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The effects of low-dose dopamine on splanchnic blood flow and oxygen uptake in patients with septic shock

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Abstract *Objective:* To assess the effects of low-dose dopamine on splanchnic blood flow and splanchnic oxygen uptake in patients with septic shock.
Design: Prospective, controlled trial.
Setting: University hospital intensive care unit
Patients: 11 patients with septic shock, diagnosed according the criteria of the 1992 American College of Chest Physicians/Society of Critical Care Medicine consensus conference, who required treatment with norepinephrine.
Measurements and main results: Systemic and splanchnic hemodynamics and oxygen transport were measured before and during addition of low-dose dopamine (3 μg/kg per min). Low-dose dopamine had a marked effect on total body hemodynamics and oxygen transport. The fractional splanchnic flow at baseline ranged from 0.15 to 0.57. In 7 patients with a fractional splanchnic flow less than 0.30, low-dose dopamine increased splanchnic flow and splanchnic oxygen delivery and oxygen consumption. In 4 patients with a fractional splanchnic flow above 0.30, low-dose dopamine did not appear to change splanchnic blood flow.
Conclusion: Low-dose dopamine has a potential beneficial effect on splanchnic blood flow and oxygen consumption in patients with septic shock, provided the fractional splanchnic flow is not already high before treatment.

Key words Septic shock · Sepsis · Oxygen delivery · Oxygen consumption · Splanchnic blood flow · Splanchnic oxygen delivery · Splanchnic oxygen consumption · Dopamine

Introduction

Low-dose dopamine is commonly used in critically ill patients in an attempt to prevent renal and splanchnic hypoperfusion. Goldberg [1] showed that low-dose dopamine increases renal blood flow, glomerular filtration rate, and urinary sodium excretion, but, unfortunately, there is no clear understanding of its actions and benefits. Whether low-dose dopamine can prevent renal failure in critically ill patients remains to be shown. The effects of low-dose dopamine on splanchnic blood flow are even less well known. In some animal [2, 3] and human studies [4], dopamine increased splanchnic blood flow; however, this occurred in nonseptic conditions. Nelson et al. [5] have demonstrated that in sepsis the oxygenation of the gut could become O_2-supply dependent in the presence of adequate tissue

oxygenation in other regions. Splanchnic blood flow [6] and splanchnic oxygen consumption [7, 8] have been shown to increase in patients with sepsis. It is not known whether increased splanchnic blood flow implies adequate tissue oxygenation. Nor, is it known whether low-dose dopamine can further improve a sepsis-induced increase in splanchnic blood flow and lessen the possibility of severe tissue hypoxia. We therefore tested the effects of low-dose dopamine on splanchnic blood flow and oxygenation in patients with septic shock by measuring splanchnic flow, splanchnic oxygen delivery (DO_2), splanchnic oxygen consumption (VO_2), and gastric mucosal pH (pHi).

Patients and methods

Eleven patients with septic shock were studied in a consecutive series design. Patients ranged in age between 28 and 70 years; their scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II at admission to the intensive care unit (ICU) were between 6 and 26.

Details of patients, including sex, age, diagnosis, number of organ failures at inclusion, APACHE II scores at the time of ICU admission, norepinephrine dosage, duration of stay in the ICU, and the outcome in the ICU, are given in Table 1. The definitions of organ system failure (OSF) were the following [9]: (1) cardiovascular failure (presence of one or more of the following): heart rate $\leq$ 54 beats/min; mean arterial blood pressure (MAP) $\leq$ 49 mmHg; ventricular tachycardia and/or ventricular fibrillation; serum pH $\leq$ 7.24 with a partial pressure of carbon dioxide in arterial blood ($PaCO_2$) $\leq$ 49 mmHg. (2) Respiratory failure (presence of one or more of the following): respiratory rate $\leq$ 5/min or $\geq$ 49/min; $PaCO_2 \geq$ 50 mmHg; alveolar-arterial oxygen difference $\geq$ 350 mmHg; dependent on ventilator on the fourth day of OSF. (3) Renal failure (presence of one or more of the following): urine output $\leq$ 479 ml/24 h; serum blood urea nitrogen $\geq$ 100 mg/100 ml; serum creatinine $\geq$ 3.5 mg/100 ml. (4) Hematologic failure (presence of one or more of the following): white blood cells $\leq$ 1000 mm^3; platelets $\leq$ 20 000 mm^3; hematocrit $\leq$ 20%. (5) Neurologic failure: Glasgow Coma Score $\leq$ 6.

All procedures were approved by our institutional research review committee and informed consent was received from each patient or next of kin.

The criteria for septic shock were [10] a demonstrated focus of infection or blood cultures for recognized pathogens on two or more occasions, fever or hypothermia (core temperature $>$ 38 °C or $<$ 36 °C), and an episode of hypotension (MAP $<$ 60 mmHg) or the need for vasopressors to prevent hypotension. Furthermore, at least two of the following criteria had to be met: (a) hypoxemia (arterial oxygen saturation $<$ 95%) not due to pneumonia, (b) leukocytosis or leukopenia ($>$ 12 or $<$ 4×10^9/l) and/or a demonstrable left shift in neutrophils, (c) impaired renal function (urine output $<$ 30 ml/h over 2 or more hours and creatinine clearance $<$ 70 ml/min), (d) increased serum lactate ($>$ 2.2 mmol/l), or (e) mental disorientation.

All studies were conducted during controlled mechanical ventilation (Servo 900 C, Siemens, Solna, Sweden), with an inspiratory:expiratory ratio of 1:2, a positive end-expiratory pressure of 10 cmH_2O, and a constant fractional inspired oxygen during the study period. All patients were deeply sedated with continuous infusions of fentanyl (maximum dosage 0.24 mg/h) and midazolam (maximum dosage 6.0 mg/h).

Pulmonary and radial artery pressures were measured with reference to the midaxillary line (transducer 5265 039, Viggo-Spectramed, Bilthoven, The Netherlands). Cardiac output was measured by thermodilution in triplicate, using 10 ml cold (6–12 °C) saline solution (SAT II cardiac output computer, Baxter Healthcare, Irvine, Calif., USA).

Blood samples for blood gas estimations were drawn in duplicate, stored on ice, and processed within 30 min. Oxygen tension and pH (ABL 3, Radiometer, Copenhagen, Denmark) and hemoglobin and oxygen saturation (Hemoximeter Osm 3, Radiometer) were measured immediately after sampling. The same samples were used to determine lactate concentrations with a bedside photometric test kit (Dr. Lange, Berlin, Germany).

Gastric mucosal pH was determined by a tonometric probe (Trip'TGS catheter, Tonometrics, Worcester, Mass., USA). The correct position of the pHi probe was controlled using fluoroscopy. The tonometer was filled with normal saline. The partial pressure of carbon dioxide in the saline from the pHi probe and the bicarbonate concentration in the simultaneous arterial blood sample were obtained with the same blood gas analyzer (ABL 3, Radiometer, Copenhagen, Denmark) to calculate the pHi according the Henderson–Hasselbalch equation. Equilibration time was always 60 min. None of the patients were treated with H_2 receptor antagonists, pHi was measured in only 9 of the 11 patients because 2 patients had previously had gastrectomies.

Table 1 Details of patients

Patient no.	Sex	Age (years)	Diagnosis	Organ system failure	Norepinephrine dosage (μg/kg per min)	APACHE II socre	Days in ICU	Outcome
1	M	49	Pneumonia	1	0.08	19	24	Surv.
2	M	70	Pancreatitis	2	0.08	15	40	Died
3	M	42	Pneumonia	2	0.21	6	18	Surv.
4	M	66	Urosepsis	1	0.15	2	15	Died
5	M	36	Peritonitis	1	0.10	6	63	Surv.
6	M	34	Pneumonia	2	0.28	13	31	Surv.
7	M	35	Pneumonia	2	0.05	7	21	Died
8	F	31	Pneumonia + peritonitis	1	0.33	26	29	Surv.
9	M	54	Pneumonia	3	0.52	14	63	Died
10	M	28	Pneumonia	1	0.16	25	51	Surv.
11	F	34	Peritonitis	2	0.20	22	22	Surv.

In addition to catheters for routine monitoring (radial and pulmonary artery catheters), a 7.5 F catheter was inserted into the hepatic vein via the right internal jugular vein or the right femoral vein under continuous X-ray monitoring. The correct position of the catheter was thus verified before and after the studies.

Splanchnic blood flow was evaluated by a single-bolus indocyanine-green (ICG-Pulsion, Germany) dye technique [11, 12]. With this technique the total hepatosplanchnic blood flow is assessed; gut and liver blood flow cannot be separated. The dye used was a monosodium salt of indocyanine green prepared in freeze-dried form and dissolved in sterile water [13]. A 25-mg bolus of indocyanine green was injected into the vena cava. Arterial and hepatic venous blood samples were taken after 1, 2, 3, 4, 7, and 10 min. To keep the volume of redistribution constant, no fluids were infused during the measurements. Indocyanine green was assayed spectrophotometrically at 805 nm on plasma samples. The coefficient of variation for the indocyanine green photometry in samples measured directly after blood sampling was 4.9 ± 4.0%.

Splanchnic blood flow was calculated by the equation:

$$SP = K \times V_B/E$$

where K is the decay constant of indocyanine green (ICG) in arterial blood [calculated by $\Delta \ln(\mathrm{ICG})/\Delta t$), E is the fractional hepatic extraction of ICG, calculated by the equation $E = 1 -$ hepatic venous (ICG)/arterial (ICG), and V_B is the blood volume, determined by extrapolation of the arterial indocyanine green concentration curve to zero. The extrapolation procedure for the calculation of zero-time ICG concentration was done using the following equation:

$$A_0 = \frac{\sum_{\infty}^{n=1} (t_n \cdot e^{k + [ICG]_n})}{n}$$

The indocyanine green extraction calculated for all patients was 52.1 ± 16.3% and the coefficient of variation for the six measurements after the bolus injection in each patient was 5.8 ± 5.1%. To test the reliability of this method in our clinic, we have done repeated measures in patients with stable hemodynamic conditions and found a coefficient of variation for the measurement of splanchnic blood flow of 6.3 ± 6.0%.

Oxygen content was calculated as (hemoglobin × 1.36 × percent saturation) + (oxygen tension × 0.0031). Total body and splanchnic DO_2 rates were calculated by multiplying the arterial oxygen content with the appropriate flow parameters. Total body and splanchnic VO_2 were calculated by multiplying the arteriovenous (mixed venous for VO_2, hepatic venous for splanchnic VO_2) oxygen-content difference with the appropriate flow parameters.

Before data collection was begun, all patients were stabilized by volume loading until there was no further increase in cardiac output. We included only patients who required additional vasopressor treatment with norepinephrine in a dose between 0.05 and 0.52 μg/kg per min to achieve an adequate MAP > 70 mmHg. Norepinephrine was titrated for adequate organ perfusion pressure but at least to 70 mmHg MAP. Measurements began when the patients were stable (hemodynamic parameters, and arterial, mixed venous, and hepatic venous blood samples, and pHi) and were repeated at 60 and 120 min. A single measurement of splanchnic blood flow and the calculation of variables which require splanchnic blood flow was done at 60 min. Additionally, to demonstrate hemodynamic stability and the lack of natural variations in splanchnic blood flow over the entire experiment, the coefficient of variation for the three consecutive measurements of mixed venous and hepatic venous O_2 saturation were calculated: 4.4 ± 0.4% and 5.1 ± 0.3%, respectively.

After this 2-h baseline period, low-dose dopamine (3.0 μg/kg per min) was added, and after 30 min the measurement cycle (0, 60, 120 min) was repeated. Group statistics were calculated from the mean of the three measurements taken at baseline and during dopamine infusion.

To maintain a constant pulmonary capillary wedge pressure (PCWP) during the study, the patients were infused with hydroxyethylstarch 10%. Any patient whose body temperature increased more than 1 °C during the investigation was excluded from the study.

Values are presented as mean ± standard deviation. Paired data obtained before and after the catecholamine conversion were compared with a nonparametric Wilcoxon rank-sign test. Significance was set at the $p < 0.05$ level.

Results

The systemic hemodynamic and oxygen transport data are presented in Table 2. The average increase in cardiac index with dopamine was 24%. There was no change in MAP or PCWP with low-dose dopamine. DO_2 rose by about 22% while VO_2 increased by only 7%.

Fractional splanchnic blood flow at baseline ranged widely between patients, from 0.15 to 0.57 of the cardiac index. Splanchnic blood flow increased significantly with low-dose dopamine from 1.2 l/min per m^2 to 1.6 l/min per m^2 (Table 3). Because the cardiac index increased to a similar extent, fractional splanchnic blood flow was not significantly changed (0.29 at baseline and 0.31 with dopamine). Splanchnic oxygen supply increased significantly from 172 to 226 ml/min per m^2. Splanchnic oxygen consumption was not significantly increased as splanchnic oxygen extraction decreased. Fractional splanchnic VO_2 as a function of whole body VO_2 is shown in Fig. 4.

As the individual patient data points on Fig. 1 show, the change in fractional splanchnic flow induced by dopamine varied with the baseline fractional splanchnic flow. Figure 2 shows the correlation between the baseline fractional splanchnic blood flow and the changes after dopamine infusion ($r^2 = -0.72$, $p < 0.001$). Table 3 shows the splanchnic data for all patients as well as for those with normal (≤ 0.30) and high (> 0.30) baseline fractional splanchnic blood flow. In the 7 patients with a baseline fractional splanchnic flow in the normal range (patients 1,2,4,6,9,10,11), dopamine increased the fractional blood flow from 0.21 to 0.29, which represents a mean increase in absolute splanchnic flow of 72%. Splanchnic DO_2 likewise increased 72%, while splanchnic VO_2 increased 37%. Figure 3 shows the individual plots for the changes in splanchnic VO_2 as splanchnic DO_2 changed with dopamine. For the remaining 4 patients (3,5,7,8) with a baseline fractional splanchnic flow above 0.30, low-dose dopamine did not affect total splanchnic flow, splanchnic DO_2, or splanchnic VO_2. Of these 4 patients, the two with the highest initial fractional splanchnic flow (patients 5,7) actually showed substantial decreases in the fractional flow (Figure 1) and

Table 2 Systemic hemodynamic and oxygen transport data for 11 patients

Parameter	Baseline	Dopamine	Sig.
Heart rate (beats/min)	86 ± 17	92 ± 14	
Mean arterial pressure (mmHg)	95 ± 13	98 ± 12	
Mean pulmonary artery pressure (mmHg)	32 ± 6	32 ± 4	
Mean pulmonary capillary wedge pressure (mmHg)	16 ± 2	16 ± 2	
Central venous pressure (mmHg)	15 ± 3	14 ± 3	*
Cardiac index (l/min per m^2)	4.3 ± 0.9	5.3 ± 0.8	*
Systemic vascular resistance ($dyn \times cm^{-5}$)	812 ± 215	683 ± 181	*
Pulmonary vascular resistance ($dyn \times cm^{-5}$)	162 ± 106	128 ± 58	*
Oxygen delivery (ml/min per m^2)	609 ± 122	741 ± 111	*
Oxygen consumption (ml/min per m^2)	145 ± 21	156 ± 21	*
Oxygen extraction (%)	25 ± 5	21 ± 3	*

* = $p < 0.05$

splanchnic VO_2 (Figure 3). When systemic variables in the patients with a flow less than 0.30 were compared with those whose flow was above 0.30, there were no apparent differences.

The pHi data are also presented in Table 3. In 8 of the 9 patients in whom this was measured, the pHi values were ≤ 7.32, a commonly accepted threshold for gastric mucosal hypoperfusion. There were no significant changes in pHi or lactate with dopamine infusion, even in patients with a baseline fractional splanchnic flow ≤ 0.30. Neither the pHi nor changes in pHi

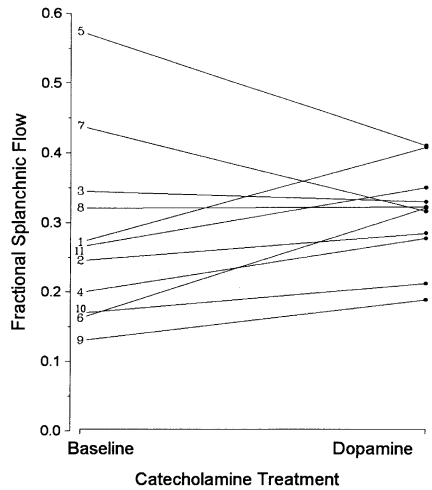

Fig. 1. Individual patient plots of change in fractional splanchnic flow from baseline to low dose dopamine infusion

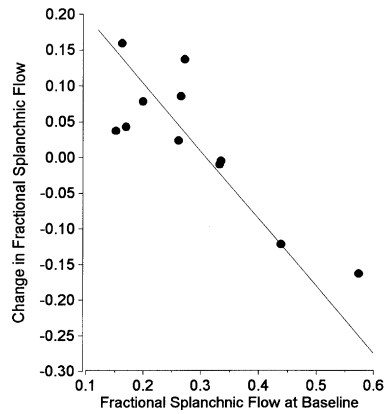

Fig. 2. Relationship between dopamine induced change in fractional splanchnic flow and baseline fractional splanchnic flow [$r^2 = 0.72$ ($y = 31.4 - 1.113*x$), $p < 0.001$]

Table 3 Splanchnic hemodynamic and oxygen transport data (*SP* fractional splanchnic blood flow)

Parameter	All patients ($n = 11$)			Patients with SP ≤ 0.30 ($n = 7$)		Patients with SP > 0.30 ($n = 4$)	
	Baseline	Dopamine	Sig.	Baseline	Dopamine	Baseline	Dopamine
Splanchnic blood flow (l/min per m^2)	1.2 ± 0.6	1.6 ± 0.5	*	0.9 ± 0.3	1.6 ± 0.6	1.8 ± 0.5	1.8 ± 0.4
Fractional splanchnic blood flow (%)	29 ± 13	31 ± 7		21 ± 5	29 ± 8	42 ± 11	35 ± 4
Splanchnic oxygen delivery (ml/min per m^2)	172 ± 84	226 ± 66	*	121 ± 33	209 ± 68	261 ± 67	255 ± 59
Splanchnic oxygen consumption (ml/min per m^2)	70 ± 22	79 ± 13		61 ± 9	82 ± 13	86 ± 29	75 ± 14
Splanchnic oxygen extraction (%)	47 ± 17	36 ± 11	*	53 ± 17	41 ± 11	36 ± 9	28 ± 5
	($n = 9$)			($n = 6$)		($n = 3$)	
Gastric mucosal pH	7.29 ± 0.05	7.28 ± 0.06		7.27 ± 0.06	7.25 ± 0.06	7.32 ± 0.03	7.32 ± 0.03

* = $p < 0.05$

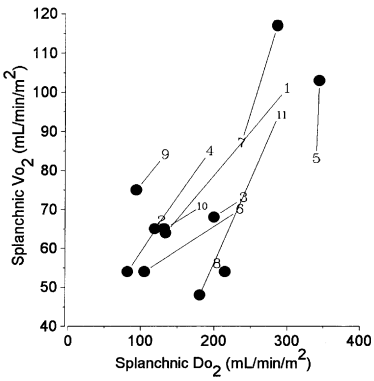

Fig. 3. Individual patient plots for the splanchnic VO_2/DO_2 relationship at baseline and with low dose dopamine [point = baseline condition, number = dopamine condition]

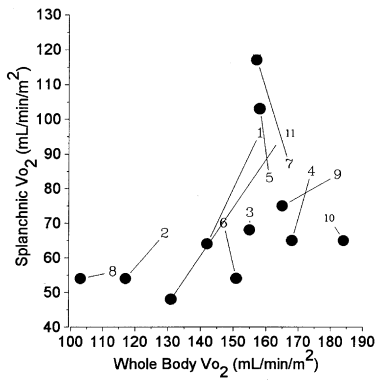

Fig. 4. Individual patient plots for the splanchnic VO_2/whole body VO_2 relationship at baseline and with low dose dopamine [point = baseline condition, number = dopamine condition]

correlated with splanchnic blood flow or splanchnic VO_2 or changes in these variables. Arterial lactate at baseline in all patients was 1.4 ± 0.5 mmol/l, mixed venous lactate 1.5 ± 0.4 mmol/l, and hepatic venous lactate 1.2 ± 0.4 mmol/l. There were no changes in lactate values or in lactate differences across the splanchnic region with dopamine treatment.

Discussion

In these patients with septic shock, who were stabilized with volume and norepinephrine, low-dose dopamine had marked effects on global hemodynamics and O_2 transport, similar to those reported in healthy volunteers [14] and in coronary bypass patients [15]. A much smaller rise in global VO_2 (7%) in our patients would suggest little improvement in tissue oxygenation; however, global parameters only reflect the summation of changes in all regions of the body and tell us nothing about specific organ blood flow and oxygenation [16].

We found a greater range in baseline fractional splanchnic flow, 15–57%, in these septic patients than the 15–25% reported in nonseptic patients [17]. An increase in splanchnic flow has also been shown in healthy volunteers receiving endotoxin [8] and in septic patients treated with dopamine in dosages high enough to reverse the hypotension of septic shock [6]. In the present study, when all 11 patients were analyzed, there was no clear effect of low-dose dopamine on the splanchnic region.

However, the initial fractional splanchnic blood flow values show that patients had two types of response to low-dose dopamine: either the potential to increase fractional splanchnic blood flow or not. In 7 patients with a flow of less than 0.30, dopamine increased the absolute as well as the fractional splanchnic blood flow, indicating a direct effect of the drug on splanchnic circulation. This is the effect we had hoped for in all patients, from previous laboratory studies. In a study in dogs, a decrease in splanchnic blood flow induced by positive end-expiratory pressure returned to normal with low-dose dopamine [2]. A larger dose of dopamine, 7.5 μg/kg per min, reversed stress-induced intenstinal vasoconstriction in cats [18]. In a rat model of peritonitis which reduced effective hepatic blood flow, dopamine 5 μg/kg per min caused a selective increase in hepatic blood flow [3].

Along with the increase in fractional splanchnic flow in the 7 patients with normal baseline flow, splanchnic DO_2 rose (72%) and as did splanchnic VO_2 (37%). It is not certain whether this increase in VO_2 actually indicates improved tissue oxygenation, because we cannot exclude the possibility of a direct metabolic effect of dopamine as reported in the literature, though there is some controversy over this. In nonseptic pigs, where O_2-supply dependency is unlikely, dopamine in dosages of 5, 10 and 15 μg/kg per min increased hepatic VO_2 [19]. On the other hand, no increase in total body VO_2 was seen in healthy volunteers infused with dopamine at 2.5 or 3.0 μg/kg per min [14, 20].

Nevertheless, improved splanchnic tissue oxygenation would not be expected unless there were some underperfused regions. Two variables which expected to help clarify the situation were hepatic venous lactate and pHi. Our lactate data lend little support for regional underperfusion, in that the values were in the normal range for 10 of the 11 patients. However, we did find that the only patient with an increased hepatic lactate at baseline also had the greatest increase (96%) in splanchnic VO_2. Conversely, pathologically low pHi in 8 of 9 patients indicates some tissue hypoxia in the splanchnic area [21]. Nevertheless, in the patients in whom splanchnic VO_2 increased with dopamine, there was no concomitant increase in pHi.

According to the literature, however, pHi may not always change with changes in tissue oxygenation [22]. It has been shown that pHi, measured at admission to the ICU, correlates well with patient outcome [23], that splanchnic ischemia in an animal model can be detected by pHi [24], and that pHi-directed treatment improves patient outcome [25]. On the other hand, it is not known whether pHi also detects short-term changes in tissue oxygenation, and it is doubtful whether pHi can represent the whole splanchnic area. Changes in blood flow were not consistent across various splanchnic organs in an animal model of sepsis [26]. Therefore, the unchanged pHi after treatment with dopamine does not necessarily rule out improvement in splanchnic tissue oxygenation.

Dye dilution techniques have been used for over 50 years to estimate hepatic blood flow [27]. Currently, indocyanine green is the most commonly used dye. Although some techniques use only systemic blood samples, it has recently been shown that the use of a hepatic venous catheter to allow calculation of hepatic dye extraction is necessary for precise flow determination in critically ill patients [28]. Uusaro et al. [28] have demonstrated the excellent reliability of a continuous infusion technique, but a direct comparison with a single-bolus method, such as we used, has not been done. Of course, independent of the technique used, hepatic venous blood flow determination has some limitations. Gut and liver blood flow cannot be separated. Only global flow without the detection of regional maldistribution is assessed. That dopamine especially can induce such regional maldistribution was reported by Giraud et al. [29], who found an increased blood flow to the gut but a redistribution of blood flow from the mucosa to the muscularis of the gut during dopamine infusion. The unchanged pHi in our study indicates that an increase in splanchnic blood flow did not necessarily result in an increase to the gastric mucosa. Animal studies showing that blood flow from the liver increased more than that from the gut in sepsis [30] indicate that the observed changes in hepatic venous blood flow may be due primarily to a change in hepatic artery flow. A similar discrepancy between pHi and splanchnic blood flow was demonstrated by Uusaro et al. [22] in cardiac surgery patients.

Due to the small number of patients with a high initial fractional splanchnic flow, we cannot definitively describe the effects of low-dose dopamine in such patients. The regression analysis suggests that the observed effects of dopamine in patients with an initial fractional splanchnic flow below 0.3 are not seen in patients with an initial high fractional splanchnic flow. However, it should be noted that at the start of the protocol, according to the routine practice of the physicians in our unit, all patients were already receiving norepinephrine infusions at doses sufficient to keep MAP fairly high. It is possible that in some patients norepinephrine prevented a dopamine-induced increase in splanchnic blood flow; therefore, a clear understanding of the effects of low-dose dopamine in the absence of norepinephrine must await further studies.

In conclusion, we suggest that the effects of low-dose dopamine on splanchnic blood flow are variable in individual patients with sepsis, depending on the initial fractional splanchnic flow. In the patients with a normal initial fractional splanchnic blood flow (≤ 0.30), there was a selective effect on the splanchnic circulation, such that both perfusion and VO_2 of the splanchnic region increased. Whether this was true improvement of tissue oxygenation remains unclear. In a small number of patients with a high initial fractional splanchnic flow, low-dose dopamine did not appear to increase splanchnic flow; however, further investigations are needed to confirm such an effect.

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