Effects of Vasopressin on Microcirculatory Blood Flow in the Gastrointestinal Tract in Anesthetized Pigs in Septic Shock

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Background: Vasopressin increases arterial pressure in septic shock even when α-adrenergic agonists fail. The authors studied the effects of vasopressin on microcirculatory blood flow in the entire gastrointestinal tract in anesthetized pigs during early septic shock.

Methods: Thirty-two pigs were intravenously anesthetized, mechanically ventilated, and randomly assigned to one of four groups (n = 8 in each; full factorial design). Group S (sepsis) and group SV (sepsis–vasopressin) were made septic by fecal peritonitis. Group C and group V were nonseptic control groups. After 300 min, group V and group SV received intravenous infusion of $0.06 \; U \cdot kg^{-1} \cdot h^{-1}$ vasopressin. In all groups, cardiac index and superior mesenteric artery flow were measured. Microcirculatory blood flow was recorded with laser Doppler flowmetry in both mucosa and muscularis of the stomach, jejunum, and colon.

Results: While vasopressin significantly increased arterial pressure in group SV ($P < 0.05$), superior mesenteric artery flow decreased by $51 \pm 16\%$ ($P < 0.05$). Systemic and mesenteric oxygen delivery and consumption decreased and oxygen extraction increased in the SV group. Effects on the microcirculation were very heterogeneous; flow decreased in the stomach mucosa (by $23 \pm 10\%$; $P < 0.05$), in the stomach muscularis (by $48 \pm 16\%$; $P < 0.05$), and in the jejunal mucosa (by $27 \pm 9\%$; $P < 0.05$), whereas no significant changes were seen in the colon.

Conclusion: Vasopressin decreased regional flow in the superior mesenteric artery and microcirculatory blood flow in the upper gastrointestinal tract. This reduction in flow and a concomitant increase in the jejunal mucosa-to-arterial carbon dioxide gap suggest compromised mucosal blood flow in the upper gastrointestinal tract in septic pigs receiving low-dose vasopressin.

HYPOTENSION with insufficient blood flow to the gastrointestinal tract during septic shock may provoke gut mucosal barrier dysfunction and multiple organ failure. Therefore, vasoconstrictors are frequently used together with fluid therapy to increase blood pressure in septic patients. In recent years, vasopressin has emerged as an alternative therapeutic option in septic shock[1–4] and

vasodilatory shock,[5,6] because of limited response to catecholamine vasoconstrictors and the fact that endogenous vasopressin concentrations are sometimes inappropriately low in septic shock.[7]

It is not clear whether increased perfusion pressure from vasopressin is beneficial for gastrointestinal blood flow in septic shock. A few clinical trials on patients in septic[1–3] or vasodilatory[5] shock suggest beneficial effects of vasopressin for systemic hemodynamics, but increase in liver enzymes and bilirubin have been observed.[5] It is also known that the potent pressor action of vasopressin can lead to ischemic injury in the gastrointestinal tract[8,9] as well as in other organs.[10–13] Until now, no prospective randomized multicenter outcome trials have been published on the use of vasopressin in septic shock, but a recent multicenter clinical trial using a nitric oxide inhibitor to raise blood pressure resulted in increased mortality.[14]

Conflicting results have been reported by several groups regarding the effects of vasopressin on the hepatosplanchnic circulation in pigs.[15–18] All of these studies were performed in endotoxin shock but not bacterial septic shock, and none of them focused on microcirculatory blood flow in the intestine. Therefore, little is known about the effects of vasopressin on the intestinal microcirculation in septic shock. A recent experimental study in septic rats[19] suggests that vasopressin may have deleterious effects on microcirculatory flow in the gut in septic shock. Two other studies in hamsters show intense vasoconstriction in microcirculatory blood flow[20] resulting in decreased tissue oxygenation.[21]

We hypothesized that therapy with vasopressin could hamper microcirculatory blood flow in the gastrointestinal tract in septic shock. The aim of the study was to test the effects of a clinically relevant dose of vasopressin on systemic blood flow, regional flow in the superior mesenteric artery, and microcirculatory blood flow measured simultaneously in the mucosa and muscularis layers of the stomach, small bowel, and colon in anesthetized septic pigs.

Materials and Methods

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

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Thirty-two domestic pigs (weight, 28–32 kg) were fasted overnight but were allowed free access to water. The pigs were sedated with intramuscular ketamine (20 mg/kg) and xylazine (2 mg/kg). After induction of anesthesia with intravenous metomidate (5 mg/kg) and azaperan (2 mg/kg), the pigs were orally intubated and ventilated with oxygen in air (fraction of inspired oxygen = 0.40). Inhaled concentration of oxygen was continuously monitored with a multi-gas analyzer (S/5 Critical Care Monitor; Datex-Ohmeda, GE Health Care, Helsinki, Finland). 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_2O (Servo 900C; Siemens, Solna, Sweden). 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 (Pa_{CO_2}) at 40 $\pm$ 4 mmHg (5.3 kPa). The stomach was emptied with an orogastric tube.

Surgical Preparation

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

With the pig in supine position, a midline laparotomy was performed. A catheter was inserted into the urinary bladder for drainage of urine. A second catheter was inserted into the mesenteric vein for blood sampling. The superior mesenteric artery was identified close to its origin from the aorta. After dissection to free the vessel from the surrounding tissues, a precalibrated 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 probe (LDF; Oxford Optronix, Oxford, United Kingdom) was sutured to the gastric mucosa in the corpus region for measurements of microcirculatory blood flow in the mucosa. Through small antimesenteric incisions in the jejunum and ascending colon, the second and third LDF flow probes were sutured to the mucosa of the jejunum and colon at the respective sites. The antimesenterial incision in the jejunum also allowed controlled positioning of a tonometer tube (TRIP Sigmoid catheter; Datex-Ohmeda, GE Health Care). 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. Additional LDF probes were sutured on the serosal side of the stomach, jejunum, and colon for measurements of microcirculatory blood flow in the muscularis. All LDF probes were attached with six microsutures to ensure continuous and steady contact with the tissue under investigation, preventing motion disturbance from respiration and gastrointestinal movements throughout the experiment. The signals of the LDF probes were visualized on a computer monitor. If the signal quality of a probe was poor, the probe's position was corrected immediately. Once 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° $\pm$ 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 stabilize for 45–60 min.

Groups

A full factorial design was used. Consequently, the animals were randomly assigned into one of the following four groups:

Group C (n = 8), nonseptic control group: After baseline measurements, lactated Ringer's solution was given at a rate of 20 ml · $kg^{-1} · h^{-1}$ throughout the experiment.

Group V (n = 8), nonseptic vasopressin control group: After baseline measurements, the animals were treated the same way as animals in group C, except that at 300 min, a continuous intravenous infusion of ornithin-8-vasopressin (POR-8®; Ferring, Wallisellen, Switzerland) at a rate of 0.06 U · $kg^{-1} · h^{-1}$ was started and continued for another 180 min.

Group S (n = 8), septic control group: After baseline measurements, the animals were exposed to fecal peritonitis by instillation of 20 g autologous feces suspended in 200 ml warm (37°C) 5% dextrose through the abdominal tubes. Simultaneously, intravenous lactated Ringer's solution was discontinued. After 240 min of peritonitis and development of septic shock, an intravenous fluid bolus (4% gelatin, Physiogel®, molecular weight 30 kd; B. Braun Medical, Sempach, Switzerland) of 15 ml/kg was given over 45 min followed by intravenous lactated Ringer's solution at a rate of 20 ml · $kg^{-1} · h^{-1}$ until the end of the study.

Group SV (n = 8), septic test group treated with vasopressin: The animals were treated the same way as in

Table 1. Systemic, Regional, and Microcirculatory Data during the Development of Septic Shock—before Vasopressin Administration

	Control (Group C)			Vasopressin (Group V)		
	0 min	240 min	300 min	0 min	240 min	300 min
Heart rate, beats/min	84 ± 10	119 ± 13*	126 ± 12*	92 ± 10	122 ± 27*	125 ± 19*
MAP, mmHg	87 ± 10	80 ± 13	80 ± 12	88 ± 14	79 ± 10	80 ± 9
CI, ml · kg^{-1} · min^{-1}	112 ± 12	143 ± 23*	148 ± 31*	119 ± 20	132 ± 25	147 ± 26*
SVRI, mmHg · kg^{-1} · min^{-1}	729 ± 157	524 ± 121*	514 ± 134*	693 ± 126	553 ± 81	512 ± 90*
CVP, mmHg	6.6 ± 1.3	6.9 ± 1.4	7.0 ± 1.4	6.1 ± 1.6	6.5 ± 1.3	6.5 ± 1.4
PAP, mmHg	16.6 ± 1.5	19.9 ± 3.7	20.5 ± 3.6	17.8 ± 1.7	19.9 ± 1.7	21.6 ± 2.7
PCWP, mmHg	6.1 ± 0.8	6.6 ± 0.5	6.4 ± 0.9	5.6 ± 1.2	5.8 ± 1.4	5.6 ± 1.4
SMAI, ml · kg^{-1} · min^{-1}	25 ± 6	25 ± 6	25 ± 5	27 ± 6	24 ± 5	25 ± 5
Svo$_2$, %	57 ± 4	64 ± 5.0*	66 ± 5*	55 ± 7	61 ± 11	64 ± 10
Pco$_2$ gap, mmHg	28 ± 4	29 ± 5	28 ± 5	26 ± 7	27 ± 5	28 ± 5
MBF gastric mucosa, %	100 ± 0	109 ± 14	110 ± 16	100 ± 0	102 ± 17	104 ± 17
MBF jejunal mucosa, %	100 ± 0	102 ± 9	98 ± 15	100 ± 0	100 ± 14	100 ± 11
MBF colon mucosa, %	100 ± 0	99 ± 9	99 ± 12	100 ± 0	91 ± 5	96 ± 8
MBF gastric muscularis, %	100 ± 0	108 ± 20	103 ± 9	100 ± 0	102 ± 14	106 ± 17
MBF jejunal muscularis, %	100 ± 0	105 ± 20	97 ± 20	100 ± 0	102 ± 18	90 ± 16
MBF colon muscularis, %	100 ± 0	105 ± 37	97 ± 34	100 ± 0	104 ± 24	94 ± 12

Data are presented as mean ± SD. All microcirculatory blood flows were set at 100% at t = 0 min. Septic shock was induced in groups S and SV at t = 0; at t = 240 min, intravenous fluids were administered to convert hypodynamic septic shock to normodynamic/hyperdynamic sepsis. t = 300 min was after fluid administration but before vasopressin infusion. Group C served as nonseptic control, group V served as nonsepsic vasopressin control, group S served as septic control group, and group SV served as septic vasopressin intervention group. Because of small sample size, the smallest P value used in the table was $P < 0.05$.

* $P < 0.05$ compared with baseline.   † $P < 0.05$ compared with 240 min of peritonitis.

CI = cardiac index; CVP = central venous pressure; MAP = mean arterial blood pressure; MBF = microcirculatory blood flow; PAP = mean pulmonary artery pressure; Pco$_2$ gap = jejunum mucosa to arterial carbon dioxide gradient; PCWP = mean pulmonary artery occlusion pressure; SMAI = superior mesenteric artery flow index; Svo$_2$ = mixed venous oxygen saturation; SVRI = systemic vascular resistance index.

the septic control group (group S), except that at 300 min after induction of septic shock, a continuous intravenous infusion of ornithin-8-vasopressin at a rate of 0.06 U · kg^{-1} · h^{-1} was started and continued for 180 min.

Experimental Design

Four hours after induction of peritonitis, the animals in groups S and SV were given an intravenous infusion of 15 ml/kg gelatin, 4% (Physiogel®), over 45 min followed by continuous infusion of 20 ml · kg^{-1} · h^{-1} lactated Ringer's solution. The purpose of this fluid resuscitation was to convert hypodynamic septic shock to normodynamic/hyperdynamic septic shock.

Three hundred minutes after baseline measurements, animals in groups V and SV were infused with vasopressin for 180 min. Four hundred eighty minutes after the first measurement, all animals were killed with an intravenous injection of 20 mmol potassium chloride.

Measurements

Mean arterial blood pressure (MAP, mmHg), central venous pressure (CVP, mmHg), mean pulmonary artery pressure (mmHg), and pulmonary capillary wedge pressure (mmHg) were recorded with quartz pressure transducers. Heart rate was measured from the electrocardiogram. Heart rate, MAP, pulmonary artery pressure, and CVP were displayed continuously on a multimodular monitor (S/5 Critical Care Monitor; Datex-Ohmeda, Du-

isburg, Germany). Cardiac output (l/min) was measured with a continuous thermodilution method (Vigilance CCO Monitor; Edwards Lifescience, Irvine, CA).

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 (mmHg), and inspired and expired oxygen fractions (mmHg) were monitored continuously throughout the study.

Microcirculatory blood flow was continuously monitored in the mucosa and the muscularis of the stomach, jejunum, and colon using a multichannel laser Doppler flowmeter system (Oxford Optronix). A detailed description of the theory of laser Doppler flowmetry operation and practical details of laser Doppler flowmetry measurements have been published before.[22,23] The LDF data were acquired online with a sampling rate of 10 Hz *via* a multichannel interface (Mac Paq MP 100; Biopac Systems Inc., Goleta, CA) with acquisition software (Acqknowledge 3.2.1.; Biopac Systems Inc.) and saved on a portable computer.

Laser Doppler flowmeters are not calibrated to measure absolute blood flow but indicate microcirculatory blood flow in arbitrary perfusion units. Because of a relatively large variability of baseline values, the results are usually expressed as changes relative to baseline,[24–27] and that was also the case in this study. The quality of the laser Doppler flowmetry signal was controlled on-line by visualizing it on a computer screen, so

Table 1. Continued.

Sepsis (Group S)			Sepsis–Vasopressin (Group SV)		
0 min	240 min	300 min	0 min	240 min	300 min
95 ± 17	148 ± 46*	120 ± 23	89 ± 12	151 ± 20*	126 ± 10*
86 ± 10	52 ± 7*	68 ± 9*†	82 ± 13	55 ± 11*	74 ± 9
129 ± 24	66 ± 9*	174 ± 22*†	115 ± 11	59 ± 12*	168 ± 46*†
644 ± 170	749 ± 147	352 ± 71*†	667 ± 123	879 ± 220*	424 ± 125*†
5.9 ± 1.6	3.8 ± 0.7*	6.5 ± 1.2†	5.5 ± 1.3	3.5 ± 1.2*	7.0 ± 1.6*†
19 ± 1.8	17 ± 1.5	22.4 ± 2.7†	15.6 ± 1.9	16.4 ± 2.6	22.6 ± 3.5*†
6.1 ± 1.4	4.6 ± 1.1	7.6 ± 1.2†	5.6 ± 1.5	3.9 ± 0.9*	6.4 ± 1.3†
24 ± 6	13 ± 3*	36 ± 9*†	24 ± 2	13 ± 3*	34 ± 9*†
59 ± 5	34 ± 7*	59 ± 5†	56 ± 6	40 ± 4*	61 ± 6†
26 ± 8	53 ± 9*	35 ± 7*†	26 ± 5	53 ± 9*	34 ± 7†
100 ± 0	75 ± 9*	102 ± 7†	100 ± 0	65 ± 13*	108 ± 16†
100 ± 0	84 ± 11	108 ± 12†	100 ± 0	83 ± 13	105 ± 12†
100 ± 0	80 ± 13*	114 ± 14†	100 ± 0	71 ± 12*	113 ± 20†
100 ± 0	68 ± 9*	124 ± 30†	100 ± 0	62 ± 13*	118 ± 30†
100 ± 0	53 ± 16*	66 ± 10*	100 ± 0	47 ± 13*	69 ± 19*†
100 ± 0	44 ± 13*	68 ± 26	100 ± 0	47 ± 20*	68 ± 11*

that motion artifacts and noise due to inadequate probe attachment could be immediately detected and corrected before the measurements started.

Blood flow in the superior mesenteric artery was continuously measured in all animals throughout the experiments with ultrasonic transit time flowmetry (ml/min) using an HT 206 flowmeter (Transonic Systems Inc., Ithaca, NY).

Fig. 1. Blood flow in the superior mesenteric artery (SMAI, ml · kg^{-1} · min^{-1}; *A* and *C*) and mucosal–arterial carbon dioxide (Pco$_2$) gap (mmHg; *B* and *D*). After baseline measurements (t = 0 min), animals in both nonseptic groups (n = 8 in each; *A* and *B*) were observed during 300 min. Animals in both septic groups (n = 8 in each; *C* and *D*) were subjected to fecal peritonitis and fluid resuscitation. At t = 300 min, a continuous intravenous infusion of vasopressin (0.06 U · kg^{-1} · h^{-1}) was started in the vasopressin and vasopressin–sepsis groups. The nonseptic and septic control groups received intravenous saline only. The figures represent the results (mean ± SD) at t = 300 min and later. * $P < 0.05$ compared with t = 300 min. # $P < 0.05$ compared with sepsis–vasopressin group.
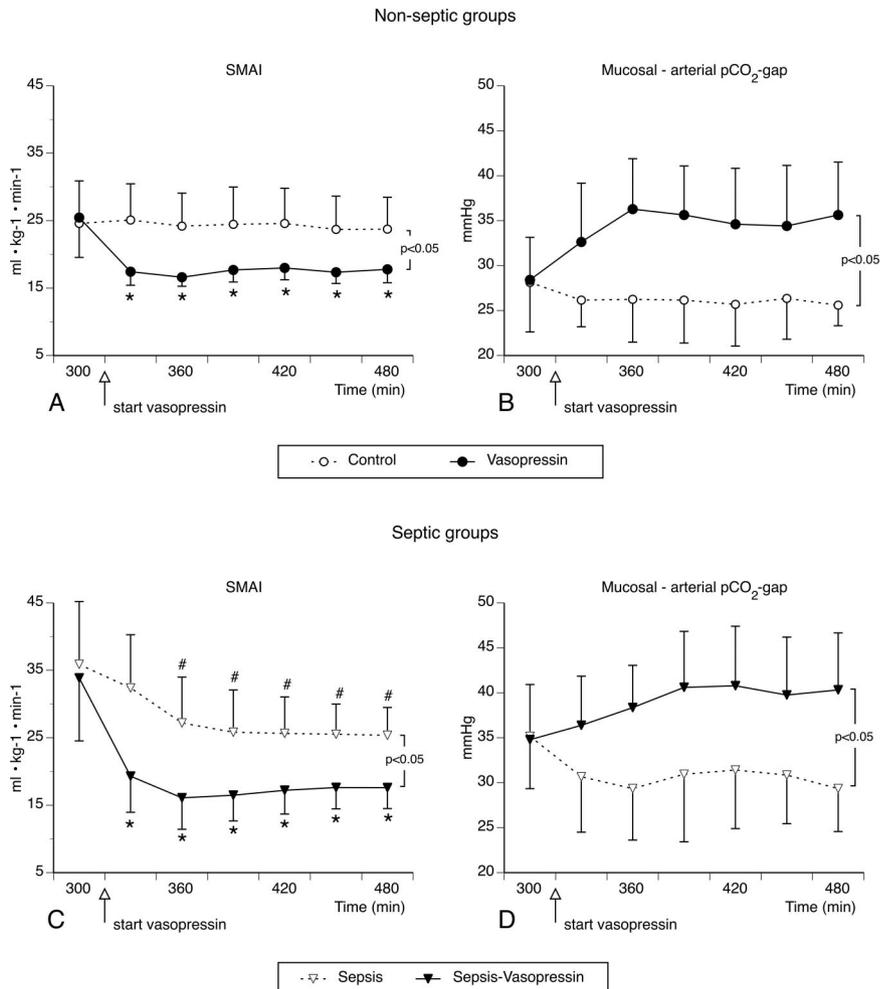
Table 2. Systemic, Regional, and Microcirculatory Data in the Four Groups

	Control (Group C)			Vasopressin (Group V)		
	300 min	360 min	480 min	300 min	360 min	480 min
Heart rate, beats/min	126 ± 24	131 ± 26	136 ± 29	125 ± 15	$90 \pm 8\ddagger$	$104 \pm 14*\ddagger$
MAP, mmHg	80 ± 12	80 ± 13	77 ± 13	80 ± 9	$97 \pm 9\ddagger$	$100 \pm 11*\ddagger$
CI, ml $\cdot$ kg^{-1} $\cdot$ min^{-1}	148 ± 31	147 ± 33	149 ± 34	147 ± 27	$96 \pm 13\ddagger$	$118 \pm 12*\ddagger$
SVRI, mmHg $\cdot$ kg^{-1} $\cdot$ min^{-1}	519 ± 128	537 ± 226	506 ± 220	512 ± 90	$944 \pm 176\ddagger$	$793 \pm 93*\ddagger$
CVP, mmHg	7.0 ± 1.4	6.9 ± 1.5	7.5 ± 1.3	6.5 ± 1.4	$7.9 \pm 1.3\ddagger$	$7.1 \pm 1.3\ddagger$
PAP, mmHg	20.5 ± 3.6	21.5 ± 5.0	23.5 ± 5.7	22 ± 2.7	21 ± 3.3	24 ± 5.7
PCWP, mmHg	6.4 ± 0.9	6.6 ± 0.5	6.4 ± 0.9	5.6 ± 1.4	$7.9 \pm 1.4\ddagger$	$7.5 \pm 1.8*\ddagger$
SMAIR, mmHg $\cdot$ kg^{-1} $\cdot$ min^{-1}	$3{,}083 \pm 832$	$3{,}169 \pm 833$	$3{,}061 \pm 923$	$2{,}953 \pm 475$	$5{,}373 \pm 657\ddagger$	$5{,}310 \pm 847*\ddagger$
MBF colon mucosa	99 ± 12	95 ± 8	101 ± 15	96 ± 8	$83 \pm 6\ddagger$	$87 \pm 6*$
MBF colon muscularis	97 ± 34	91 ± 32	85 ± 34	94 ± 12	$67 \pm 20\ddagger$	$57 \pm 24\ddagger$

Data are presented as mean $\pm$ SD. All microcirculatory blood flows were set at 100% at t = 0 min and are presented as percent of the baseline. Septic shock was induced in groups S and SV at t = 0; at t = 240 min, intravenous fluids were administered to convert hypodynamic septic shock to normodynamic/ hyperdynamic sepsis. t = 300 min was after fluid administration but before vasopressin infusion. A continuous vasopressin infusion of 0.06 U $\cdot$ kg^{-1} $\cdot$ h^{-1} was given after t = 300 min in groups V and SV. Group C served as nonseptic control, group V served as nonseptic vasopressin control, and group S served as septic control group. Because of small sample size, the smallest P value used in the table was $P < 0.05$.

* $P < 0.05$, time–group interaction for nonseptic groups. † $P < 0.05$, time–group interaction for septic groups. ‡ $P < 0.05$, changes within group compared with 300 min (before vasopressin in groups V and SV).

CI = cardiac index; CVP = central venous pressure; MAP = mean arterial blood pressure; MBF = microcirculatory blood flow; PAP = mean pulmonary artery pressure; PCWP = mean pulmonary artery occlusion pressure; SMAIR = superior mesenteric artery flow resistance index; SVRI = systemic vascular resistance index.
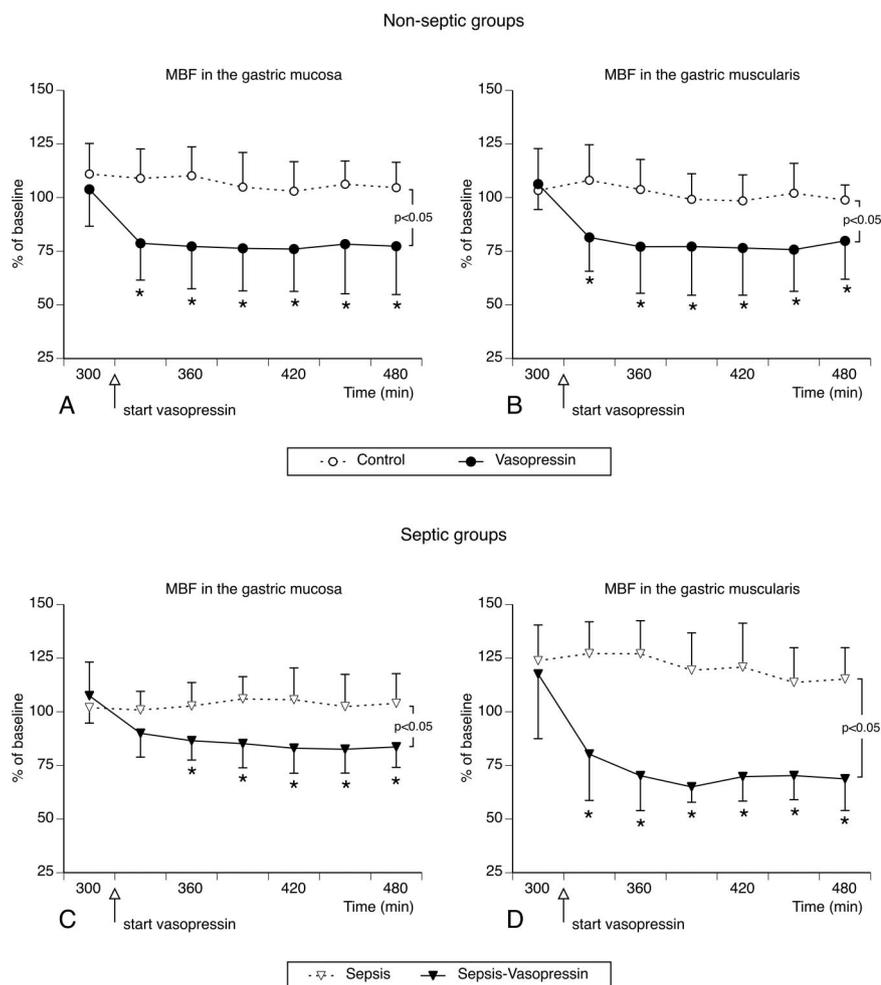

Fig. 2. **Relative changes of microcirculatory blood flow (MBF, % of baseline) in the mucosa (*A* and *C*) and muscularis (*B* and *D*) of the stomach. After baseline measurements (t = 0 min, 100%), animals in both nonseptic groups (n = 8 in each; *A* and *B*) were observed during 300 min. Animals in both septic groups (n = 8 in each; *C* and *D*) were subjected to fecal peritonitis and fluid resuscitation. At t = 300 min, a continuous intravenous infusion of vasopressin (0.06 U $\cdot$ kg^{-1} $\cdot$ h^{-1}) was started in the vasopressin and vasopressin–sepsis groups. The nonseptic and septic control groups received intravenous saline only. The figures represent the results (mean $\pm$ SD) at t = 300 min and later. * $P < 0.05$ compared with t = 300 min.**

Table 2. Continued

	Sepsis (Group S)			Sepsis–Vasopressin (Group SV)	
300 min	360 min	480 min	300 min	360 min	480 min
120 ± 23	135 ± 26	155 ± 28‡	126 ± 10	106 ± 21	117 ± 22†
68 ± 9	67 ± 9	67 ± 7	74 ± 9	100 ± 22‡	95 ± 20†‡
174 ± 22	166 ± 20	179 ± 14	168 ± 47	107 ± 13‡	125 ± 27†‡
352 ± 72	373 ± 63	340 ± 52	424 ± 126	885 ± 257‡	732 ± 220†‡
7.4 ± 1.2	6.4 ± 0.7	6.5 ± 1.2	7.0 ± 1.6	6.5 ± 2.2	6.4 ± 2
22.4 ± 2.7	20.5 ± 5.1	19.6 ± 3.5	22.6 ± 3.5	18.6 ± 2.2‡	19.6 ± 2.9
7.6 ± 1.2	6.4 ± 1.2	6.3 ± 1.7	6.4 ± 1.3	6.1 ± 1.6	5.6 ± 2
1,817 ± 673	2,397 ± 763	2,453 ± 581	2,098 ± 608	6,369 ± 2,349‡	5,310 ± 1,918†‡
114 ± 14	97 ± 10	93 ± 13	113 ± 20	98 ± 17	101 ± 20
68 ± 26	59 ± 26	64 ± 35	68 ± 11	50 ± 13	46 ± 14†‡

The jejunal intramucosal carbon dioxide pressure was measured with air tonometry (Tonocap® Monitor; Datex-Ohmeda, Helsinki, Finland). The jejunal mucosal-to-arterial carbon dioxide pressure gap was calculated at each measurement point.[28] It has previously been shown that the mucosal carbon dioxide pressure gap may reflect the mucosal microcirculatory perfusion more adequately than the calculated intramucosal pH.[28]

In all animals, arterial and mixed venous and mesenteric venous blood samples were withdrawn at each measurement point from the indwelling catheters and immediately analyzed in a human blood gas analyzer (ABL 620; Radiometer, Copenhagen, Denmark) for oxygen pressure (mmHg), carbon dioxide pressure (mmHg), pH, lactate (mM), oxygen saturation (So_2, %), base excess, and total hemoglobin concentration (hemoglobin, g/dl). All values were adjusted to body temperature.

Cardiac index (CI, ml · kg^{-1} · min^{-1}), superior mesen-

Non-septic groups

Fig. 3. Relative changes of microcirculatory blood flow (MBF, % of baseline) in the mucosa (*A* and *C*) and muscularis (*B* and *D*) of the jejunum. After baseline measurements (t = 0 min, 100%), animals in both nonseptic groups (n = 8 in each; *A* and *B*) were observed during 300 min. Animals in both septic groups (n = 8 in each; *C* and *D*) were subjected to fecal peritonitis and fluid resuscitation. At t = 300 min, a continuous intravenous infusion of vasopressin (0.06 U · kg^{-1} · h^{-1}) was started in the vasopressin and vasopressin–sepsis groups. The nonseptic and septic control groups received intravenous saline only. The figures represent the results (mean ± SD) at t = 300 min and later. * *P* < 0.05 compared with t = 300 min.
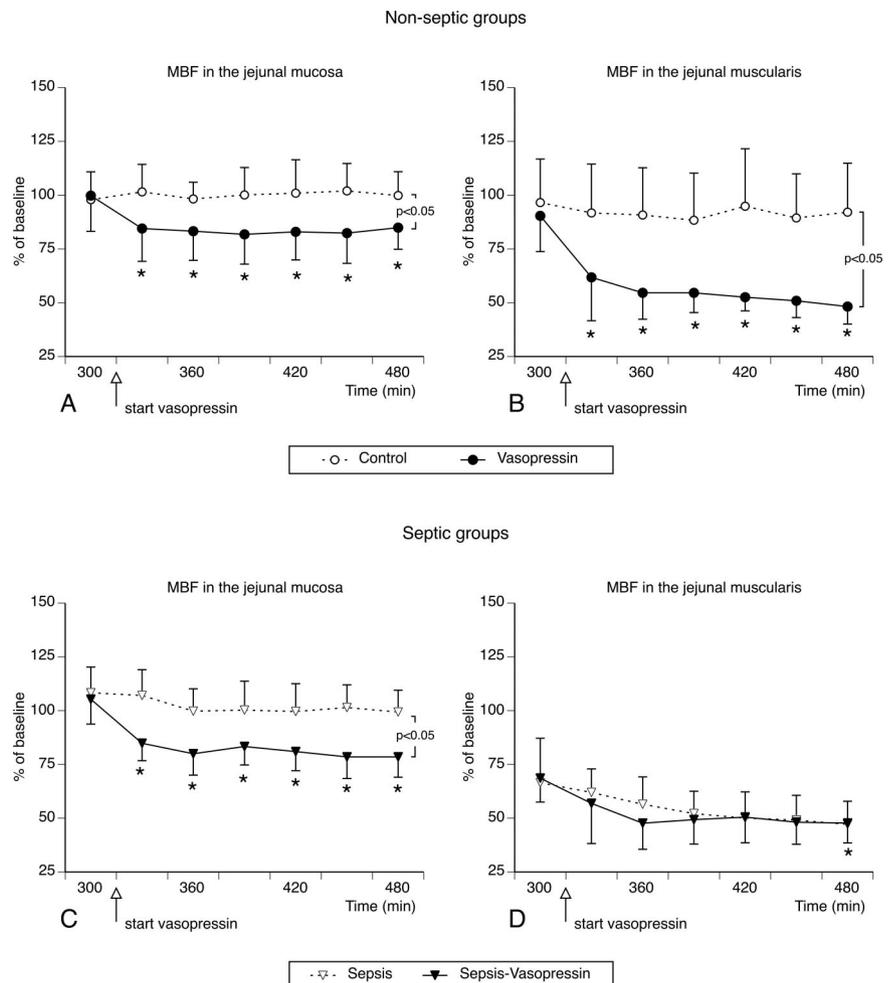
Table 3. Arterial, Mixed Venous, and Mesenteric Venous Blood Gas Data in the Four Groups

	Control (Group C)			Vasopressin (Group V)		
	300 min	360 min	480 min	300 min	360 min	480 min
Pa_{O_2}, mmHg	162 ± 19	156 ± 21	152 ± 25	161 ± 16	143 ± 29‡	141 ± 21‡
Pa_{CO_2}, mmHg	41 ± 1.6	41 ± 2.9	41 ± 4.3	39 ± 2.1	40 ± 3.0	41 ± 4.1
pH art.	7.45 ± 0.03	7.45 ± 0.03	7.44 ± 0.04	7.44 ± 0.02	7.44 ± 0.04	7.44 ± 0.05
pH mes.	7.40 ± 0.03	7.39 ± 0.03	7.39 ± 0.04	7.40 ± 0.02	7.36 ± 0.03	7.37 ± 0.05
Art. lactate, mM	0.99 ± 0.15	0.96 ± 0.12	0.95 ± 0.17	0.98 ± 0.12	1.1 ± 0.24	1.11 ± 0.26*
Mes. lactate, mM	1.13 ± 0.17	1.09 ± 0.17	1.1 ± 0.17	1.11 ± 0.15	1.28 ± 0.2	1.3 ± 0.2*
Do_2, ml · kg^{-1} · min^{-1}	17.7 ± 2.6	17.5 ± 2.7	18.7 ± 2.6	16.2 ± 2.7	9.4 ± 1.9‡	11.4 ± 1.8*‡
Vo_2, ml · kg^{-1} · min^{-1}	6.1 ± 0.8	6 ± 1.1	6.2 ± 1.1	5.7 ± 0.7	5.6 ± 1.2	5.7 ± 1.1
Svo_2, %	66 ± 5	65 ± 6	66 ± 5	64 ± 9	42 ± 9‡	49 ± 10*‡
Mes. Do_2, ml · kg^{-1} · min^{-1}	2.9 ± 0.6	2.9 ± 0.7	3.0 ± 0.6	2.8 ± 0.5	1.6 ± 0.2‡	1.7 ± 0.2*‡
Mes. Vo_2, ml · kg^{-1} · min^{-1}	0.85 ± 0.13	0.88 ± 0.17	0.94 ± 0.15	0.86 ± 0.10	0.75 ± 0.11	0.67 ± 0.12

Data are presented as mean ± SD. Septic shock was induced in groups S and SV at t = 0; at t = 240 min, intravenous fluids were administered to convert hypodynamic septic shock to normodynamic/hyperdynamic sepsis. t = 300 min was after fluid administration but before vasopressin infusion. A continuous vasopressin infusion of 0.06 U · kg^{-1} · h^{-1} was given after t = 300 min in groups V and SV. Group C served as nonseptic control, group V served as nonseptic vasopressin control, and group S served as septic control group. Because of small sample size, the smallest P value used in the table was $P < 0.05$.

* $P < 0.05$, time–group interaction for nonseptic groups.   † $P < 0.05$, time–group interaction for septic groups.   ‡ $P < 0.05$, changes within group compared with 300 min.

Art. lactate = arterial lactate concentration; Do_2 = systemic oxygen delivery; mes. Do_2 = mesenteric (splanchnic) oxygen delivery; mes. lactate = mesenteric venous (splanchnic) lactate concentration; mes. Vo_2 = mesenteric (splanchnic) oxygen consumption; $Paco_2$ = arterial carbon dioxide tension; Pao_2 = arterial oxygen tension; pH art. = arterial pH; pH mes. = mesenteric (splanchnic) pH; Svo_2 = mixed venous oxygen saturation; Vo_2 = systemic oxygen consumption.

teric artery flow index (SMAI, ml · kg^{-1} · min^{-1}), systemic vascular resistance index (SVRI, mmHg · kg^{-1} · min^{-1}), and superior mesenteric artery resistance index (SMARI, mmHg · kg^{-1} · min^{-1}) were indexed to body weight. Systemic vascular resistance index was calculated as SVRI = (MAP − CVP)/CI,[24,25] and superior mesenteric artery resistance index was calculated as SMARI = (MAP − CVP)/SMAI.

Systemic oxygen delivery index (Do_2I, ml · kg^{-1} · min^{-1}), systemic oxygen consumption index (Vo_2I, ml · kg^{-1} · min^{-1}), and the correspondent mesenteric (splanchnic) variables (mes-Do_2I and mes-Vo_2I, ml · kg^{-1} · min^{-1}) were calculated using the following formulas:

Systemic (total body) oxygen delivery index (sys-Do_2I) = (CI × Cao_2),

where Cao_2 is the arterial oxygen content;

Systemic (total body) oxygen consumption index (sys-Vo_2I) = (CI × (Cao_2 − Cvo_2)),

where Cvo_2 is the mixed venous oxygen content;

Mesenteric (splanchnic) oxygen delivery index (mes-Do_2I) = SMAI × Cao_2;

Mesenteric (splanchnic) oxygen consumption index (mes-Vo_2I) = SMAI × (Cao_2 − Cmo_2),

where Cmo_2 is the mesenteric vein oxygen content; and

Oxygen content (ml · O_2/ml blood) = ((Po_2 × 0.0031) + (hemoglobin × So_2 × 1.36))/100,

where Po_2 is the partial pressure of oxygen and So_2 is oxygen saturation.

Statistical Analysis

The data are presented as mean ± SD for the four study groups. Differences between the four groups were assessed by analysis of variance for repeated measurements using one dependent variable, one grouping factor (controls, controls with vasopressin, sepsis, sepsis with vasopressin), and one within-subject factor (time). When there was a significant group–time interaction, the effect of vasopressin was assessed separately in the two groups with and without sepsis by again using analysis of variance for repeated measurements. In this design, a significant time–group interaction is interpreted as an effect of vasopressin. Finally, the effects of vasopressin in the groups with and without sepsis were compared by calculating the area under the variable–time curve during vasopressin infusion (Mann–Whitney test). The area under the variable–time curve was calculated as the sum of the differences between each measurement and the baseline before vasopressin (300 min) times time (180 min). Calculations for microcirculatory blood flow were performed using changes relative to baseline (t = 0 min). Absolute values were used for all other calculations. Changes within a group were analyzed with an analysis of variance for repeated measurements followed by a Tukey *post hoc* test to correct for multiple comparisons. $P < 0.05$ was considered significant. All of the P values are two-tailed and represent the calculated P value for the time–group interaction between septic groups (SV and S) and nonseptic groups (V and C).

Table 3. Continued

Sepsis (Group S)			Sepsis–Vasopressin (Group SV)		
300 min	360 min	480 min	300 min	360 min	480 min
163 ± 17	163 ± 16	161 ± 29	165 ± 10	157 ± 21	160 ± 13
43 ± 2.0	42 ± 2.4	42 ± 3.4	42 ± 3.1	42 ± 3.7	42 ± 3.5
7.43 ± 0.02	7.44 ± 0.02	7.43 ± 0.02	7.43 ± 0.04	7.43 ± 0.04	7.43 ± 0.04
7.39 ± 0.02	7.38 ± 0.02	7.37 ± 0.02	7.37 ± 0.04	7.35 ± 0.04	7.35 ± 0.04
1.36 ± 0.48	1.11 ± 0.31	1.1 ± 0.3	1.46 ± 0.25	1.25 ± 0.17	1.20 ± 0.16
1.56 ± 0.41	1.35 ± 0.24	1.34 ± 0.22	1.6 ± 0.38	1.46 ± 0.23	1.46 ± 0.2
17.1 ± 2.1	17.8 ± 3.3	20.0 ± 2.8	18.9 ± 5.5	12.8 ± 2.2‡	15.2 ± 3.6†‡
7.3 ± 1.3	7.3 ± 1.5	7.7 ± 0.5†	7.5 ± 1.8	6.0 ± 0.9	6.2 ± 1.1
59 ± 5	59 ± 5	61 ± 5*	61 ± 6	53 ± 7	58 ± 5†
3.5 ± 0.9	2.9 ± 0.7‡	2.8 ± 0.5‡	3.9 ± 1.3	1.9 ± 0.6‡	2.1 ± 0.4†‡
1.01 ± 0.28	0.99 ± 0.35	1.01 ± 0.33	1.07 ± 0.34	0.87 ± 0.33	0.87 ± 0.12‡

Results

One series of laser Doppler flow measurements on the gastric muscularis and two on the colon muscularis were excluded from data analysis because of loss of optical coupling to the tissue. All other results were included in the final data analysis.

During the first 300 min, all of the animals in groups C and V remained hemodynamically stable. On the other hand, all animals in group S and SV first developed classic signs of hypodynamic septic shock, with low MAP, low CI, and decreased microcirculatory blood flow, followed by signs of normodynamic septic shock after fluid administration (table 1). The changes in systemic and regional hemodynamics during this period were comparable to those published in previous studies from our laboratory.[24,29]

Administration of vasopressin in the nonseptic animals (group V) resulted in a significant increase in MAP (by 25 ± 15%) and SVRI (by 87 ± 30%), whereas heart rate decreased by 27 ± 12%, CI decreased by 34 ± 10%, and superior mesenteric artery flow decreased by 32 ± 13% ($P < 0.05$ for all compared with group C; fig. 1 and table 2). Microcirculatory blood flow decreased during vasopressin administration in all parts of the gastrointestinal tract in group V ($P < 0.05$ for all compared with group C; figs. 2 and 3), whereas in the untreated controls (group C), all variables remained virtually unchanged throughout the study.

In septic animals, administration of vasopressin (group SV) was followed by an increase in MAP (by 36 ± 16%) and a concomitant decrease in heart rate (by 16 ± 10%) and CI (by 33 ± 13%), indicating a significantly increased SVRI (by 108 ± 36%; table 2). Although SVRI decreased slightly with time, heart rate, MAP, CI, and SVRI remained significantly different compared with the septic controls ($P < 0.05$ for all).

In septic animals, regional blood flow in the superior mesenteric artery decreased by 51 ± 16% after start of vasopressin infusion and remained low throughout the study (table 2 and fig. 1). Mesenteric vascular resistance increased by 300 ± 97% (table 2) after the start of vasopressin infusion, and mesenteric oxygen delivery decreased from 3.9 ± 1.2 ml · kg^{-1} · min^{-1} to 1.9 ± 0.6 ml · kg^{-1} · min^{-1}. These changes were more pronounced as compared with the septic controls ($P < 0.05$ for variables between the groups S and SV; table 3). Therefore, vasopressin had more pronounced effects on the mesenteric circulation than on the systemic circulation, and the effect on mesenteric circulation was stronger in septic than in control animals receiving vasopressin. On the other hand, systemic circulation was better preserved in septic than in control animals receiving vasopressin. Vasopressin administration decreased microcirculatory blood flow in septic animals predominantly in the upper gastrointestinal tract. In the stomach, microcirculatory blood flow in the mucosa and muscularis decreased by 23 ± 10 and 48 ± 16%, respectively, after vasopressin administration ($P < 0.05$ for both compared to group S; fig. 2). In the jejunum, microcirculation in the mucosa decreased by 27 ± 9% ($P < 0.05$ compared with group S) in the septic animals treated with vasopressin. In the muscularis of the jejunum, microcirculation was already decreased before administration of vasopressin, with 62 ± 15% of the flow recorded before induction of peritonitis (fig. 3). Vasopressin had no further effect on microcirculatory blood flow in the jejunal muscularis. In the colon mucosa, microcirculatory blood flow was virtually unchanged during vasopressin administration. In septic animals, the blood flow of the colon muscularis was already decreased, with 68 ± 10% of the flow measured before induction of peritonitis. Vasopressin administration resulted in a further reduction of microcirculatory blood flow of 22 ± 13% ($P < 0.05$ compared with group S; table 2).

In the jejunum, the mucosal-to-arterial carbon dioxide gap increased from 35 ± 5 mmHg before vasopressin to 40 ± 6 mmHg during administration of vasopressin. During the same period, the carbon dioxide gap in the

septic shock group decreased from 35 ± 6 mmHg to 29 ± 5 mmHg. This resulted in a significantly higher carbon dioxide pressure gap in group SV compared with group S ($P < 0.05$; fig. 1).

Metabolic parameters are shown in table 3. Administration of vasopressin resulted in a decrease in mesenteric venous saturation from $74 \pm 6\%$ to $51 \pm 6\%$ and an increase in the mesenteric oxygen extraction from 28 ± 5 to $51 \pm 6\%$. Both variables were significantly different compared with group S ($P < 0.05$; fig. 4). The effect of vasopressin administration on other metabolic variables in septic animals, such as mesenteric vein pH and mesenteric lactate, was not as pronounced. Compared with the animals in group S, mesenteric pH tended to be lower, whereas mesenteric lactate was increased (table 3).

Effects of vasopressin in the groups with and without septic shock were compared by calculating the area under the variable–time curve. Values were as follows (controls/vasopressin *versus* sepsis/vasopressin): SMAI: -718 *versus* $-1,483$; muscularis laser Doppler flow: $-3,294$ *versus* $-1,671$; mixed venous saturation: -741 *versus* -211; arterial lactate: 6 *versus* -11; mesenteric venous lactate: 7 *versus* -6.

Discussion

This study in anesthetized septic pigs was conducted in full factorial design to measure the effects of vasopressin on the microcirculation in the stomach, small intestine, and colon. The effects of vasopressin in the septic animals were remarkably heterogeneous. There was a significant reduction in mesenteric and microcirculatory blood flow in the upper gastrointestinal tract, whereas there were virtually no changes noted in the colon. The observed changes in blood flow during vasopressin administration also resulted in metabolically relevant alterations compared with the septic animals (group S), as indicated by increased mesenteric oxygen extraction, decreased mesenteric oxygen consumption, and increased intramucosal carbon dioxide gap.

The current study may seem to be similar to a work recently published by Knotzer *et al.*,[18] which showed abnormalities in the mucosal oxygenation of the small bowel during vasopressin administration in endotoxemic pigs. However, Knotzer *et al.*[18] used a different experimental model from that used in the current study, such as acute endotoxemia and measurements of tissue
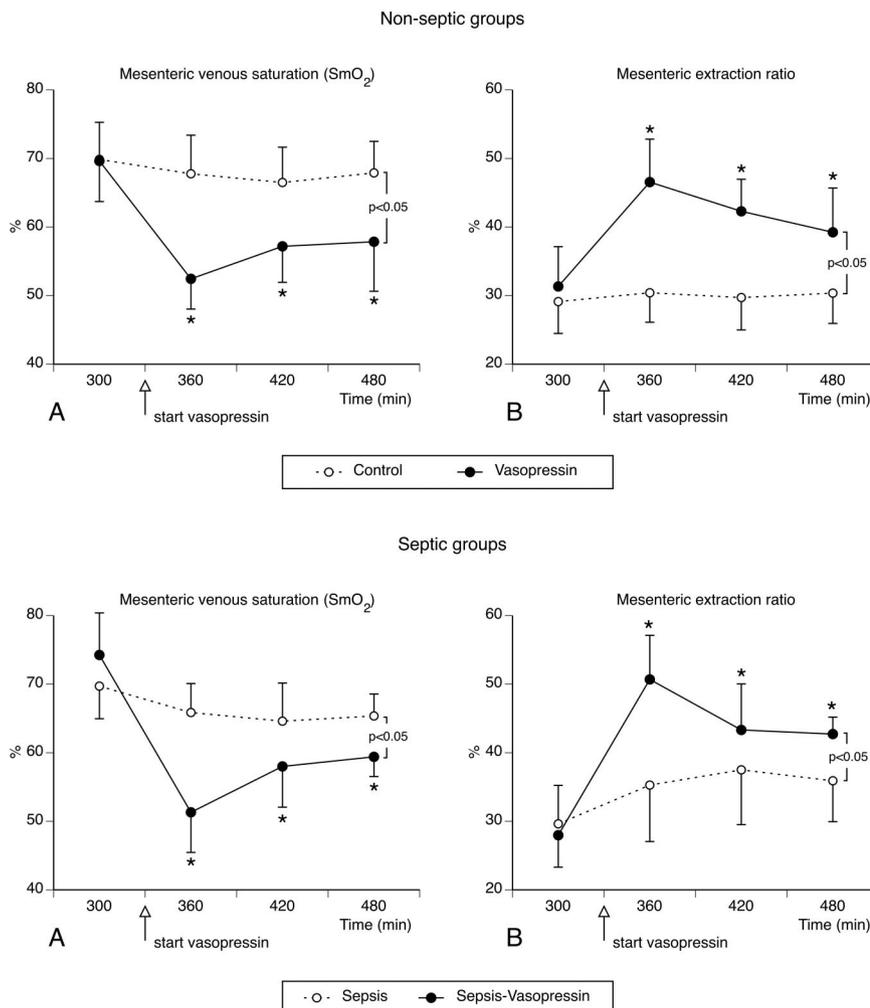

Fig. 4. Mesenteric venous saturation (Smo_2, %; *A* and *C*) and mesenteric extraction ratio (%; *B* and *D*). After baseline measurements (t = 0 min), animals in both nonseptic groups (n = 8 in each; *A* and *B*) were observed during 300 min. Animals in both septic groups (n = 8 in each; *C* and *D*) were subjected to fecal peritonitis and fluid resuscitation. At t = 300 min, a continuous intravenous infusion of vasopressin (0.06 U · kg^{-1} · h^{-1}) was started in the vasopressin- and vasopressin-sepsis groups. The nonseptic and septic control groups received intravenous saline only. The figures represent the results (mean ± SD) at t = 300 min and later. * *P* < 0.05 compared to t = 300 min.

$P_{O_2}/H_{b_{O_2}}$ as compared with bacterial septic shock and measurements of microcirculatory blood flow in our study. In addition, in the current study, we measured microcirculatory blood flow in the mucosa and muscularis simultaneously in three different parts of the gastrointestinal tract (stomach, small bowel, and colon) in intact anesthetized animals. It was shown that vasopressin had different effects on the microcirculation depending on the site measured (mucosa *vs.* muscularis and small bowel *vs.* colon).

In a recent study, Malay *et al.*[17] suggested that low-dose vasopressin does not significantly impair the mesenteric circulation in septic shock. However, in that study, an acute hypodynamic endotoxic shock model was used, and neither microcirculatory nor metabolic data were reported. In our study, a fluid-resuscitated fecal peritonitis model was used. Administration of vasopressin resulted in marked increase in mesenteric vascular resistance (initially by 300%) accompanied by reduction in blood flow in the superior mesenteric artery and decreased microcirculatory blood flow in the stomach and small intestine. This suggests an intense vasoconstriction in the mesenteric vascular bed. Such changes in microcirculatory blood flow in the upper gastrointestinal tract are of particular concern because injury to the mucosal barrier due to hypoperfusion is assumed to be relevant in the development of multiorgan failure.

There were no significant changes in mesenteric lactate values during vasopressin administration, and mesenteric oxygen saturation was, although significantly decreased, still 59%, compared with 65% in septic controls. Therefore, one could argue that there was no severe intestinal hypoperfusion despite decreased superior mesenteric artery flow and decreased microcirculatory flow in the stomach and small intestine. However, it must be considered that the effects of vasopressin were very heterogeneous in our study. We found decreased flow in the mucosa and muscularis in the stomach as well as the small intestinal mucosa during vasopressin administration, whereas we observed virtually no changes in flow in the muscularis in the small intestine and colon or in the colon mucosa compared with septic control animals. This heterogeneous effect on microcirculatory flow and the fact that lactate concentrations and oxygen saturation measured in mesenteric venous blood reflect the whole regional vascular bed, suggest that local tissue hypoxia may still have developed. In addition, in a recent study, we found that an increase in mesenteric venous lactate is a late sign of hypoperfusion in anesthetized pigs, first increasing after 60% reduction in mesenteric artery flow, compared with cellular substrate that decreases already after 30% flow reduction.[30] On the other hand, vasopressin caused a 30% decrease in systemic oxygen delivery and 50% decrease in mesen-

teric oxygen delivery in the septic animals (group SV) during the first hour of vasopressin infusion. This was associated with a 20% decrease in both systemic and mesenteric oxygen consumption. This vasopressin-associated reduction in oxygen delivery and more importantly in oxygen consumption suggests an oxygen supply dependency that is usually associated with some degree of tissue ischemia.[31] Similar reduction in oxygen delivery was also noted in the nonseptic vasopressin controls, but there was no associated decrease in systemic oxygen consumption, suggesting that the nonseptic animals could compensate decreased systemic oxygen delivery with increased oxygen extraction. Despite these apparently "safe" systemic effects of vasopressin in the nonseptic group (group V), the mesenteric circulation showed clear signs of oxygen supply dependency (table 3).

The significant reduction in mucosal microcirculatory blood flow of the stomach and jejunum found in this study is in accord with Westphal *et al.*,[19] who reported severe abnormalities in the mucosal perfusion of the small bowel during vasopressin administration in septic rats. In particular, vasopressin decreased arteriolar blood flow in the jejunal villi and reduced capillary perfusion.

In conjunction with reduced microcirculatory blood flow in the upper gastrointestinal tract, we found a significant increase in jejunal carbon dioxide gap compared with the septic group—another indicator of hypoperfusion in the small intestinal mucosa during vasopressin administration. This finding is also in accord with van Haren *et al.*,[3] who reported a significantly increased gastric mucosal carbon dioxide gap in septic patients receiving low-dose vasopressin infusion.

The current study has some limitations. First, the study was performed in an animal model because direct measurements of regional and local microcirculatory blood flow in patients are invasive, are time-consuming, and require special skills and instruments that are not readily available at the bedside. We chose the pig for this study because of its anatomical and physiologic similarity to humans in respect to the cardiovascular system and the digestive tract.[32] The fecal peritonitis model was chosen rather than endotoxin shock because it simulates clinical septic shock in humans.[24,25,29] Furthermore, clinical conditions in an operating room were imitated as close as possible in the laboratory (general anesthesia, mechanical ventilation, monitoring, and drug administration). Still, the results of this study are not human data, and that is the main limitation of this study. Second, in clinical practice, vasopressin is often used together with norepinephrine or dopamine. In our study, we used vasopressin alone because we wanted to measure the effects of vasopressin without possible interactions of other vasopressors. Third, because of the small number of animals per group, some biologically relevant effects may have been missed. The full factorial design used in

this study comprising three different control groups was intended to minimize this risk. Although the septic peritonitis model is well established and in many respects comparable to clinical fecal peritonitis,[24,25,29] the follow-up of 8 h may not have been sufficient to produce the full effects of severe peritonitis often seen in the clinical setting. However, in many clinical situations, such as during emergency abdominal surgery or in the emergency room, we are facing early septic conditions that have not yet caused full vasodilatation.[33] Furthermore, we find it unlikely that greater vasodilation or lower blood pressure would have changed our results. Several studies have reported only minimal metabolic alterations during changes in MAP from 60 to 90 mmHg with different vasopressors.[20,34–36] Fourth, the spectrum of metabolic variables measured in our study was limited. Nevertheless, they support the conclusion that the reduction in microcirculatory blood flow was metabolically relevant. Fifth, because we did not test dose response, we cannot exclude the possibility that the effects of lower doses of vasopressin would have had less profound effects on the microcirculation. Yet the dose of vasopressin administered in our study is in the range of clinically recommended doses of vasopressin in septic shock (range, 0.04–0.10 U/min).[5,17,30,37] Sixth, the fact that the animals were studied during general anesthesia (as opposed to awake) may seem to be less than optimal for clinical comparison. However, the model used in our study was designed to imitate a common clinical condition, *i.e.*, a "patient" subjected to emergency laparotomy during general anesthesia due to fecal peritonitis (not endotoxin infusion). General anesthesia and most anesthetics interfere with cardiovascular regulation, resulting in a decrease in sympathetic neural drive and vascular smooth muscle tone,[38] and therefore alter the hemodynamic response to septic shock. However, in the clinical critical care unit setting, general anesthesia/sedation is also a common practice in septic patients.

In conclusion, this study has shown that vasopressin in clinically relevant doses rapidly increases arterial blood pressure in anesthetized septic pigs. Simultaneously, it markedly decreased superior mesenteric artery flow as well as microcirculatory blood flow in the upper gastrointestinal tract, to an extent that tissue hypoxia may have occurred in the small intestinal mucosa.

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