Hypotension during Fluid-restricted Abdominal Surgery

Effects of Norepinephrine Treatment on Regional and Microcirculatory Blood Flow in the Intestinal Tract

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ABSTRACT

Background: Vasopressors, such as norepinephrine, are frequently used to treat perioperative hypotension. Increasing perfusion pressure with norepinephrine may increase blood flow in regions at risk. However, the resulting vasoconstriction could deteriorate microcirculatory blood flow in the intestinal tract and kidneys. This animal study was designed to investigate the effects of treating perioperative hypotension with norepinephrine during laparotomy with low fluid volume replacement.

Methods: Twenty anesthetized and ventilated pigs were randomly assigned to a control or treatment (norepinephrine) group. Both groups received 3 ml · kg^{-1} · h^{-1} Ringer's lactate solution. In addition, the norepinephrine group received norepinephrine to stepwise increase blood pressure to 65 and 75 mmHg. Regional blood flow was measured in the splanchnic arteries. In the small bowel and colon, microcirculatory blood flow was measured using laser Doppler flowmetry. Intestinal tissue oxygen tension was measured with intramural Clark-type electrodes.

Results: Hepatosplanchnic and kidney blood flow remained unchanged after reversal of arterial hypotension to a mean arterial pressure of 75 mmHg with norepinephrine. For the norepinephrine group *versus* the control group, the mean ± SD microcirculatory blood flow in the jejunum (96 ± 41% *vs.* 93 ± 18%) and colon (98 ± 19% *vs.* 97 ± 28%) and intestinal tissue oxygen tension (jejunum, 45 ± 13 *vs.* 43 ± 5 mmHg; colon, 50 ± 10 *vs.* 45 ± 8 mmHg) were comparable.

Conclusions: In this model of abdominal surgery in which clinical conditions were imitated as close as possible, treatment of perioperative hypotension with norepinephrine had no adverse effects on microcirculatory blood flow or tissue oxygen tension in the intestinal tract.

What We Know about This Topic

- There is a lack of correlation between intestinal microcirculation and regional splanchnic or systemic blood flow.
- It is not known whether norepinephrine, a potent vasoconstrictor, reduces intestinal microcirculatory blood flow when it is used to increase systemic perfusion pressure.

What This Article Tells Us That Is New

- Reversal of mild perioperative hypotension with norepinephrine, increased systemic blood flow, but did not significantly affect regional hepatosplanchnic blood flow nor affect oxygen tension in intestinal tissue.

ARTERIAL hypotension is common both after induction and during maintenance of anesthesia. Traditionally, treatment of perioperative hypotension consisted primarily of fluid administration, whereas vasopressors were rarely used in elective surgery because of their potentially detrimental effects on nutritive organ blood flow. Recently, several investigators[1,2] have suggested that restricted fluid volume administration (approximately 3 ml · kg^{-1} · h^{-1}) may result in better outcome compared with higher fluid volume therapy. Therefore, many hospitals have changed their perioperative fluid management to a more restrictive

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approach. Consequently, treatment of anesthesia-related hypotension that is not obviously the result of blood loss frequently consists primarily of vasopressor administration.

However, the effects of this procedure on gastrointestinal blood flow and tissue oxygen tension are poorly understood; and data regarding the effects of vasopressor administration on intestinal microcirculatory blood flow (MBF) and tissue oxygen tension in the perioperative nonseptic setting are scarce.[3] This is relevant because intraoperative gut hypoperfusion was identified in 63% of patients undergoing major surgery and was associated with increased morbidity and hospital stay.[4]

Because of its mainly α-adrenergic properties, norepinephrine is often used to treat anesthesia-induced vasodilatation. It increases blood pressure mainly by increasing systemic vascular resistance. Furthermore, norepinephrine has slight, but dose-dependent, β-adrenergic effects that might be beneficial to counteract pure vasoconstriction. The lack of correlation between intestinal microcirculation and regional splanchnic or systemic blood flow makes it virtually impossible to estimate the perfusion of the intestinal mucosal layer, which is likely the most vulnerable portion of the intestinal wall. Consequently, it remains unknown whether treatment of hypotension during anesthesia by a vasoconstrictor (*i.e.*, norepinephrine) results; however, systemic perfusion pressure is increased, in a further reduction in intestinal MBF because of additional vasoconstriction.

In the current study, we hypothesized that increasing systemic perfusion pressure with norepinephrine in the setting of fluid-restricted abdominal surgery results in decreased intestinal MBF and tissue oxygen tension.

We investigated whether the reversal of moderate intraoperative hypotension by administering norepinephrine had any adverse effects on systemic blood flow (cardiac index [CI]), regional blood flow (hepatosplanchnic flow), local blood flow (MBF in the small and large intestines), and intestinal tissue oxygen tension in a pig model of open abdominal surgery. An additional aim was to identify differences between a low and a medium dose of norepinephrine.

Materials and Methods

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

With free access to water, 20 domestic pigs (weight, 28–32 kg) fasted overnight. The pigs were sedated with intramuscular ketamine (20 mg/kg) and xylazine (2 mg/kg). Then, a peripheral intravenous catheter was inserted in an ear vein for initial administration of fluids and medications. Anesthesia was induced with midazolam (0.4 mg/kg) and atropine (1 mg). After induction, the pigs were orally intubated and ventilated with oxygen in air (fraction of inspired oxygen, 0.3). Anesthesia was maintained with midazolam (0.5 $mg \cdot kg^{-1} \cdot h^{-1}$), fentanyl (15 $\mu g \cdot kg^{-1} \cdot h^{-1}$), pancuronium (0.3 $mg \cdot kg^{-1} \cdot h^{-1}$), and low-dose propofol (0.15 $mg \cdot kg^{-1} \cdot h^{-1}$). The animals underwent ventilation with a volume-controlled ventilator with a positive end-expiratory pressure of 5 cm H_2O. Tidal volume was kept at 8–10 ml/kg, and the respiratory rate was adjusted (20–24 breaths/min) to maintain end-tidal carbon dioxide tension (P_{ACO_2}) at 40 ± 3 mmHg. Immediately after induction, all animals received 1.5 g cefuroxime intravenously as antibiotic prophylaxis. The stomach was emptied with a large-bore orogastric tube.

Surgical Preparation

Through a mid-cervical cut down, indwelling catheters were inserted into the left carotid artery 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 side of the heart into the pulmonary artery. Similarly, a fiberoptic hepatic vein catheter was inserted through the right jugular vein. Correct positioning was verified by a 15–20% decrease in the continuously measured hepatic vein saturation *versus* the mixed venous saturation and by a significant decrease in lactate concentration compared with mixed venous blood. In addition, the right carotid artery was dissected free and a 4-mm ultrasonographic transit time flow probe (Transonic Systems, Ithaca, NY) was placed around the vessel to measure carotid artery blood flow.

With the pig in the supine position, a mid-line 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, the celiac trunk, the hepatic artery, and the right renal artery were identified close to their origin. After dissection to free these vessels from the surrounding tissues, precalibrated ultrasonic transit time flow probes were placed around the vessels and connected to an ultrasonographic blood flowmeter.

Through a small incision in the jejunum, a custom-made laser Doppler flow (LDF) probe (Oxford Optronix, Oxford, United Kingdom) was sutured to the jejunum mucosa for measurements of MBF in the mucosa. A second LDF probe was sutured to the adjacent jejunum muscularis. Both LDF probes were attached with six microsutures to ensure continuous and steady contact with the tissue being investigated, 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. The incision in the jejunum allowed controlled positioning of an air tonometer tube (TRIP Sigmoid catheter; Datex-Ohmeda, GE Health Care, Helsinki, Finland). The bowel incision was then closed with continuous sutures.

For intramural intestinal tissue oxygen tension measurement, a polarographic tissue oxygen tension sensor was inserted into a section of healthy jejunum between the serosal

and mucosal tissue planes. The method has been described previously.[5–8] Care was taken to minimize handling of the small intestine and to return the bowel to a neutral position. An additional polarographic tissue oxygen tension sensor was sublingually inserted into the tongue muscle and fixed with a tape.

After preparation, the abdominal incision was closed and the animals were allowed to recover from instrumentation and stabilize for 60 min.

Throughout the entire study, all animals received a basal infusion of 3 ml · kg^{-1} · h^{-1} of Ringer's lactate solution to avoid excessive fluid administration. This fixed fluid administration resulted in a low central venous and pulmonary capillary wedge pressure between 2 and 4 mmHg at baseline. The body temperature of the animals was maintained at 38.0 ± 0.5°C (mean±SD) by using a warming mattress and a patient air-warming system.

Baseline measurements were performed after stabilization at a time of 0 min. Subsequently, all hemodynamic measurements were repeated hourly for 4 h. Blood samples were drawn hourly, after the measurements of the hemodynamic parameters.

At the end of the study, all animals were euthanized with an intravenous bolus of 20 mM potassium chloride.

Immediately after baseline measurements, the pigs were randomly assigned to either the norepinephrine group or the control group using a reproducible set of computer-generated random numbers. The assignments were kept in sealed, opaque, and sequentially numbered envelopes until used. The treatment was started 15 min after the first measurement. The groups will be described further.

Groups

The control group (n = 10) received fixed administration of 3 ml · kg^{-1} · h^{-1} lactated Ringer's solution throughout the experiment without additional fluids. One animal died after insertion of the pulmonary artery catheter because of untreatable arrhythmia.

The norepinephrine group (n = 10) received fixed administration of 3 ml · kg^{-1} · h^{-1} lactated Ringer's solution throughout the experiment. In addition, norepinephrine was administered to increase blood pressure in two steps to target blood pressures of 65 and 75 mmHg. The target pressure was maintained for 2 h, and the dose of norepinephrine was adjusted every 30 min if blood pressure was not in the range of 10% of the target.

Measurements

Respiratory Monitoring. Expired respiratory minute volume, tidal volume, respiratory rate, peak and other respiratory pressures, positive end-expiratory pressure, inspired and end-tidal carbon dioxide fraction, and inspired/expired oxygen fraction were monitored (S/5 Critical Care Monitor; Datex-Ohmeda, GE Health Care) throughout the study.

Hemodynamic Monitoring. Mean arterial blood pressure (MAP) and central venous, mean pulmonary artery, hepatic vein, and pulmonary capillary wedge pressures were recorded with quartz pressure transducers. Heart rate was measured from the electrocardiogram. Heart rate, MAP, and mean pulmonary artery and central venous pressures were displayed continuously on a multimodular monitor. A thermodilution method was used to measure cardiac output at each measurement point (*i.e.*, mean value of three consecutive manually performed measurements with 5 ml cold saline). Core temperature was measured from the thermistor in the pulmonary artery catheter.

Regional blood flow in the celiac trunk and the carotid, superior mesenteric, renal, and hepatic arteries was continuously measured throughout the experiments with ultrasonic transit time flowmetry using flowmeters (model HT 206; Transonic Systems).

The MBF was continuously monitored in the mucosa and the muscularis of the jejunum and colon using a multichannel LDF system. A detailed description of the theory of LDF operation and practical details of LDF measurements have been published previously.[9,10] The regional blood flow and the LDF data were acquired online with a sampling rate of 10 Hz *via* a multichannel interface (MP 150; Biopac Systems, Inc., Goleta, CA) with acquisition software (Acqknowledge 3.9; Biopac Systems, Inc.) and saved on a portable computer.

The LDF meters are not calibrated to measure absolute blood flow; instead, they indicate MBF in arbitrary perfusion units. Because of the relatively large variability of baseline values, the results are usually expressed as changes relative to baseline[11–13]; this was the case in the current study.

The jejunal intramucosal carbon dioxide pressure was measured with air tonometry.

Arterial, mixed venous, mesenteric, and renal venous blood samples were withdrawn hourly from the indwelling catheters and immediately analyzed in a blood gas analyzer (ABL 620; Radiometer, Copenhagen, Denmark) for oxygen pressure, carbon dioxide pressure, pH, lactate, and base excess. Hemoglobin oxygen saturation and arterial hemoglobin content were analyzed with a blood gas analyzer precalibrated for porcine blood (OSM 3; Radiometer). All values were adjusted to body temperature. Mixed and hepatic venous saturation values were displayed continuously on two continuous cardiac output monitors (Vigilance; Edwards Lifesciences, Baxter, Irvine, CA).

The CI and the superior mesenteric artery flow, renal artery flow, truncus celiacus flow, stroke volume, and systemic vascular resistance indexes were determined according to body weight. The systemic vascular resistance index was calculated as follows: systemic vascular resistance index = (MAP − central venous pressure)/CI.[14,15]

The systemic oxygen delivery, mesenteric (splanchnic), and renal oxygen delivery indexes were calculated using the following formulas:

Systemic Oxygen Delivery Index = CI × CaO_2, where CaO_2 is the arterial oxygen content.

Table 1. Systemic Hemodynamic Variables

Variable	Control Group			Norepinephrine Group		
	Baseline	P65	P75	Baseline	P65	P75
MAP, mmHg*	58.3 ± 3.5	60.5 ± 6.3	58.5 ± 7.1	59.3 ± 3.9	66.0 ± 4.2	73 ± 3.6†
CI, ml · kg^{-1} · min^{-1}*	79.3 ± 8.5	71.7 ± 7.9	68.8 ± 7.3	79.6 ± 12.3	71.7 ± 7.2	78.7 ± 11.2†
Heart rate, beats/min	116.9 ± 1.7	119.9 ± 8.7	128.1 ± 18.4	117.3 ± 16.1	124.3 ± 21.1	116.5 ± 26.7
SVI, ml · beat^{-1}kg^{-1}	0.68 ± 0.08	0.61 ± 0.09	0.55 ± 0.09	0.68 ± 0.12	0.58 ± 0.11	0.68 ± 0.13†
SVRI, mmHg · kg^{-1} · min^{-1}	711 ± 75	813 ± 132	822 ± 146	764 ± 131	932 ± 169	986 ± 203
PAP, mmHg	13.5 ± 1.5	14.5 ± 1.7	14.5 ± 1.7	13.1 ± 2.6	13.5 ± 2.3	14.2 ± 2.3
CVP, mmHg	2.8 ± 1.0	3.2 ± 0.8	2.9 ± 0.9	2.5 ± 0.5	2.6 ± 0.8	2.5 ± 0.8
HVP, mmHg	3.8 ± 1.4	4.0 ± 1.4	3.9 ± 1.1	3.9 ± 1.1	3.9 ± 1.2	4.1 ± 1.1
PCWP, mmHg	3.1 ± 0.6	3.1 ± 0.8	3.0 ± 0.7	3.4 ± 0.7	3.3 ± 1.3	3.1 ± 1.1
SvO_2, %*	49.5 ± 4.3	48.0 ± 4.4	48.2 ± 3.5	48.8 ± 4.7	49.3 ± 5.1	52.5 ± 4.5†
$HvSO_2$, %	31.9 ± 5.5	29.5 ± 5.8	30.2 ± 5.1	33 ± 7.0	33.1 ± 5.0	30.6 ± 6.1
sDO_2, ml O_2/min*	108 ± 13	101 ± 9	96 ± 12	109 ± 23	100 ± 17	126 ± 21†
Urine output, ml/h	25.8 ± 13.7	15.8 ± 8.7	12.1 ± 5.4	12.5 ± 10.2	15.0 ± 6.0	17.1 ± 6.9
Glucose, mM	4.8 ± 1.0	4.7 ± 0.76	4.2 ± 0.69	4.8 ± 0.65	4.8 ± 0.62	4.9 ± 0.55
aHb, g/l*	102 ± 7	101 ± 6	102 ± 6	101 ± 11	107 ± 10	115 ± 6†

Data are given as mean ± SD.

* $P < 0.05$ for differences between the control and norepinephrine groups for slope (P75 − baseline). † $P < 0.05$ for differences between the control and norepinephrine groups at P75.

aHb = arterial hemoglobin content; CI = cardiac index; CVP = central venous pressure; Glucose = arterial blood glucose content; HVP = hepatic venous pressure; $HvSO_2$ = hepatic venous oxygen saturation; MAP = mean arterial pressure; PAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; P65, values measured at a target MAP of 65 mmHg in both groups; P75, values measured at a target MAP of 75 mmHg in both groups; sDO_2 = systemic oxygen delivery index; SVI = stroke volume index; SvO_2 = mixed venous oxygen saturation; SVRI = systemic vascular resistance index.

Mesenteric (Splanchnic) Oxygen Delivery Index = Superior Mesenteric Artery Flow Index × CaO_2.

Renal Oxygen Delivery Index = Renal Artery Flow Index × CaO_2.

The following equation was used to determine oxygen content: [PaO_2 (mmHg) × 0.0031] + [hemoglobin content (g/l) × 1.36 × hemoglobin oxygen saturation (%)] = ml O_2/l.

Statistical Analysis

The sample size analysis was conducted as follows. It was assumed that norepinephrine leads to a 20% decrease in intestinal MBF between the two groups, with an average SD of ±15%, derived from previous studies. To detect this difference with an $\alpha = 0.05$ and a power of 80%, 10 animals per group were needed.

Before statistical analysis, data were tested for normality by a QQ plot and a Kolmogorov–Smirnov test. All baseline data (*i.e.*, before the start of the respective treatment, at a time of 0 min) were compared with an ANOVA or a Kruskal–Wallis test to analyze overall group discrepancies. Differences between the two treatment groups were assessed by a two-way repeated-measurements ANOVA using group as the between-subject factor and time as the within-subject factor, with a Tukey *post hoc* test to correct for multiplicity by measuring at multiple points for each parameter. In addition, the area under the variable–time curve for each variable of interest was calculated and compared with an ANOVA for group differences. A similar analysis was conducted for parameter slopes (*i.e.*, value at 75 mmHg − value at baseline). A correction for testing several parameters for differences was not performed. All tests were performed as two-tailed tests. Measurements of MBF were transformed with baseline set to 100% (time of 0 min) before statistical analysis. Absolute values were used for all other calculations.

All hemodynamic and blood flow data, including LDF measurements, are presented as time-averaged mean ± SD over 30 min. Blood gas–derived parameters were not averaged and are presented as mean ± SD. $P < 0.05$ was considered significant. For statistical calculations, computer software (SAS Version 8; SAS Institute, Inc., Cary, NC) was used.

Results

One animal in the control group died during the instrumentation because of untreatable arrhythmias after insertion of the pulmonary artery catheter. The data of the 19 animals that survived until the end of the experiment were included in the final data analysis. The amounts of continuous intravenous infusion of basal Ringer's lactate solution administered during the entire experiments (induction until end of study) to the control and norepinephrine groups were 985 ± 34 and 964 ± 69 ml, respectively.

At baseline, there were no significant differences between the two groups in any parameter measured. The animals were moderately hypotensive, as planned, after instrumentation and stabilization. The MAP values in the control and norepinephrine groups were 58.3 ± 3.5 and 59.3 ± 3.9 mmHg, respectively. The administration of 0.035 ± 0.012 μg · kg^{-1} · min^{-1} norepinephrine was needed to increase blood pressure to 65 mmHg and 0.12 ± 0.05 μg · kg^{-1} · min^{-1} to reach the target blood pressure of 75 mmHg in the norepinephrine group (table 1).

Table 2. Regional Blood Flow Variables

Variable	Control Group			Norepinephrine Group		
	Baseline	P65	P75	Baseline	P65	P75
CarI, ml · kg^{-1} · min^{-1}	4.6 ± 1	4.4 ± 1	4.7 ± 1.3	4.4 ± 0.9	4.1 ± 0.6	4.4 ± 1.1
SMAI, ml · kg^{-1} · min^{-1}	17.1 ± 1.9	15.6 ± 2.1	14.6 ± 1.2	16.3 ± 3.0	16.0 ± 3.4	15.4 ± 3.0
TruncI, ml · kg^{-1} · min^{-1}	4.3 ± 0.5	4.4 ± 0.8	4.6 ± 0.9	5.4 ± 1.6	4.8 ± 1.6	5.0 ± 1.3
HepI, ml · kg^{-1} · min^{-1}	1.8 ± 0.8	1.7 ± 0.6	1.9 ± 0.6	2.0 ± 0.5	1.5 ± 0.6	1.4 ± 0.5
RenI, ml · kg^{-1} · min^{-1}	7.0 ± 0.9	6.6 ± 0.9	6.4 ± 1.0	6.6 ± 1.0	6.6 ± 1.2	6.5 ± 1.0
rDO$_2$, ml · kg^{-1} · min^{-1}	9.6 ± 1.4	9.1 ± 1.5	8.8 ± 1.5	8.8 ± 1.5	9.3 ± 1.8	9.5 ± 1.9
ren Lac, mM	1.1 ± 0.2	1.0 ± 0.4	0.9 ± 0.3	0.9 ± 0.1	1.0 ± 0.4	0.9 ± 0.3
mes DO$_2$, ml · kg^{-1} · min^{-1}	24.6 ± 2.3	22.7 ± 2.3	20.1 ± 1.3	21.1 ± 4.6	22.3 ± 6.0	22.7 ± 5.0
mes Lac, mM	1.0 ± 0.6	0.9 ± 0.5	0.8 ± 0.2	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.2

Data are given as averaged mean ± SD.

CarI = right carotid artery blood flow index; HepI = arteria hepatica flow index; mes DO2 = mesenteric oxygen delivery index; mes Lac = mesenteric vein lactate concentration; P65, values measured at a target mean arterial pressure of 65 mmHg in both groups; P75, values measured at a target mean arterial pressure of 75 mmHg in both groups; rDO2 = renal oxygen delivery index; RenI = arteria renalis flow index; ren Lac = renal venous lactate concentration; SMAI = arteria mesenterica superior flow index; TruncI = truncus celiacus flow index.

Systemic hemodynamic data and filling pressures are presented in table 1. In the control group, heart rate, MAP, and mean pulmonary artery, central venous, hepatic venous, and pulmonary capillary wedge pressures remained largely unchanged. In the norepinephrine group, heart rate remained unchanged and mean pulmonary artery pressure increased at the higher dose. In the control group, CI, mixed venous saturation, and hepatic vein saturation values at baseline were as follows: 79.3 ± 8.5 ml · kg^{-1} · min^{-1}, 49.5 ± 4.3%, and 31.9 ± 5.5%, respectively. All variables remained unchanged (table 1). In the norepinephrine group, values were comparable at baseline. The CI, stroke volume variation index, mixed venous saturation, and systemic oxygen delivery index increased with the higher dose of norepinephrine, whereas hepatic vein saturation remained unchanged (table 1).

Regional blood flow variables in the carotid, superior mesenteric, and left renal arteries and regional oxygen delivery are shown in table 2. Carotid, superior mesenteric, celiac, and renal artery blood flow values were virtually unaffected by the higher perfusion pressures in the norepinephrine group, despite increased CI. Consequently, regional oxygen delivery did not change either.

Tissue oxygen tension values in the tongue muscle at baseline were 32 ± 7 and 28 ± 9 mmHg in the norepinephrine and control groups, respectively. There was no statistically significant difference in the tongue tissue oxygen tension between the groups at MAPs of 65 and 75 mmHg (table 3). The results of MBF in the jejunum mucosa and muscularis and the corresponding layers in the colon are shown in table 3. Similar to MBF, tissue oxygen tension in both the jejunum and colon remained virtually unchanged in both groups. In addition, no changes in intramucosal carbon dioxide pressure of the jejunum mucosa were found during increased perfusion pressure in the norepinephrine group. Analysis of parameter slopes (*i.e.*, value at 75 mmHg − baseline value) revealed similar results, with the

Table 3. Intestinal Microcirculatory Blood Flow and Tissue Oxygen Measurements

Variable	Control Group			Norepinephrine Group		
	Baseline	P65	P75	Baseline	P65	P75
PtiO$_2$ Ton, mmHg	28.0 ± 9.0	25.4 ± 9.8	23.2 ± 10.0	32.1 ± 7.2	28.3 ± 6.5	28.4 ± 6.7
MBF Jejunum, %	100.0 ± 0	99.8 ± 18.4	92.7 ± 17.5	100.0 ± 0	103.1 ± 32.8	96.3 ± 40.7
MBF Jej Mus, %*	100.0 ± 0	91.8 ± 17.54	78.2 ± 10.0	100.0 ± 0	105.8 ± 32.4	103.6 ± 31.1
PtiO$_2$ Jej, mmHg	45.9 ± 10.2	45.0 ± 6.0	42.8 ± 4.5	46.8 ± 10.5	51.2 ± 14.5	44.8 ± 12.7
PtiCO$_2$ Jej, mmHg	67.0 ± 4.4	65.0 ± 4.0	66.0 ± 3.8	67.6 ± 4.7	64.7 ± 4.5	64.6 ± 5.5
MBF Colon, %	100.0 ± 0	104.8 ± 37.1	96.6 ± 27.7	100.0 ± 0	103.8 ± 11.7	98.4 ± 18.9
MBF Col Mus, %	100.0 ± 0	120.2 ± 32.4	127.5 ± 50.0	100.0 ± 0	113.5 ± 29.4	99.7 ± 41.7
PtiO$_2$ Col, mmHg	48.0 ± 6.1	46.4 ± 5.9	44.8 ± 7.7	49.8 ± 8.6	52.8 ± 9.6	50.0 ± 10.1

Data are given as averaged mean ± SD.

* $P < 0.05$ for differences between the control and norepinephrine groups for slope (P75 − baseline).

MBF Colon = microcirculatory blood flow in the colon mucosa; MBF Col Mus = microcirculatory blood flow in the colon serosa/muscularis; MBF Jejunum = microcirculatory blood flow in the jejunum mucosa; MBF Jej Mus = microcirculatory blood flow in the jejunum serosa/muscularis; PtiCO$_2$ Jej = intramucosal carbon dioxide tension in the jejunum; PtiO$_2$ Col = intramural tissue oxygen tension in the colon wall; PtiO$_2$ Jej = intramural tissue oxygen tension in the jejunum wall; PtiO$_2$ Ton = tissue oxygen tension in the tongue; P65 = values measured at a target mean arterial pressure of 65 mmHg in both groups; P75 = values measured at a target mean arterial pressure of 75 mmHg in both groups.

exception of MBF in the jejunum muscularis, which was significantly different between the groups ($P = 0.04$).

Arterial hemoglobin (table 1) increased slightly in the norepinephrine group.

Discussion

The main findings of the current study are that increasing arterial blood pressure with norepinephrine from lower than 60 to 65 and 75 mmHg resulted in virtually no changes in regional blood flow in the hepatosplanchnic area or the renal artery. The MBF and tissue oxygen tension in the intestinal tract were also unaffected by norepinephrine. These findings suggest that low to moderate doses of norepinephrine to increase perioperative blood pressure do not adversely affect MBF or intestinal tissue oxygenation in moderately hypotensive fluid-restricted pigs subjected to abdominal surgery.

Although several studies have reported the effects of increased perfusion pressure by administration of vasopressors, such as norepinephrine or phenylephrine, for septic shock[15–18] and vasodilatory state after cardiac surgery,[19] we are not aware of any study investigating the effects of normalizing arterial blood pressure on intestinal microcirculation in the setting of elective abdominal surgery. However, this is an important question in the perioperative period because several recent studies[20] have suggested that perioperative fluid administration should be goal directed, resulting in more restrictive use of intravenous crystalloid fluids. Furthermore, the use of colloids should be restricted mainly to replace intraoperative blood loss.[20,21] Consequently, hypotension occurring after induction and during maintenance of general anesthesia without significant blood loss should be treated with vasoconstrictor agents.

The effects of increased perfusion pressure during norepinephrine administration seem to be heterogeneous and specific for different tissues.[18,22] For cerebral tissue oxygenation, a recent study[22] reported a decrease in cerebral tissue oxygen saturation during deliberate increase of blood pressure in volunteers.

In contrast to our hypothesis, we found no difference in intestinal microcirculation or tissue oxygen tension between the hypotensive animals and those treated with norepinephrine. It can be speculated whether the hypotensive animals in this study remained above autoregulatory threshold and, thus, MBF could not be increased.

Because intestinal microcirculation and tissue oxygen tension are of major importance for perioperative outcome[4,23–25] and for critically ill patients, it is often argued that vasopressor drug administration might decrease intestinal mucosal oxygenation, leading to tissue injury and mucosal barrier failure; and might initiate or promote a systemic inflammatory response.[26] A further potential danger of vasopressor use, once the norepinephrine is started, is that systemic hemodynamic variables normalize and provide no indication of a potentially compromised intestinal MBF. Thus, a serious derangement of intestinal oxygen supply could be easily missed, looking only at standard systemic hemodynamic monitoring.

Interestingly, increased systemic blood flow at the higher norepinephrine dose did not translate into improved regional or local blood flow. On the other hand, low- to moderate-dose norepinephrine administration in our study resulted in no reduction of regional or microcirculatory intestinal blood flow, intestinal tissue oxygen tension, or pH in the intestinal mucosa compared with the control animals. In addition, the mesenteric oxygen extraction ratio and hepatic vein oxygen saturation remained largely unchanged, which is in line with other studies[19,27] in patients after cardiac surgery. Consequently, the results of this study provide evidence that low- to moderate-dose norepinephrine does not further decrease intestinal MBF and tissue oxygen tension in this fluid-restricted model of abdominal surgery.

Similar to the results in our study, Schwarz *et al.*[3] found, in an experimental model investigating the short-term effects of norepinephrine administration, no significant effect on intestinal mucosal tissue oxygen tension. However, the design of the current study is considerably different. The animals were given restrictive fluid therapy, resulting in mild hypotension (MAP <60 mmHg), which was then treated with norepinephrine up to a target MAP of 65–75 mmHg, simulating clinical conditions during fluid-restricted abdominal surgery in humans. In the study by Schwarz *et al.*, the animals were given intravenous fluids (Ringer's lactate solution and hydroxyethyl starch) to maintain a constant filling pressure (pulmonary capillary wedge pressure, 13–14 mmHg), resulting in a baseline MAP of 104 mmHg in the norepinephrine group. Such a high MAP is rarely an indication for vasopressor therapy with norepinephrine in the clinical setting. This is important because autoregulation of intestinal perfusion is supposed to be less pronounced than for the brain or kidney. Thus, increasing blood pressure from hypotension (*i.e.*, MAP <60 mmHg) to normotension is likely to result in a considerably different response to the same vasopressor.

We are aware that the study has some limitations. The main limitation of this study is the relatively short (4-h) observation time, which is too short to verify the effect of norepinephrine on outcome. However, the aim of this study was to identify possible effects of increasing arterial blood pressure during fluid-restricted nonseptic abdominal surgery on MBF and several markers of tissue oxygenation and metabolism in the gut. Furthermore, in the clinical setting, hypotension resolves frequently at the end of general anesthesia; thus, the duration of norepinephrine administration is often short-lived.

The study was performed in an animal model because direct measurements of regional and local MBF in patients are invasive and time-consuming and require special skills and instruments that are not available at the bedside. This is also the reason why no clinical study measured the direct effects of increased perfusion pressure on intestinal microcirculation, tissue oxygen tension, and metabolism. Therefore, the pathophysiological background of improved perfusion pressure on intestinal microcirculation and tissue oxygen

tension was only based on other animal studies with significantly different starting points[3] or postoperative cardiac patients experiencing vasodilatory shock.[19,27]

Although no bowel resection was performed in this study, the animals were exposed to substantial surgical trauma, including laparotomy, urine bladder incision, and two enterotomies (in the jejunum and colon for insertion of the LDF and tonometer probes). Although every attempt was made to avoid bowel content spill into the abdomen, minor contamination cannot be excluded because it frequently occurs during bowel surgery. In addition, dissection of the mesenteric artery at its origin from the aorta and dissections of the celiac trunk and the right renal artery are rather invasive procedures, resulting in temporary opening of the retroperitoneal space, substantial lymphatic vessel trauma, and autonomic nerve injury. Thus, the surgical trauma of this model is substantial and comparable to open abdominal bowel surgery.

We chose the pig for this study because of its anatomic and physiologic similarity to humans with respect to the cardiovascular system and digestive tract.[28] Furthermore, this setting allowed us to assess both MBF and tissue oxygen tension in the jejunum and colon simultaneously. However, pigs have a distinctly lower hemoglobin concentration, a specifically higher hemoglobin oxygen affinity, and an increased body temperature compared with humans. These factors lead to a right shift in the oxyhemoglobin dissociation curve, thus resulting in lower mixed venous oxygen saturation compared with humans.[28]

Total intravenous anesthesia based on midazolam and fentanyl was chosen to minimize the effects on cardiovascular function. The aim was to have minimal myocardial depression and minimal effect on vascular tone to avoid excessive vasodilatation and consequent hypotension in this fluid-restricted animal model. The use of a different anesthetic agent (*i.e.*, an inhalational agent) may have influenced the results. Yet, different inhalational agents have considerably different effects on microcirculation themselves.[29] Thus, it is difficult to predict in which way a different type of anesthesia would have influenced the findings.

In the current study, we hypothesized that increasing blood pressure by norepinephrine would have detrimental effects on intestinal microcirculation. None of our microcirculatory parameters showed a statistically significant or clinically relevant difference between the groups. Taking several parameters into account at once for a study result (superiority study) generally requires a correction for multiplicity to be not overly statistically liberal; however, this is common practice in many publications. Even with such a liberal approach, no significant differences were detected between the two groups concerning parameters of MBF or tissue oxygen tension in the intestinal tract. This strengthens our conclusion that norepinephrine had no significant effect on microcirculation in the doses used in this study.

The target MAPs of 65 and 75 mmHg might be either too high or too low. However, for higher arterial blood pressure, intestinal oxygenation is not changed.[3] An MAP of 65–75 mmHg is generally considered a reasonable target in clinical practice.

Another limitation of this study may be that we used too mild conditions in otherwise healthy subjects (*i.e.*, mild hypotension that required only low doses of norepinephrine to reverse). Thus, the question remains whether it is possible that the results of this study would have been different if the animals had been more hypovolemic/hypotensive and if higher norepinephrine doses been used. The answer to that question remains unknown. However, our aim was to study clinically relevant perioperative conditions in which mild hypotension was treated with adequate doses of norepinephrine. We did not intend to study the effects of norepinephrine on severe hypotension/shock.

In summary, normalizing arterial blood pressure with norepinephrine during fluid-restricted abdominal surgery had neither beneficial nor detrimental short-term effects on nutritive blood flow to the intestine.

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