# Effects of Dopamine, Dobutamine, and Dopexamine on Microcirculatory Blood Flow in the Gastrointestinal Tract during Sepsis and Anesthesia

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*Background:* Insufficient blood flow to the splanchnic organs is believed to be an important contributory factor for the development of organ failure after septic shock. It has been suggested that increasing systemic flow also may improve splanchnic blood flow in septic patients. The aim of this study was to compare the effects of three commonly used inotropic agents, dopamine, dobutamine, and dopexamine, on systemic (cardiac index), regional (superior mesenteric artery), and local (microcirculatory) blood flow during septic shock in pigs.

*Methods:* Eight pigs were intravenously anesthetized, mechanically ventilated, and exposed to sepsis induced by fecal peritonitis. Cardiac index was measured with thermodilution, superior mesenteric artery flow was measured with ultrasound transit time flowmetry, and microcirculatory blood flow was continuously measured with a six-channel laser Doppler flowmetry in the gastric, jejunal, and colon mucosa as well as in the kidney, pancreas, and jejunal muscularis. Each animal received, in a random-order, crossover design, the three test drugs, one at a time: 5 and 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dopamine, 5 and 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dobutamine, and 1 and 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dopexamine. Administration of each drug at each dose continued for 30 min and was followed by a 40- to 60-min recovery period. A new baseline was taken before the next drug was administered.

*Results:* All three drugs significantly increased cardiac index; dopamine by 18%, dobutamine by 48%, and dopexamine by 35%, compared with baseline ($P < 0.001$ for each). At the same time, superior mesenteric artery flow increased by 33% ($P < 0.01$) with dopamine and 13% ($P < 0.01$) with dopexamine, whereas it did not change with dobutamine. Microcirculatory blood flow did not change significantly in any of the organs studied with any of the drugs tested.

*Conclusion:* All the inotropic agents markedly increased cardiac output in this sepsis model. However, increased systemic flow did not reach the microcirculation in the gastrointestinal tract. This may in part explain why some of the clinical trials, in which systemic oxygen delivery was deliberately increased by administration of inotropic drugs, have failed to improve survival in critically ill patients.

IT is now widely recognized that rapid resuscitation of splanchnic perfusion is an important factor for successful outcome of severely ill and injured patients. Insufficient blood flow to the gastrointestinal tract during sepsis may provoke gut mucosa barrier dysfunction, resulting in bacterial translocation and multiple organ failure.[1–4] The concept that oxygen consumption in the hepatosplanchnic region may be dependent on oxygen delivery in sepsis has recently been confirmed.[5] Therefore, increasing systemic flow, which may also improve splanchnic blood flow, is one of the current therapeutic goals in perioperative treatment of high-risk patients and in intensive care medicine.[6–11] This concept is based on the assumption that the gastrointestinal mucosa receives its share of increased systemic and regional oxygen delivery. However, a recent study from our institution has shown that under septic conditions, distribution of microcirculatory blood flow in the abdominal organs is highly heterogeneous and cannot be predicted from systemic or regional perfusion.[12] There was little correlation between changes in systemic flow and in microcirculatory flow in the splanchnic organs, including the gastrointestinal mucosa.

In clinical practice, usually the first step to increase systemic and splanchnic oxygen delivery in patients in septic shock includes adequate fluid volume resuscitation. If that is insufficient, it is usually followed by administration of inotropic agents such as dopamine, dobutamine, or dopexamine. However, the scientific background for the choice of a particular inotropic agent for this purpose is still poorly established, and many factors regarding their effects on regional and local blood flow, particularly in the splanchnic region, remain unknown.

To our knowledge, there is no previous comparative dynamic study that investigates the differential effects of dopamine, dobutamine, and dopexamine on the splanchnic microcirculation. Therefore, we tested these drugs in a clinically relevant septic pig model. The aims of the study were (1) to correlate changes in systemic, regional, and local blood flow for each tested drug during normodynamic sepsis and (2) to compare the effects of these agents on microcirculatory blood flow in different abdominal organs. Considering the results of our previous study,[12] we assumed that there would be no correlation between changes in cardiac output (CO) and changes in microcirculatory blood flow in the gastrointestinal tract by any of the drugs tested.

## Materials and Methods

This study was performed according to the National Institutes of Health guidelines for the use of experimental animals. The protocol was approved by the Animal Ethics Committee of Canton, Berne, Switzerland. Eight

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**Table 1. Systemic, Regional, and Microcirculatory Data before Induction of Septic Shock (t = 0 min), during Hypodynamic Septic Shock (t = 240 min), and after Administration of Intravenous Fluids (t = 300 min)**

| | t = 0 min | t = 240 min | t = 300 min |
|---|---|---|---|
| Heart rate, beats/min | 118 ± 29 | 185 ± 60* | 162 ± 47 |
| MAP, mmHg | 100 ± 10 | 54 ± 10† | 78 ± 17† |
| CI, ml · kg$^{-1}$ · min$^{-1}$ | 169 ± 46 | 75 ± 18† | 144 ± 36§ |
| SVRI, mmHg · kg$^{-1}$ · min$^{-1}$ | 599 ± 239 | 681 ± 124 | 544 ± 123 |
| PVRI, mmHg · kg$^{-1}$ · min$^{-1}$ | 95 ± 27 | 226 ± 67† | 159 ± 69 |
| CVP, mmHg | 6.8 ± 3.0 | 4.5 ± 1.9† | 5.6 ± 2.0 |
| PAP, mmHg | 21.0 ± 4.6 | 20 ± 2.1 | 26.3 ± 6.8 |
| PCWP, mmHg | 5.5 ± 2.1 | 4.0 ± 1.4 | 5.3 ± 1.0 |
| SMAI, ml · kg$^{-1}$ · min$^{-1}$ | 28.5 ± 11.4 | 14.9 ± 4.5† | 23.4 ± 5.7‡ |
| Svo$_2$, % | 67.8 ± 5.8 | 41.6 ± 12.4† | 59.0 ± 4.6§ |
| Smo$_2$, % | 77.0 ± 9.3 | 53.6 ± 11.93† | 70.9 ± 6.8§ |
| MBF gastric mucosa | 100 ± 0 (266 ± 36) | 78 ± 5† | 94 ± 5§ |
| MBF jejunal mucosa | 100 ± 0 (338 ± 82) | 94 ± 21 | 112 ± 30 |
| MBF jejunal muscularis | 100 ± 0 (1,215 ± 258) | 47 ± 17† | 60 ± 18† |
| MBF colonic mucosa | 100 ± 0 (492 ± 99) | 96 ± 35 | 119 ± 22 |
| MBF pancreas | 100 ± 0 (272 ± 174) | 46 ± 18† | 67 ± 27† |
| MBF kidney | 100 ± 0 (584 ± 238) | 67 ± 18* | 89 ± 27 |

Data are presented as mean ± SD. Peritonitis/sepsis was induced at t = 0; at t = 240 min, intravenous fluids were administered to convert hypodynamic septic shock to normodynamic sepsis. t = 300 min was after fluid administration. All microcirculatory blood flows were set at 100% at t = 0, *i.e.*, before induction of generalized peritonitis. The real laser Doppler readings in perfusion units are shown in parentheses.

* $P < 0.05$, † $P < 0.01$ compared with baseline.   ‡ $P < 0.05$, § $P < 0.01$ compared with 240 min of peritonitis.

CI = cardiac index; CVP = central venous pressure; MAP = mean arterial blood pressure; MBF colonic mucosa = microcirculatory blood flow in the colonic mucosa; MBF gastric mucosa = microcirculatory blood flow in the gastric mucosa; MBF jejunal mucosa = microcirculatory blood flow in the jejunal mucosa; MBF jejunal muscularis = microcirculatory blood flow in the muscularis of the jejunum; MBF kidney = microcirculatory blood flow in the cortex of the kidney; MBF pancreas = microcirculatory blood flow in the pancreas; PAP = mean pulmonary artery pressure; PCWP = mean pulmonary artery occlusion pressure; PVRI = pulmonary vascular resistance index; SMAI = superior mesenteric artery flow index; Smo$_2$ = mesenteric venous oxygen saturation; Svo$_2$ = mixed venous oxygen saturation; SVRI = systemic vascular resistance index.

domestic pigs (weight, 20–25 kg) were fasted overnight but were allowed free access to water. The pigs were sedated with intramuscular ketamine (20 mg/kg) and xylazinum (2 mg/kg). Anesthesia was induced with intravenous metomidate (5 mg/kg) and azaperone (2 mg/kg). The pigs were orally intubated after intravenous injection of succinylcholine (1 mg/kg) and ventilated with oxygen in air (fraction of inspired oxygen [F$_{IO_2}$] = 0.45). Inhaled concentration of oxygen was continuously monitored with a multigas analyzer (Hellige SMU 611; Hellige, Freiburg, Germany). Anesthesia was maintained with continuous intravenous infusions of midazolam (0.5 mg · kg$^{-1}$ · h$^{-1}$), fentanyl (20 μg · kg$^{-1}$ · h$^{-1}$), and pancuronium (0.3 mg · kg$^{-1}$ · h$^{-1}$). The animals were ventilated with a volume-controlled ventilator with a positive end-expiratory pressure of 5 cm H$_2$O (Tiberius 19; Drägerwerk, Lübeck, Germany). Tidal volume was kept at 10–15 ml/kg, and the respiratory rate was adjusted (14–16 breaths/min) to maintain end-tidal carbon dioxide tension (Paco$_2$) at 40 ± 4 mmHg.

*Surgical Preparation*

Through a left cervical cut down indwelling catheters were inserted into the thoracic aorta and vena cava superior. A balloon-tipped catheter was inserted into the pulmonary artery through the left femoral vein. Location of the catheter tip was determined by observing the characteristic pressure trace on the monitor as it was advanced through the right heart into the pulmonary artery.

With the pig in the supine position, a midline laparotomy was performed. The spleen was removed to avoid autotransfusion during shock, and a catheter was inserted into the urinary bladder for drainage of urine. A catheter was inserted into the mesenteric vein for blood sampling. The superior mesenteric artery (SMA) was identified close to its origin and dissected free from the surrounding tissues. An ultrasonic transit time flow probe (Transonic Systems, Ithaca, NY) was placed around the vessel and connected to an ultrasound blood flowmeter (T 207; Transonic Systems). Through an incision in the anterior gastric wall, a small custom-made laser Doppler flow (LDF) probe (Oxford Optronix, Oxford, United Kingdom) was attached to the gastric mucosa in the corpus region. Through small antimesenteric incisions in the jejunum and ascending colon, the second and third LDF probes were sutured to the mucosa of the jejunum at the respective sites. Through the incision in the colon, 20 g autologous feces was collected for later use to induce peritonitis and septic shock. All bowel incisions were then closed with continuous sutures. A fourth LDF probe was sutured on the pancreas. LDF probe Nos. 5 and 6 were attached to the kidney and the serosa side of the jejunal muscularis. All the LDF probes were attached with six microsutures to ensure continuous and steady contact with the tissue under

**Table 2. Systemic and Regional Hemodynamic Parameters before Administration of the Test Drugs (at Baseline)**

| | Before Dopamine (Baseline) | Before Dobutamine (Baseline) | Before Dopexamine (Baseline) |
|---|---|---|---|
| Heart rate beats/min | 175 ± 37 | 166 ± 27 | 175 ± 44 |
| MAP, mmHg | 71 ± 13 | 70 ± 14 | 70 ± 13 |
| CI, ml · kg$^{-1}$ · min$^{-1}$ | 167 ± 53 | 160 ± 36 | 154 ± 38 |
| SVRI, mmHg · kg$^{-1}$ · min$^{-1}$ | 409 ± 109 | 411 ± 100 | 430 ± 123 |
| PVRI, mmHg · kg$^{-1}$ · min$^{-1}$ | 101 ± 33 | 111 ± 29 | 106 ± 29 |
| CVP, mmHg | 6.9 ± 2.2 | 6.7 ± 1.8 | 6.9 ± 1.3 |
| PAP, mmHg | 21.2 ± 4.8 | 22.6 ± 5.5 | 21.4 ± 5.8 |
| PCWP, mmHg | 5.6 ± 1.9 | 5.1 ± 1.7 | 5.2 ± 1.6 |
| SMAI, ml · kg$^{-1}$ · min$^{-1}$ | 26.2 ± 6.4 | 25.8 ± 6.7 | 24.1 ± 6.0 |
| Svo$_2$, % | 60.4 ± 9.0 | 59.5 ± 9.7 | 58.5 ± 8.4 |
| Smo$_2$, % | 69.7 ± 7.7 | 68.4 ± 7.4 | 65.4 ± 8.1 |
| Temperature, °C | 39.3 ± 0.5 | 39.4 ± 0.2 | 39.3 ± 0.4 |

Data are presented as mean ± SD. Before administration of each test drug, effort was made to reach certain hemodynamic criteria (see text) by giving additional intravenous fluids. There was no significant difference between the individual mean values in the three different sets of baseline data.

CI = cardiac index; CVP = central venous pressure; MAP = mean arterial blood pressure; PAP = mean pulmonary artery pressure; PCWP = mean pulmonary artery occlusion pressure; PVRI = pulmonary vascular resistance index; SMAI = superior mesenteric artery flow index; Smo$_2$ = mesenteric venous oxygen saturation; Svo$_2$ = mixed venous oxygen saturation; SVRI = systemic vascular resistance index; Temperature = central body temperature.

investigation, preventing motion disturbance from respiration and gastrointestinal movements throughout the experiment. When the experiment was started, care was taken to avoid any movement of the LDF probes and to avoid any pressure, traction, or injury to the tissue under investigation during the experiment. At the end of the surgical preparation, two large bore tubes (32 French) were placed with the tip in the abdominal cavity before the laparotomy was closed.

During surgery, the animals received 15–20 ml · kg$^{-1}$ · h$^{-1}$ lactated Ringer's solution, which kept central venous and pulmonary capillary wedge pressure constant between 6 and 8 mmHg. The body temperature of the animals was maintained at 37.5° ± 0.5°C by the use of a warming mattress and a patient air-warming system (Warm Touch 5700; Mallinckrodt, Hennef, Germany).

After the surgical preparation was completed, the animals were allowed to recover for 30–60 min before the protocol was started, and the infusion of lactated Ringer's solution was reduced to 10 ml · kg$^{-1}$ · h$^{-1}$. As soon as the protocol was started, the infusion was discontinued. No measure was taken to keep the body temperature constant after the induction of peritonitis.

*Experimental Design*

After completing the first measurements, all animals were exposed to fecal peritonitis by instillation of 20 g autologous feces suspended in 200 ml warm isotonic saline (37°C) through the abdominal tubes to induce generalized peritonitis and sepsis. Microcirculatory blood flow was continuously measured in all animals. Systemic hemodynamics and blood samples were mea-

sured every 30 min. Four hours after induction of peritonitis, all animals were given an intravenous infusion of 10 ml/kg pentastarch (6% hydroxyethyl starch 0.5, 200; Fresenius Pharma, Stans, Switzerland) over 40 min followed by continuous infusion of 15–20 ml · kg$^{-1}$ · h$^{-1}$ lactated Ringer's solution. This infusion rate was adjusted to maintain central venous pressure (CVP) and pulmonary capillary wedge pressure values at 6–8 mmHg, which was our endpoint for fluid therapy together with CO values near the t = 0 value. It allows sufficient tissue perfusion to maintain urine output and near normal jejunal mucosa blood flow during severe sepsis.[12] The aim of this fluid resuscitation was to achieve a reasonably stable normodynamic septic condition in which CO (l/min) and mean arterial pressure (MAP; mmHg) did not change more than 15% for at least 20 min. As soon as that goal had been reached, baseline measurements (baseline 1) were performed, before starting administration of the first test drug. The systemic, regional, and microcirculatory blood flows were set at 100% to evaluate the effect of each studied drug on the microcirculation. The administration of the first test drug followed at predefined dose through the central venous line using a syringe pump. Thirty minutes later, a complete set of measurements was taken before the dose of the first test drug was doubled for another 30 min, followed by new measurements. Finally, measurements were performed 30 min after discontinuing the test drug. Then, the animals were allowed to stabilize for another 10 min, and if they remained reasonably stable (CO and MAP did not change more than 15% for at least 20 min), a new baseline was taken (baseline 2), immediately followed by administration of the second test drug in the same manner as the first. Most of the animals needed additional fluids (0–20 ml/kg lactated Ringer's solution) during the stabilization period to reach the predefined CVP and pulmonary capillary wedge pressure levels of 6–8 mmHg. In this way, the effects of all three drugs were subsequently tested. After completing the experiment, all animals were killed with an intravenous injection of 20 mmol KCl. The drugs tested were dopamine at 5 and 10 $\mu$g · kg$^{-1}$ · min$^{-1}$, dobutamine at 5 and 10 $\mu$g · kg$^{-1}$ · min$^{-1}$, and dopexamine at 1 and 2 $\mu$g · kg$^{-1}$ · min$^{-1}$. The sequence of test drug administration was randomized.

**Respiratory Monitoring.** Expired minute volume, tidal volume, respiratory rate, peak and end-inspiratory pressures, positive end-expiratory pressure (cm H$_2$O), inspired and end-tidal carbon dioxide concentrations (ET$_{CO_2}$; mmHg), and inspired (F$_{IO_2}$) and expired oxygen fraction were monitored continuously throughout the study.

**Hemodynamic Monitoring.** Mean arterial pressure, CVP, mean pulmonary artery pressure (mmHg) and pulmonary capillary wedge pressure were recorded with quartz pressure transducers (129A; Hewlett-Packard, Andover, MA). Heart rate (beats/min) was measured from

**Fig. 1. Dopamine: Systemic, regional, and microcirculatory blood flow during administration of dopamine. Relative changes (percent of baseline; mean ± SEM) in cardiac index (CI), superior mesenteric artery flow index (SMAI), and microcirculatory blood flow (MBF) in the mucosa of the stomach, jejunum, and colon as well as in the muscularis of the jejunum, the pancreas, and the kidney before and during continuous infusion of dopamine (5 and 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and 30 min after discontinuing drug administration. ** $P < 0.01$, *** $P < 0.001$ compared with baseline.**
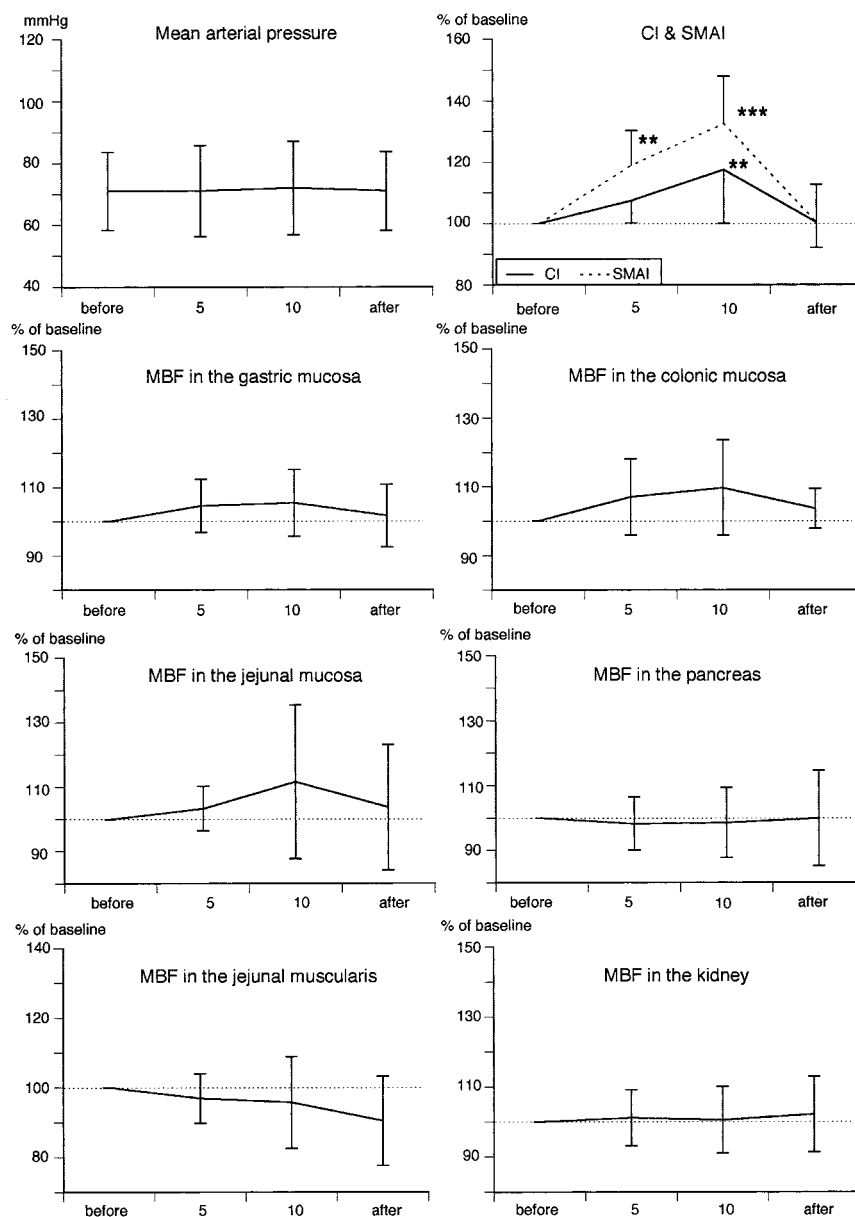
the electrocardiogram. Heart rate, MAP, pulmonary artery pressure, and CVP were displayed continuously on a multimodular monitor (Hellige SMU 611). CO (l/min) was determined with a thermodilution method. The value was calculated from three consecutive measurements at each time point (CO module, Hellige SMU 611). Central venous blood temperature (°C) was recorded from the thermistor in the pulmonary artery catheter.

**Laser Doppler Flowmetry.** Microcirculatory blood flow (MBF) was continuously measured with a six-channel laser Doppler flowmeter system (Oxford Array; Oxford Optronix). The suturable miniature surface probes were designed to measure microcirculatory blood flow at a depth of 0.5 mm into the tissue. The laser Doppler flowmeter signals were exported *via* analog outputs and acquired on line *via* a multichannel interface (Mac Paq MP 100; Biopac Systems Inc., Goleta, CA) with acquisi-

tion/analysis software (Acqknowlege 3.0; Biopac Systems Inc.) to a portable computer.

A detailed description of the theory of laser Doppler flowmetry operation and practical details has been published before. Laser Doppler flowmeters are not calibrated to measure absolute blood flow but indicate microcirculatory blood flow in arbitrary perfusion units. Because of large variability of baseline values, the results are usually expressed as changes relative to baseline,[13] and that was also the case in this study. However, laser Doppler flowmetry has been validated in many organs, including the gastrointestinal mucosa,[14,15] the pancreas,[16] and the kidney cortex,[17] and correlated well with other validated techniques of measuring local blood flow, *e.g.*, reflectance spectrophotometry,[15] microspheres,[14,18] hydrogen gas clearance,[19,20] and XE133 washout method.[21]
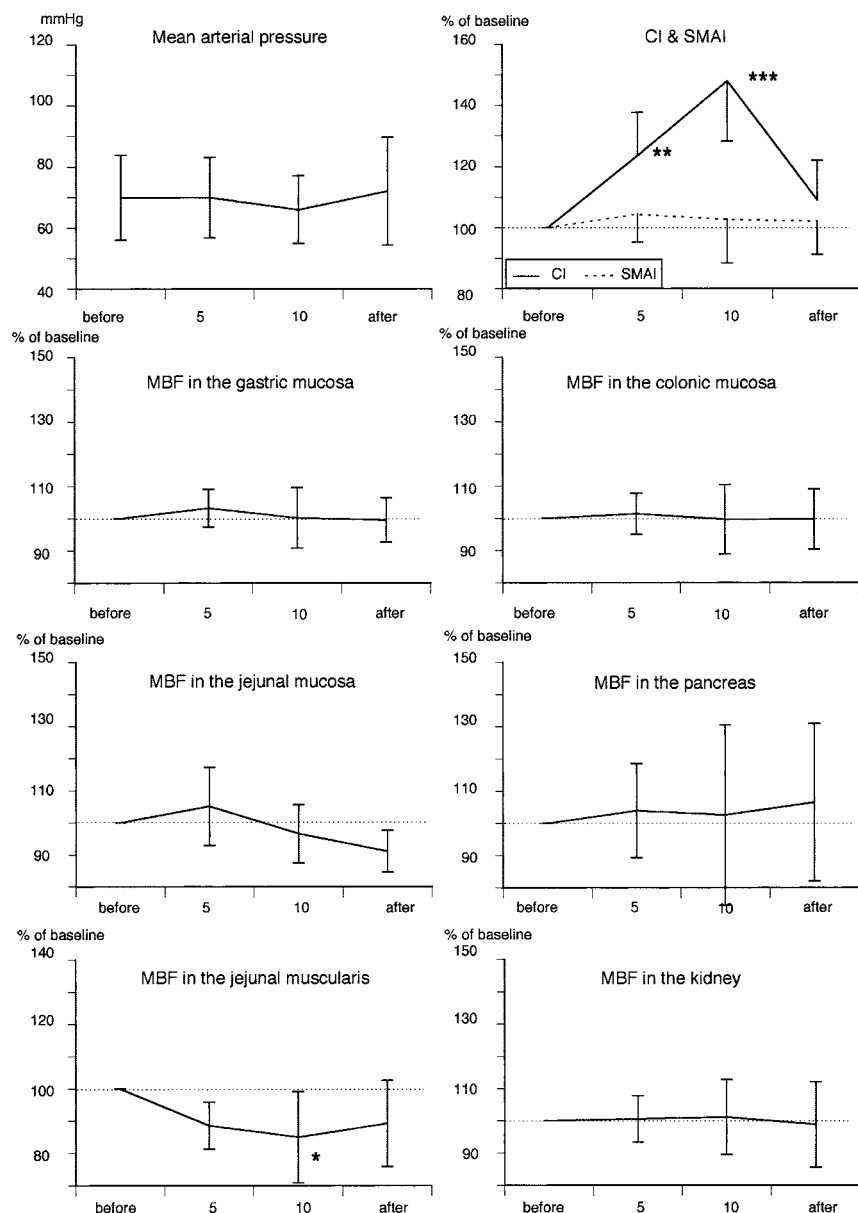
**Fig. 2. Dobutamine: Systemic, regional, and microcirculatory blood flow during administration of dobutamine. Relative changes (percent of baseline; mean ± SEM) in cardiac index (CI), superior mesenteric artery blood flow index (SMAI), and microcirculatory blood flow (MBF) in the mucosa of the stomach, jejunum, and colon as well as in the muscularis of the jejunum, the pancreas, and the kidney before and during continuous infusion of dobutamine (5 and 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and 30 min after discontinuing drug administration. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$ compared with baseline.**

The quality of the LDF signal was controlled on-line by visualizing it on a computer screen, so that motion artifacts and noise due to inadequate probe attachment could be immediately detected and corrected before the measurements started. When the experiment was started, any manipulation was avoided to minimize the possibility of artificial influence on microcirculation in the tissue under investigation.

**Ultrasonic Transit Time Flowmetry.** Blood flow in the SMA was continuously measured throughout the experiments with ultrasonic transit time flowmetry (ml/min) using an HT 206 flowmeter (Transonic Systems Inc.).

**Laboratory Analysis.** In all animals, arterial, mixed venous, and mesenteric venous blood samples were drawn every 60 min during the onset of generalized peritonitis. Further samples were drawn before (base-line), during, and after the infusion of each drug studied from the indwelling catheters. They were immediately analyzed in a blood gas analyzer (ABL 620; Radiometer, Copenhagen, Denmark) for partial pressure of oxygen ($Po_2$; mmHg), partial pressure of carbon dioxide ($Pco_2$; mmHg), pH, lactate (mM), oxygen saturation ($Sao_2$), base excess, and hemoglobin concentration (g/l). The values were adjusted to body temperature.

**Calculations and Data Analysis.** Cardiac index (CI), superior mesenteric artery flow index (SMAI), and systemic vascular resistance index (SVRI) were indexed to body weight. SVRI was calculated as SVRI = (MAP − CVP)/CI.[22,23]

Systemic oxygen delivery index, systemic oxygen consumption index, and the correspondent mesenteric (splanchnic) variables were calculated using the following formulas:

**Fig. 3. Dopexamine: Systemic, regional, and microcirculatory blood flow during administration of dopexamine. Relative changes (percent of baseline; mean ± SEM) in cardiac index (CI), superior mesenteric artery blood flow index (SMAI), and microcirculatory blood flow (MBF) in the mucosa of the stomach, jejunum, and colon as well as in the muscularis of the jejunum, the pancreas, and the kidney before and during continuous infusion of dopexamine (1 and 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and 30 min after discontinuing drug administration. ** $P < 0.01$, *** $P < 0.001$ compared with baseline.**
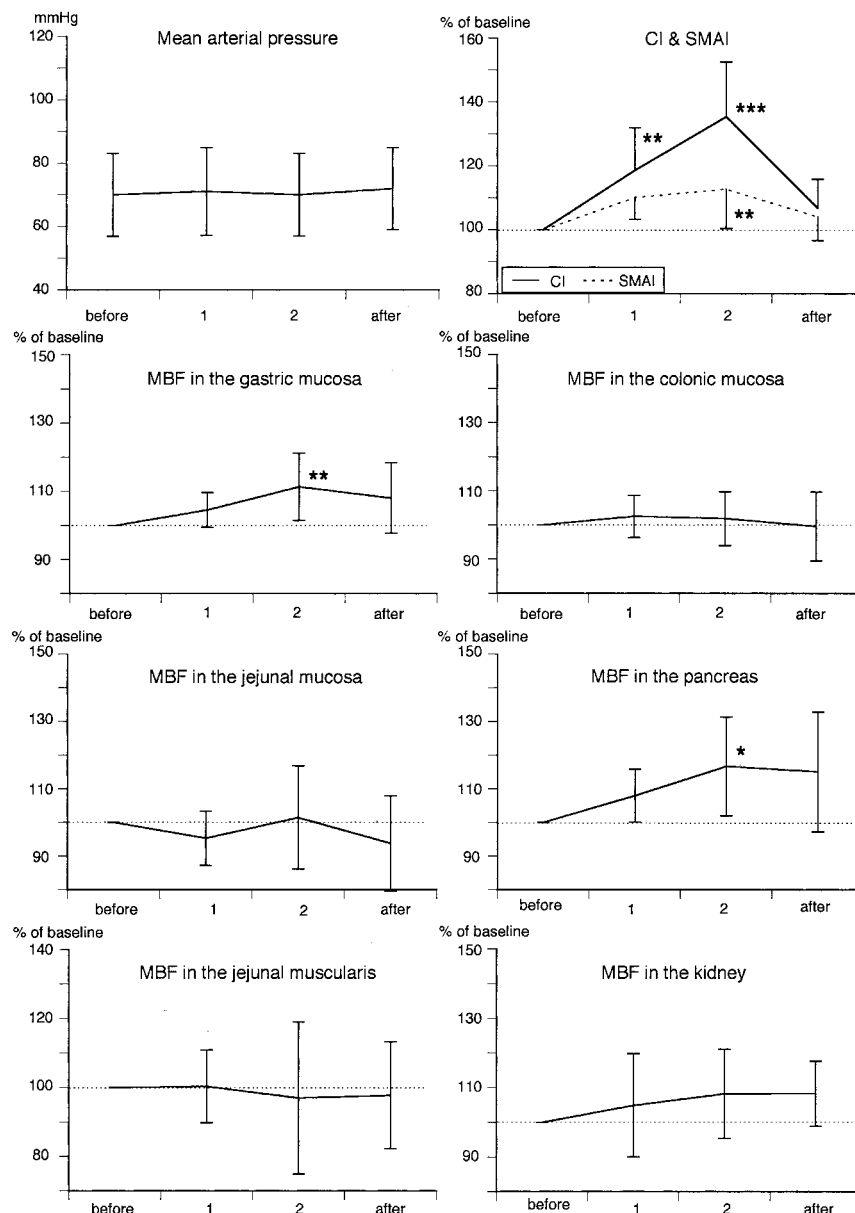
- systemic (total body) oxygen delivery index = (CI × $Cao_2$), where $Cao_2$ is the arterial oxygen content;
- $Cao_2$ = ($Pao_2$ × 0.003) + (hemoglobin × $SO_2$ × 1.36), where hemoglobin is the hemoglobin concentration and $Sao_2$ is the arterial oxygen saturation;
- systemic (total body) oxygen consumption index = (CI × ($Cao_2$ − $Cvo_2$)), where $Cvo_2$ is the mixed venous oxygen content;
- mesenteric (splanchnic) oxygen delivery index = SMAI × $Cao_2$; and
- mesenteric (splanchnic) oxygen consumption index = SMAI × ($Cao_2$ − $Cmo_2$), where $Cmo_2$ is the mesenteric vein oxygen content.

*Statistical Analysis*

The data are presented as mean ± SD of the absolute value or of percent change from the baseline. Calcula-tions for systemic, regional, and microcirculatory blood flow were performed using changes relative to baseline. Absolute values were used for all other calculations. Statistical analysis was performed using a computer-based program (Instat 3.0; Graph Pad Inc., San Diego, CA). All data were tested for normal distribution with a Kolmogorov-Smirnov test, which yielded no reason to reject the normality assumption. One-way paired analy-ses of variance for repeated measurements were used to describe changes compared with baseline. Before the administration of each substance tested, a new baseline was set. No comparison between the drugs was made. $P < 0.05$ was considered statistically significant. If sta-tistical significance was reached, the data were analyzed with a *post hoc* Bonferroni correction for repeated measurements.
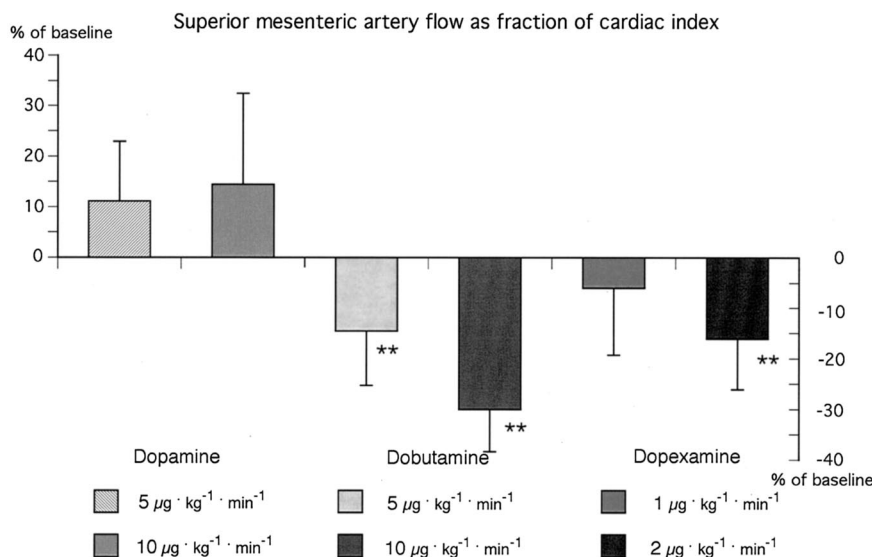
Fig. 4. Changes in superior mesenteric artery blood flow index compared with changes in cardiac index during administration of the inotropic agents. The ratio between superior mesenteric artery blood flow index and cardiac index at baseline was set at 0%. Dopamine administration increased the fraction of cardiac index going to the superior mesenteric artery, whereas during dobutamine and dopexamine administration, the fraction of cardiac index perfusing the superior mesenteric artery significantly decreased. ** $P < 0.01$ compared with baseline.

## Results

Systemic, regional, and microcirculatory hemodynamics before and 4 h after the induction of peritonitis and 60 min after fluid resuscitation are presented in table 1. Baseline data before administration of the test drug were comparable for all three agents tested (table 2).

As shown in figure 1, dopamine at doses of 5 and 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ increased CI to 108 and 118%, respectively ($P < 0.01$), and increased SMA flow to 119 and 133%, respectively ($P < 0.01$ for both). Dopamine seemed to have little effect on microcirculatory blood flow, which remained virtually unchanged in the gut mucosa and muscularis as well as in the pancreas and kidney (fig. 1). Of the three drugs tested in the current study, dobutamine had the most marked effects on CI (fig. 2). CI increased to 124 and 148%, respectively, at doses of 5 and 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ ($P < 0.001$ for both). However, SMA flow and microcirculatory flow in the different organs studied remained unchanged. As shown in figure 3, 1 and 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dopexamine increased CI significantly to 119 and 135%, respectively ($P < 0.01$ for both), and increased SMA flow to 110 and 113%, respectively ($P < 0.01$). Microcirculatory blood flow remained unchanged in all the organs studied, except for a slight increase in the gastric mucosa (fig. 3). Figure 4 shows relative changes in SMA flow as a fraction of CI for the different drugs.
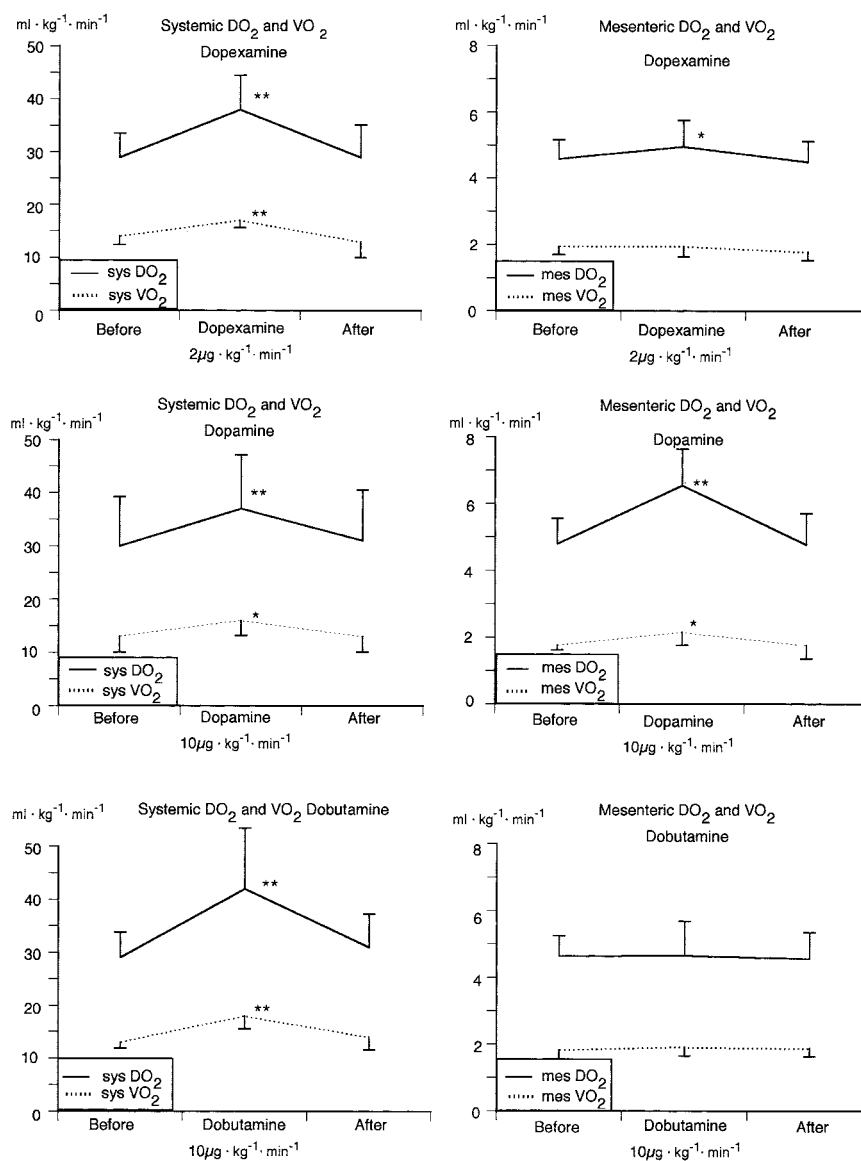
Systemic oxygen delivery and systemic oxygen consumption increased with all three drugs (fig. 5). Similar results were found for mixed venous oxygen saturation, which increased by 3.5% with dopexamine, 3.2% with dopamine, and 2.8% with dobutamine, reflecting the increase in CI. Mesenteric oxygen delivery, mesenteric oxygen consumption, and mesenteric venous oxygen saturation followed the changes in regional blood flow, *i.e.*, increased during dopexamine and dopamine administration but remained virtually unchanged during dobut-amine administration. Other results from systemic and regional blood gases are presented in table 3.

## Discussion

Despite apparently efficient initial resuscitation and advanced supportive therapy after septic shock, some patients still experience multiorgan failure. It has been suggested that inadequate splanchnic blood flow may play an important role in the pathogenesis of multiorgan failure in these cases.[24-26] With increased awareness of the apparent vulnerability of the splanchnic circulation, many investigators have attempted to treat "hidden" local hypoperfusion in vital organs by increasing systemic oxygen delivery both in severely ill and in injured patients. Several studies in which patients were submitted to deliberate increase in oxygen delivery have shown improved outcome, both in high-risk surgical patients[27,28] and in septic patients.[29] On the other hand, many studies have not shown any beneficial effects or even reported adverse effects of such therapy.[30,31] Although there were many similarities among the different studies, the design of the studies varied widely. This included variable start of the treatment protocol, *i.e.*, the patients entered the study at an early stage of the disease in some studies but first when the illness was established in others. The studies also had different endpoints, followed different protocols for intravenous fluid management, and used different inotropic agents. In addition, the underlying condition of the patients in the different studies varied widely.

Therefore, there are many factors regarding this treatment concept that need to be studied in more detail. The factor we analyzed in the current study was the effect of different β-adrenergic inotropic agents on regional and microcirculatory blood flow under septic conditions. Despite intensive research, it still remains unclear which

Fig. 5. Systemic oxygen delivery (sys $Do_2$) and systemic oxygen consumption (sys $Vo_2$) are presented on the *left*, and the corresponding mesenteric (splanchnic) variables (mes $Do_2$; mes $Vo_2$) are presented on the *right* (all mean ± SD). Dopamine was the only drug that increased mesenteric oxygen consumption. * $P$ < 0.05, ** $P$ < 0.01 compared with baseline.

inotropic agent has the most favorable effects on the splanchnic microcirculation in sepsis. In the current study, an animal model was used to simulate the clinical setting of septic patients exposed to surgery during general anesthesia as closely as possible. This model reproduces characteristic features of sepsis.[12,22] Generalized peritonitis resulted in a severe hypodynamic septic shock, which, after intravenous administration of plasma expanders, was transformed into normodynamic sepsis.

All the inotropic agents significantly increased CI (figs. 1–3). Administration of dobutamine increased CO by almost 50%, whereas dopexamine increased it by 35%, and dopamine increased it by 18%. These results are consistent with results reported by other groups.[11,32,33] SMA flow increased to a much smaller extent (figs. 1–3). In fact, the fraction of CO going to the SMA significantly decreased both during dobutamine and dopexamine administration (fig. 4). Considering the common use of dobutamine in sepsis, it is remarkable that despite al-

most a 50% increase in CO, only a negligible proportion of that increase seems to profit the gastrointestinal tract. One explanation could be that the animals were hypovolemic before starting the inotropic agents. However, the fact that CO, CVP, and pulmonary artery wedge pressure were maintained at presepsis levels before starting administration of the inotropic agents does not support that hypothesis. Therefore, it is suggested that the apparent redistribution of flow away from the splanchnic region was due to the different pharmacologic properties of the inotropic agents used. It is well known that dobutamine, beside its $\beta$ receptor activity, has considerable effects on the $\alpha$ receptors,[7] which may have prevented the expected increase in flow in the splanchnic bed (fig. 2). That would be in accordance with the physiologic "fight and flight" response—sympathetic stimulation—resulting in vasoconstriction in the splanchnic bed. However, because there was no associated increase in arterial blood pressure (in fact, there

**Table 3. Arterial, Mixed Venous, and Mesenteric Venous Blood Gas Data before Administration of Each Drug (at Baseline) and during 10 $\mu$g · kg$^{-1}$ · min$^{-1}$ Dopamine, 10 $\mu$g · kg$^{-1}$ · min$^{-1}$ Dobutamine, and 2 $\mu$g · kg$^{-1}$ · min$^{-1}$ Dopexamine**

| | Dopamine | | Dobutamine | | Dopexamine | |
|---|---|---|---|---|---|---|
| | Before | 10 $\mu$g | Before | 10 $\mu$g | Before | 2 $\mu$g |
| Pao$_2$, mmHg | 156 ± 27 | 165 ± 22 | 173 ± 18 | 166 ± 15 | 174 ± 16 | 167 ± 18 |
| Paco$_2$, mmHg | 44 ± 3 | 43 ± 3 | 45 ± 4 | 44 ± 3 | 42 ± 4 | 43 ± 2 |
| pH | 7.35 ± 0.04 | 7.36 ± 0.04 | 7.34 ± 0.05 | 7.35 ± 0.05 | 7.37 ± 0.06 | 7.37 ± 0.04 |
| Sao$_2$, % | 94.4 ± 0.8 | 94.5 ± 0.7 | 94.9 ± 0.2 | 94.8 ± 0.1 | 94.8 ± 0.2 | 94.8 ± 0.1 |
| HCO$_3^-$, mM | 23.1 ± 1.5 | 23.0 ± 1.5 | 23.3 ± 1.2 | 23.5 ± 1.4 | 23.4 ± 1.5 | 23.2 ± 1.9 |
| BE | −1.43 ± 1.9 | −1.45 ± 1.9 | −1.31 ± 1.9 | −0.94 ± 1.9 | −0.84 ± 2.1 | −1.2 ± 2.1 |
| Arterial lactate, mM | 1.51 ± 0.8 | 1.38 ± 0.7 | 1.79 ± 0.9 | 1.56 ± 0.6 | 1.57 ± 0.6 | 1.5 ± 0.7 |
| Svo$_2$, % | 60.4 ± 8.9 | 63.5 ± 9.0 | 59.6 ± 9.7 | 62.3 ± 9.9 | 58.5 ± 8.4 | 62 ± 6.9 |
| Venous lactate, mM | 1.5 ± 0.9 | 1.35 ± 0.7 | 1.9 ± 1.0 | 1.7 ± 0.7 | 1.6 ± 0.7 | 1.5 ± 6.4 |
| Smo$_2$, % | 69.7 ± 7.7 | 73.7 ± 6.5 | 68.4 ± 7.7 | 65.5 ± 7.8 | 65.4 ± 8.0 | 68.2 ± 4.6 |
| Mesenteric lactate, mM | 1.7 ± 0.8 | 1.5 ± 0.7 | 2.3 ± 0.9 | 2.0 ± 0.7 | 1.9 ± 0.6 | 1.7 ± 0.7 |

Data are presented as mean ± SD.

Arterial lactate = arterial lactate concentration; BE = arterial base excess; HCO$_3-$ = arterial bicarbonate concentration; mesenteric lactate = mesenteric venous lactate concentration; Paco$_2$ = arterial carbon dioxid tension; Pao$_2$ = arterial oxygen tension; Sao$_2$ = arterial oxygen saturation; Smo$_2$ = mesenteric venous oxygen saturation; Svo$_2$ = mixed venous oxygen saturation; venous lactate = mixed venous lactate concentration.

was a slight decrease), it is more likely that the redistribution of flow was predominantly caused by the $\beta_2$-agonistic effects of dobutamine. Dobutamine may cause more profound vasodilatation in other vascular beds, *e.g.*, in skeletal muscle and skin, than in the splanchnic region during sepsis. This hypothesis warrants further studies.

Dopexamine is a potent $\beta_2$ receptor agonist but a weak $\beta_1$ and dopamine DA-1 and DA-2 receptor agonist. It is more than likely that the dopaminergic receptor activity of dopexamine mediated the slight but significant increase in SMA blood flow observed in this study (fig. 3). However, the relative effect of dopexamine on splanchnic blood flow was similar to that of dobutamine (fig. 4), suggesting a considerable $\beta_2$-induced vasodilatation in peripheral vascular beds. Consequently, it may be speculated if profound $\beta_2$ effects are favorable for the splanchnic microcirculation in sepsis.

In this study, dopamine was the most potent agent in increasing regional splanchnic blood flow (fig. 1). Even if the increase in CO was moderate, perhaps because of less profound $\beta_2$-adrenergic effects, dopamine was the only drug that significantly increased both the absolute splanchnic (SMA) flow and the fraction of CO going to the splanchnic bed (fig. 4). The profound dopaminergic receptor effects of this agent can explain this effect of dopamine on the splanchnic circulation.

Despite positive effects, of all the inotropic agents on CO and systemic oxygen delivery, none of them had any significant effects on microcirculatory blood flow in the intestinal mucosa. The fact that the fluid volume resuscitation shortly before administration of the inotropic agents had significantly improved splanchnic microcirculatory blood flow in most organs (table 1) indicates that the microcirculation could still be rescued at this time and was not all plugged with microthrombi and adherent leukocytes.[29] The results of this study are in

accord with a recent clinical study of Lebuffe *et al.*,[34] who evaluated the effect of early dobutamine infusion on gastric mucosal pH, an indirect measure of gastrointestinal perfusion, in patients with severe sepsis. They found that dobutamine infusion did not significantly improve tonometric parameters within the first 72 h and had no particular beneficial effect in this patient population. On the other hand, our results are in contrast with those of Neviere *et al.*,[11] who reported a significant increase in jejunal microcirculatory blood flow in dobutamine-treated pigs exposed to endotoxic hypotension. That study, however, is not comparable with ours, because the endotoxin model used by Neviere *et al.* caused hypotension without affecting CO or oxygen delivery. In contrast, the sepsis model used in the current study caused initially hypotension with decreased oxygen delivery (hypodynamic septic shock), which was altered to normodynamic sepsis after intravenous fluid resuscitation. Furthermore, Cain and Curtis[33] found an increased intestinal oxygen consumption and a decreased lactate output in the gut of endotoxemic dogs, suggesting that microcirculatory blood flow to the mucosa was improved during dopexamine administration, and Hasibeder *et al.*[35] found an improved mucosal oxygenation in the jejunal mucosa of endotoxemic pigs during dopamine infusion. Neither of these studies used a septic shock model, and neither of them measured microcirculatory blood flow directly.

Therefore, despite significantly improved systemic flow and oxygen delivery treatment with dopamine, dobutamine and dopexamine failed on the microcirculatory level. This may explain the conflicting results after optimizing oxygen delivery in patients with sepsis and septic shock. Some studies have reported beneficial,[29] indifferent,[30] or even adverse effects[31] of increasing oxygen delivery.

The results of this study show that dobutamine, dopa-

mine, and dopexamine all improved systemic blood flow and oxygen delivery. Despite the greatest increase in CI, Dobutamine did not increase regional blood flow. None of these $\beta$-adrenergic agents, however, increased microcirculatory blood flow either in the gastrointestinal mucosa or in the pancreas or kidney. Hence, the concept of supranormal systemic oxygen delivery as a result of administration of inotropic agents in sepsis may fail because the increased systemic flow does not reach the microcirculation in splanchnic organs.

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