients, and it appears that gastric tonometry and the MEGX test permit the early detection of this ischemia. A number of studies have demonstrated that a low intramucosal pH (intramucosal pH), as measured by gastric tonometry, indicates inadequate splanchnic oxygenation, and that this seems to be associated with a poor outcome. Similarly, the assessment of lidocaine metabolism to

Table 4—Control Subjects*

<table>
<thead>
<tr>
<th>HR</th>
<th>Baseline</th>
<th>After Dopamine</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP</td>
<td>108 (82-140)</td>
<td>106 (76-130)</td>
<td>NS</td>
</tr>
<tr>
<td>PAOP</td>
<td>90 (76-102)</td>
<td>87 (72-100)</td>
<td>NS</td>
</tr>
<tr>
<td>CI</td>
<td>13 (8-19)</td>
<td>14 (10-17)</td>
<td>NS</td>
</tr>
<tr>
<td>Dtex</td>
<td>4.2 (2.9-5.3)</td>
<td>3.8 (2.7-5.6)</td>
<td>NS</td>
</tr>
<tr>
<td>O2UI</td>
<td>760 (590-880)</td>
<td>776 (670-890)</td>
<td>NS</td>
</tr>
<tr>
<td>SVR</td>
<td>142 (136-160)</td>
<td>146 (120-156)</td>
<td>NS</td>
</tr>
<tr>
<td>pHart</td>
<td>7.40 (7.32-7.44)</td>
<td>7.40 (7.37-7.45)</td>
<td>NS</td>
</tr>
<tr>
<td>pHim</td>
<td>7.27 (7.23-7.31)</td>
<td>7.26 (7.24-7.33)</td>
<td>NS</td>
</tr>
<tr>
<td>ICG PDR</td>
<td>10.1 (5.6-14.3)</td>
<td>9.6 (7.2-19.4)</td>
<td>NS</td>
</tr>
<tr>
<td>MEGX</td>
<td>14 (8-16)</td>
<td>12 (6-18)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*See Table 2 for expansion of abbreviations and units of measure. Values are medians with ranges. The p values refer to the significance of any difference between presaline solution and postsaline solution.
MEGX by the liver provides a dynamic, flow-dependent assessment of hepatic function, and failure to metabolize lidocaine to MEGX is also associated with a poor outcome. If splanchnic ischemia is evident, it is, of course, essential to ensure that resuscitation is adequate, with prompt correction of hypoxia and hypotension, and simply increasing oxygen delivery may well be sufficient to return a low intramucosal pH or MEGX value toward normal. It is not always appropriate, however, to increase systemic oxygen delivery to supranormal values, and indeed there is often a dissociation between changes in intramucosal pH and the changes in the global measurements induced by inotropes, the reduction in intramucosal pH probably being due to α-adrenergic stimulation. Thus, it may be inappropriate (or even deleterious) to continue in attempts to increase systemic oxygen delivery. Indeed, in a recent study on a heterogeneous group of critically ill patients, the use of inotropes to boost the CI and systemic oxygen delivery up to previously established goals led to a higher mortality compared with a control group.

When all the global measures of adequacy of resuscitation are considered normal, attention should turn to pharmacologic enhancement of regional blood flow if, and only if, splanchnic ischemia persists. This study has demonstrated that the infusion of low-dose dopexamine leads to a significant increase in gastric intramucosal pH, ICG clearance, and MEGX formation from lidocaine. The infusion of low-dose dopamine had no such effect.

The receptor profile of dopamine is complex, and its pharmacologic effect depends largely on the dose. At lower doses, dopamine stimulates dopamine 1 receptors, which leads to systemic vasodilatation and an increase in organ blood flow. Indeed, “low-dose dopamine” at 2 to 3 mg·kg⁻¹·min⁻¹ is frequently used to promote renal blood flow in the critically ill in the hope of preventing renal failure while having no discernible effects on systemic hemodynamics (although there is very little evidence to support this hypothesis). Higher doses (5 to 10 mg·kg⁻¹·min⁻¹) cause β₁-adrenoceptor-mediated positive inotropy and, at much higher doses still (>10 mg·kg⁻¹·min⁻¹), α-adrenoceptor-mediated vasoconstriction is seen. Several groups have reported an increase in splanchnic blood flow with dopamine. In rabbits, high doses (25 and 60 mg·kg⁻¹·min⁻¹) of dopamine lead to a dose-dependent increase in GI tract blood flow. More recently, Leier, using a relatively low dose of dopamine (3.8 mg·kg⁻¹·min⁻¹), demonstrated no effect on hepatic-splanchnic blood flow in patients with congestive cardiac failure. In this study, we have used a low dose of dopamine (2.5 mg·kg⁻¹·min⁻¹) and found no effect on splanchnic blood flow or systemic hemodynamics.

Dopexamine hydrochloride was developed as an analogue of dopamine, to act as a peripheral arterial vasodilator, retaining the beneficial renal vasodilating effects of dopamine, but free of α-adrenoceptor agonist activity. It produces systemic vasodilatation through stimulation of β₂-adrenoceptors, peripheral dopamine 1 and prejunctional dopamine 2 receptors. It has a weakly positive inotropic activity that may be mediated via cardiac β₂-adrenoceptors or by indirect β₁-adrenoceptor activity, secondary to inhibition of neuronal catecholamine reuptake (uptake-1 mechanism). The overall result is an increase in cardiac output, mainly through an increase in heart rate and a reduction in afterload, with a contribution from some positive inotropy. Its main use is in the treatment of heart failure and low cardiac output states following cardiac surgery.

The effects of dopexamine on splanchnic blood flow were investigated by Biro and colleagues using radio-labeled microspheres in the anesthetized dog and they demonstrated an increase in blood flow to the GI tract but not to the liver. In humans with congestive heart failure, a low dose of dopexamine (1 mg·kg⁻¹·min⁻¹) leads to significantly enhanced hepatic-splanchnic blood flow, which is proportional to the increase in cardiac output. At high doses, there was a significantly smaller increase in blood flow. In a canine model of hemorrhagic shock, an increase in resistance in the splanchnic vascular beds led to a significant decrease in splanchnic blood flow during hypovolemia. Reinfusion of blood led to only a partial recovery of blood flow, but infusion of dopexamine restored splanchnic blood flow to control levels that were then maintained.

Previous work carried out in our department examined the effect of dopexamine at a high dose (4 to 6 mg·kg⁻¹·min⁻¹) on intramucosal pH and ICG clearance in a group of critically ill patients. A 2-h infusion of dopexamine led to an increase in median intramucosal pH from 7.21 to 7.29 (p<0.05). Moreover, when intramucosal pH was less than 7.35, dopexamine consistently improved the acidosis. ICG clearance also improved with dopexamine, although this change was not statistically significant, but 1 h after the end of the infusion, ICG clearance had deteriorated significantly. These improvements were associated with a significant increase in CI and oxygen delivery with a fall in SVR. The present study has demonstrated that low-dose dopexamine hydrochloride leads to a consistent increase in intramucosal pH, MEGX formation, and ICG clearance in a group of critically ill patients, but with no change in systemic hemodynamics, suggesting that the effects were likely to be due to selective vasodilation of the splanchnic vessels. One patient in the dopexamine group had a fall in intramucosal pH (7.29 to 7.28) and in two other patients there was no improvement in intramucosal pH while there was a slight fall in ICG plasma disappearance rate. These
three patients had lower PAOPs than the other patients, and it is likely that dopexamine did not lead to an improvement in splanchnic blood flow because they were relatively hypovolemic.

It is conceivable that the lack of effect of dopamine was related to the dose, any effect of dopamine on splanchnic blood flow being dose dependent. Alternatively, dopamine had no effect because it has minimal $\beta_2$ activity, $\beta_2$ receptors being primarily responsible for the dopexamine-induced vasodilatation. This latter view is supported by work using isoprenaline, a general $\beta$-agonist, which has been shown to induce increases in blood flow and capillary filtration coefficient in feline small intestine when used in conjunction with practolol.\textsuperscript{50} Indeed, administration of propranolol (a $\beta_1$- and $\beta_2$-blocker) and a selective $\beta_2$-adrenoceptor blocking agent have both been shown to have a greater effect on reducing portal pressure and hepatic blood flow in cirrhotics with portal hypertension than metoprolol (a selective $\beta_1$-blocker).\textsuperscript{51,52}

Cain and Curtis\textsuperscript{53} looked at the effect of dopexamine in endotoxic dogs and found that blood flow in an isolated loop of ileum was not increased, but that the intestine stopped producing lactate when dopexamine was given. Since lactate output from the gut may in part result from an inadequate oxygen supply to the mucosa, it may be that dopexamine improved gut oxygenation without increasing blood flow. A redistribution of blood flow within the gut wall, with the mucosa being favored over the muscularis, is one possible explanation. Isoprenaline is known to do this,\textsuperscript{54} which suggests that it is a $\beta_2$-adrenoceptor-mediated effect. Since the mucosa is the major site of oxygen consumption in the gut, increased blood flow through the mucosa will reduce arteriovenous oxygen shunting,\textsuperscript{55} anaerobic metabolism, and lactate production. Thus, although this study demonstrated a significant improvement in intramucosal pH to normal levels, this may not represent an absolute increase in blood flow to the gut.

Although precise estimation of hepatic blood flow is not possible in the absence of hepatic venous catheterization, both systemic ICG clearance and MEGX formation from lidocaine are predominantly flow dependent (both lidocaine and ICG have high hepatic extraction ratios); acute changes in MEGX formation and ICG clearance are likely to represent changes in liver blood flow.\textsuperscript{56,57} The significant improvement in both ICG clearance and MEGX formation with dopexamine would seem to suggest an increase in hepatic blood flow, but since there was no change in global hemodynamics or oxygen transport, this is likely to be due to selective vasodilatation of the hepatic and splanchnic vessels. Interestingly, changes in MEGX were not correlated with either changes in ICG clearance or changes in intramucosal pH in patients receiving dopexamine, although in an earlier noninterventional study,\textsuperscript{31} we have demonstrated a significant correlation between MEGX and intramucosal pH. The MEGX test quantitates a very particular enzymatic reaction in the hepatocytes, and it may be that dopexamine not only increases blood flow to the liver but also has a direct effect on hepatocellular function.

There seems little doubt that attention to the adequacy of splanchnic perfusion must play a fundamental role in the resuscitation of the critically ill patient. This study has demonstrated a specific pharmacologic intervention that reverses gut and liver ischemia, and there is already some evidence that therapy guided by gastric intramucosal pH might improve outcome.\textsuperscript{58} More research is essential in order to see whether these measures (and others such as the early institution of enteral feeding) can improve outcome from sepsis and MOF. It seems that we can no longer afford to neglect the gut in the critically ill.

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