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Redistribution of Microcirculatory Blood Flow within the Intestinal Wall during Sepsis and General Anesthesia

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Background: **Hypoperfusion of the intestinal mucosa remains an important clinical problem during sepsis. Impairment of the autoregulation of microcirculatory blood flow in the intestinal tract has been suggested to play an important role in the development of multiple organ failure during sepsis and surgery. The authors studied microcirculatory blood flow in the gastrointestinal tract in anesthetized subjects during early septic shock.**

Methods: **Eighteen pigs were intravenously anesthetized and mechanically ventilated. Regional blood flow in the superior mesenteric artery was measured with ultrasound transit time flowmetry. Microcirculatory blood flow was continuously measured with a six-channel laser Doppler flowmetry system in the mucosa and the muscularis of the stomach, jejunum, and colon. Eleven pigs were assigned to the sepsis group, while seven animal served as sham controls. Sepsis was induced with fecal peritonitis, and intravenous fluids were administered after 240 min of sepsis to alter hypodynamic sepsis to hyperdynamic sepsis.**

Results: **In the control group, all monitored flow data remained stable throughout the study. During the hypodynamic phase of sepsis, cardiac output, superior mesenteric artery flow, and microcirculatory blood flow in the gastric mucosa decreased by 45%, 51%, and 40%, respectively, compared to baseline ($P < 0.01$ in all). Microcirculatory blood flow in the muscularis of the stomach, jejunum, and colon decreased by 55%, 64%, and 70%, respectively ($P < 0.001$ in all). In contrast, flow in the jejunal and colonic mucosa remained virtually unchanged. During the hyperdynamic phase of sepsis, there was a threefold increase in cardiac output and superior mesenteric artery flow. Blood flow in the gastric, jejunal, and colonic mucosa also increased (22%, 24%, and 31% above baseline, respectively). Flow in the muscularis of the stomach returned to baseline, while in the jejunum and colon, flow in the muscularis remained significantly below baseline (55% and 45%, respectively, $P < 0.01$).**

Conclusions: **It appears that in early septic shock, autoregulation of microcirculatory blood flow is largely intact in the intestinal mucosa in anesthetized pigs, explaining why microcirculatory blood flow remained virtually unchanged. This may be facilitated through redistribution of flow within the intestinal wall, from the muscularis toward the mucosa.**

ABDOMINAL sepsis is a common condition among patients subjected to emergency surgery under general anesthesia.[1–3] Despite advances in surgery and perioperative anesthesia management during the past decade or two, mortality remains high.[3,4] Insufficient blood flow in the gastrointestinal tract during sepsis and surgery is believed to be a common denominator in many of these patients, eventually resulting in multiple organ failure and death.[5–7] Thus, therapy aiming at increasing global oxygen delivery has frequently been applied in the hope that it would also increase splanchnic blood flow. As a result, the concept that oxygen consumption in the gut may, under certain conditions, be dependent on oxygen delivery is now widely accepted, and increasing oxygen delivery is one of the current therapeutic goals in perioperative management of high-risk patients[3,8,9] and in critical care.[10] Although clinical trials based on this concept have confirmed its legitimacy in some groups of patients,[3] it has apparently failed in others,[11] particularly in septic patients.[12]

The reason for inadequate tissue oxygenation in the gastrointestinal tract in septic subjects, despite apparently sufficient global hemodynamics, is not clear. Some investigators have suggested that autoregulation of microcirculatory blood flow in the gastrointestinal tract is severely impaired in sepsis,[13–15] meaning that blood flow in the gut would become primarily dependent on systemic flow.[8,10,16] This is in fact in agreement with the concept mentioned above, that oxygen consumption may become dependent on oxygen delivery. However, this concept could not be confirmed in clinical trials in septic patients,[12] highlighting the fact that available data on microcirculatory blood flow in septic shock is still inadequate and inconsistent.[13–15,17–19]

In recent years, laser Doppler flowmetry (LDF) has become an accepted technique to measure continuously microcirculatory blood perfusion in various organs.[18,20] With the introduction of multichannel laser Doppler flowmeters, measurements of perfusion in several organs simultaneously has become possible.[21,22] In the current study, this technique was applied to measure changes in microcirculatory blood flow simultaneously in the mucosa and the muscularis of the stomach, jejunum, and colon in anesthetized septic pigs. Our hypothesis assumes that the autoregulation of blood flow in the intestinal mucosa is intact in anesthetized subjects during early septic shock. Thus, our aim was to study the distribution of microcirculatory flow within different

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parts of the gastrointestinal tract during the development of hypodynamic septic shock and during hyperdynamic sepsis.

Materials and Methods

This study was performed according to the National Institutes of Health guidelines for the use of experimental animals. The protocol was approved by the Animal Ethics Committee of Canton, Berne, Switzerland. Eighteen domestic pigs (weight, 20–25 kg) were fasted overnight but were allowed free access to water. The pigs were sedated with intramuscular ketamine (2 mg/kg) and xylazinum (2 mg/kg). Anesthesia was induced with intravenous metomidate (5 mg/kg) and azaperan (2 mg/kg). The pigs were orally intubated after intravenous injection of succinylcholine (1 mg/kg) and ventilated with oxygen in air (fraction of inspired oxygen [F_{IO_2}] = 0.4). Inhaled and exhaled concentrations of oxygen were continuously monitored with a multigas analyser (Hellige SMU 611; Hellige, Freiburg, Germany). Anesthesia was maintained with continuous intravenous infusions of midazolam (0.5 mg $\cdot$ kg^{-1} $\cdot$ h^{-1}), fentanyl (10 μg $\cdot$ kg^{-1} $\cdot$ h^{-1}), and pancuronium (0.5 mg $\cdot$ kg^{-1} $\cdot$ h^{-1}) in isotonic NaCl (10 ml $\cdot$ kg^{-1} $\cdot$ h^{-1}). The animals were ventilated with a volume-controlled ventilator with a positive end-expiratory pressure (PEEP) of 5 cm H_2O (Tiberius 19; Drägerwerk, Lübeck, Germany). Tidal volume was kept at 10–15 ml/kg, and the respiratory rate was adjusted (14–16 breaths/min) to maintain end-tidal arterial carbon dioxide tension (Pa_{CO_2}) at 40 $\pm$ 4 mmHg.

Surgical Preparation

After tracheal intubation, a gastric tonometry tube (TRIP NGS catheter; Tonometerics, Worecester, MA) was inserted to drain gastric fluids and to measure gastric mucosal partial pressure of carbon dioxide (P_{CO_2}).

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

With the pig in supine position, a midline laparotomy was performed. The spleen was removed to avoid autotransfusion during shock. In five animals assigned to the sepsis group and in all control animals, a catheter was inserted into the portal vein for blood sampling. In the same animals, the superior mesenteric artery (SMA) was identified close to its origin and dissected free from the surrounding tissues. An ultrasonic 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 in the corpus region, a small custom-made laser Doppler probe was attached to the gastric mucosa with six microsutures in all animals. A second probe was fixed on the serosal side to the gastric muscularis. Through small antimesenteric incisions in the jejunum and ascending colon, the third and fourth LDF probes were sutured to the mucosa at the respective sites. Fifth and sixth LDF probes were sutured onto the muscularis of the jejunum and the ascending colon. The antimesenterial incision in the jejunum also allowed a controlled positioning of a tonometry tube (TRIP sigmoid catheter; Tonometrics). Through the incision in the colon, 20 g autologous feces was collected for later use to induce peritonitis and sepsis. All bowel incisions were then closed with continuous sutures. Care was taken to avoid any movement of the LDF probes during the experiment and to avoid any pressure, traction, or injury to the tissue under investigation. At the end of the surgical preparation, two large bore tubes (32-French) were placed with their tips in the abdominal cavity before the laparotomy was closed.

During the surgical preparation, the animals received 20 ml $\cdot$ kg^{-1} $\cdot$ h^{-1} Ringer's lactate (in addition to the 10 ml $\cdot$ kg^{-1} $\cdot$ h^{-1} NaCl, 0.9%, with the anesthetics) to maintain central venous pressure (CVP) between 6 and 8 mmHg. After the surgical preparation was completed, the animals were allowed to recover for 30–60 min before the measuring protocol was started. Ringer's lactate infusion was reduced to 10 ml $\cdot$ kg^{-1} $\cdot$ h^{-1} in the control group and was discontinued in the sepsis group.

Central venous blood temperature (°C) was recorded from the pulmonary artery catheter. Body temperature of the animals was maintained during the surgical preparation at 37.5 $\pm$ 0.5°C with a warming mattress and a patient air-warming system (Warm Touch 5700; Mallinckrodt, Hennef, Germany). In the sepsis group, no measure was taken to keep the body temperature constant after the induction of peritonitis.

Respiratory Monitoring

Expired minute volume, tidal volume, respiratory rate, peak and end inspiratory pressures, PEEP (cm H_2O), inspired and end-tidal carbon dioxide concentrations (ET_{CO_2}, mmHg) and inspired (F_{IO_2}, mmHg) and expired oxygen fractions were monitored continuously throughout the study.

Hemodynamic Monitoring

Mean arterial blood pressure (MAP, mmHg), CVP (mmHg), mean pulmonary artery pressure (mmHg), and pulmonary capillary wedge pressure (mmHg) were recorded with quartz pressure transducers (129A; Hewlett-Packard, Andover, MA). Heart rate (beats/min) was measured from the electrocardiogram. Heart rate, MAP, and CVP were displayed continuously on a multimodular

monitor (Hellige SMU 611). Cardiac output (CO) was determined with a thermodilution method. The value was calculated from three consecutive measurements at each time point (l/min; CO module, Hellige SMU 611).

Laser Doppler Flowmetry

The ideal technique for measuring microcirculatory blood flow should be continuous, real-time, minimally invasive, and easy to perform and should not interfere with blood flow in the organ under investigation. LDF fulfills many of these criteria, and therefore, it has become widely used to monitor microcirculatory blood flow. It has been validated in many organs, including the gastrointestinal mucosa,[18,23] and correlates well with other accepted techniques of measuring local blood flow, *e.g.*, reflectance spectrophotometry,[24] microspheres,[25,26] hydrogen gas clearance,[27] and XE133 washout method.[28] Hence, LDF is now an established noninvasive technique for continuous monitoring of the microcirculation *in vivo* and has been shown not to interfere with blood flow in the tissue under investigation.

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 Optronics, Oxford, United Kingdom). A detailed description of the theory of LDF operation and practical details of LDF measurements have been described elsewhere. Briefly, low-energy (2 mW) laser light from a solid-state diode laser operating in the spectrum of visible red light (780 nm) is guided to the measurement site *via* an optical fiber of 120-μm core diameter. An identical adjacent fiber at a distance of 250 μm from the light-emitting fiber receives the back-scattered light from the tissue. The volume of tissue in which blood flow is measured (0.7–1.0 mm^3) is determined by the geometry and fiber separation of the used laser Doppler flow probe. The back-scattered light is transmitted to two independent photodetectors. This portion consists of light scattered from the static tissue matrix, which has not been Doppler shifted, and a spectrally broadened component resulting from Doppler shifting on moving blood cells. Optical mixing of these components at the photodetector surface produces an electrical signal containing all the Doppler frequency shift information, which varies linearly to the blood cell flux or blood flow. In this study, the flowmeter output was expressed in perfusion units (PU), where 1,000 PU was equivalent to 1 V output signal. The LDF data were acquired on-line 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.) to 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,[22,29] and that was also the case in this study. The quality of the LDF signal was controlled on-line by visualizing it on a computer screen so that motion artifacts and noise due to inadequate probe attachment could be immediately detected and corrected before the measurements started.

Ultrasonic Transit Time Flowmetry

Blood flow in the mesenteric artery was continuously measured in five animals of the sepsis group and in all animals in the control group throughout the experiments with ultrasonic transit time flowmetry (ml/min) using an HT 206 flowmeter (Transonic Systems Inc.).

Laboratory Analysis

In all animals, arterial and mixed venous blood samples were withdrawn at each measurement point from the indwelling catheters and immediately analyzed in a blood gas analyser (ABL 620; Radiometer, Copenhagen, Denmark) for partial pressure of oxygen (Po_2, mmHg), Pco_2 (mmHg), pH, lactate (mM), SO_2, base excess (BE), and total hemoglobin concentration (g/l). All values were adjusted to body temperature. In five septic and seven control animals, blood samples from the portal vein were withdrawn at each measurement point and analyzed in the same way.

Mucosal pH

The tonometric method for calculation of mucosal pH (pHi) has previously been described.[30–32] The balloon of the tonometer placed in the stomach was filled with 2.5 ml saline. After 30 and 60 min, respectively, of equilibration through the silastic wall of the balloon, 1 ml was aspirated and discharged (this volume represents the dead space of the tube), and the remaining 1.5 ml was aspirated. The Pco_2 of the sample was determined in a blood gas analyzer and adjusted to the equilibration time using a factor provided by the manufacturer. Using the Henderson-Hasselbalch equation, gastric intramucosal pH was then calculated. Immediately after withdrawal of the sample, the tonometer was refilled.

The jejunal intramucosal Pco_2 was measured with a Tonocap® device (Tonocap® Monitor; Datex-Ohmeda, Miami, FL). Jejunal pHi was calculated at each measurement point using the in-built Tonocap® software.[33] It has been shown that data from the two techniques we used for measuring pHi are comparable.[33]

Experimental Design

After completing the baseline measurements, the septic group received 20 g autologous feces suspended in 200 ml warm isotonic NaCl (37°C) through the abdominal tubes (t = 0 min) to induce generalized peritonitis and sepsis, while the controls did not. Microcirculatory blood flow was continuously measured in all animals.

Table 1. Hemodynamics during Septic Shock

	Heart Rate, beats/min		MAP, mmHg		PAP, mmHg		CVP, mmHg		Cardiac index, ml · kg^{-1} · min^{-1}		SVRI, mmHg · kg^{-1} · min^{-1}	
Min	Control	Sepsis	Control	Sepsis	Control	Sepsis	Control	Sepsis	Control	Sepsis	Control	Sepsis
0	88 ± 14	94 ± 17	85 ± 12	89 ± 11	18 ± 2	20 ± 3	7 ± 1	6.7 ± 1	146 ± 8	156 ± 26	535 ± 69	541 ± 98
60	92 ± 15	144 ± 37*‡	81 ± 8	76 ± 18	17 ± 2	21 ± 2§	7.3 ± 2	5.1 ± 1§	142 ± 13	141 ± 35	523 ± 69	548 ± 130
120	98 ± 19	155 ± 47†‡	80 ± 10	64 ± 9	18 ± 2	21 ± 2	7.6 ± 1	4.5 ± 1*§	145 ± 15	113 ± 26	500 ± 87	562 ± 127
180	106 ± 23	191 ± 34†§	82 ± 12	61 ± 9†§	19 ± 2	21 ± 1	7.3 ± 1	4.2 ± 2†§	154 ± 22	98 ± 21†	487 ± 98	615 ± 165
240	110 ± 29	223 ± 46†§	80 ± 18	55 ± 8†§	19 ± 2	23 ± 3§	7.6 ± 1	4.1 ± 1†§	167 ± 36	87 ± 27†	439 ± 117	649 ± 210′
270	112 ± 29†	175 ± 33†§	86 ± 19	78 ± 13	20 ± 2†	27 ± 3†§	8.3 ± 1	7.4 ± 1	174 ± 37*	242 ± 64†‡	458 ± 133	320 ± 119†
300	121 ± 28†	169 ± 31†‡	85 ± 14	81 ± 21	19 ± 1	27 ± 5†§	7.7 ± 2	7.6 ± 2	170 ± 30	246 ± 76†§	462 ± 131	307 ± 113†‡

Data shown as mean ± SD.

*$P < 0.05$, †$P < 0.01$ compared with baseline.

‡$P < 0.05$, §$P < 0.01$ compared with the control group.

CVP, central venous pressure; MAP, mean arterial blood pressure; PAP, mean pulmonary arterial pressure; SVRI, systemic vascular resistance.

Systemic hemodynamics and blood samples were measured at 60, 120, 180, 240, and 300 min. After 240 min of peritonitis, the septic animals were given an intravenous infusion of 20 ml/kg pentastarch (6% hydroxyethyl starch 0.5, 200; Fresenius Pharma, Stans, Switzerland) over 40 min followed by 20 ml/kg Ringer's lactate over 20 min. At 300 min, all animals were sacrificed, with an intravenous injection of 20 mmol KCl.

Calculations and Data Analysis

Cardiac index (CI), superior mesenteric artery flow index (SMAI), and systemic vascular resistance index (SVRI) were indexed to body weight. SVRI was calculated as:

$SVRI = (MAP - CVP)/CI$.[18,34]

Systemic oxygen delivery index (sys-DO_2I) was calculated as: sys-$DO_2I = (CI \times Cao_2)$, where Cao_2 is the arterial oxygen content. $Cao_2 = (Pao_2 \times 0.003) + (\text{hemoglobin} \times SO_2 \times 1.36)$, where hemoglobin is the hemoglobin concentration and Sao_2 is the arterial oxygen saturation.

Systemic oxygen consumption index (sys-VO_2I) was calculated as: sys-$VO_2I = (CI \times (Cao_2 - Cvo_2))$, where Cvo_2 is the mixed venous oxygen content.

Systemic oxygen extraction ratio (sys-ER) was calculated as: sys-$ER = (Cao_2 - Cvo_2)/Cao_2$.

Mesenteric (splanchnic) oxygen delivery index (mes-DO_2I), mesenteric oxygen consumption index (mes-VO_2I), and mesenteric oxygen extraction ratio (mes-ER) were calculated in five animals using the following formulas:

mes-$DO_2I = SMAI \times Cao_2$;

mes-$VO_2I = SMAI \times (Cao_2 - Cmo_2)$, where Cmo_2 is the mesenteric venous oxygen content; and

mes-$ER = (Cao_2 - CmO_2)/Cao_2^{-1}$

Statistical Analysis

The data are presented as mean ± SD. The statistical analyses within the groups and between the sepsis and the control groups were performed by two-way analysis of variance for repeated measurements followed by the Bonferroni-Dunn test. Changes between mucosal and muscularis blood flow compared to CI were analyzed with a two-tailed paired analysis of variance for repeated measurements followed by the Tukey correction for multiple comparisons. To estimate correlation between changes in CI and SMAI and between CI and microcirculatory blood flow, a linear regression analysis was performed. $P < 0.05$ was considered statistically significant.

Results

At baseline, there were no statistically significant differences in systemic hemodynamics between the two groups. As shown in table 1, hemodynamics remained stable throughout the study in the controls. Fecal peritonitis and the following sepsis resulted in a sustained decrease in MAP from 89 ± 10 mmHg at baseline to 55 ± 8 mmHg ($P < 0.001$) after 240 min. After intravenous infusion of fluids at 300 min, MAP increased again to 81 ± 21 mmHg. CI decreased by 45% ($P < 0.001$) during hypodynamic shock and increased threefold after intravenous fluid infusion (to 58% above baseline; $P < 0.001$). In other words, infusion of fluids converted hypodynamic septic shock into hyperdynamic sepsis. Similar changes were recorded in SMA flow, which decreased by 51% ($P < 0.01$) during hypodynamic septic shock and increased to 84% ($P < 0.001$) above baseline after intravenous fluid administration. Changes in CI and SMAI were essentially linearly correlated ($r^2 = 0.83$; $P < 0.001$; fig. 1).

Changes in microcirculatory blood flow in the mucosa and the muscularis in the gastrointestinal tract as measured by LDF are presented in figures 2 and 3, respectively. One series of LDF measurements in the mucosa and the muscularis of the stomach and one from the jejunal mucosa (both from the septic group) were ex-

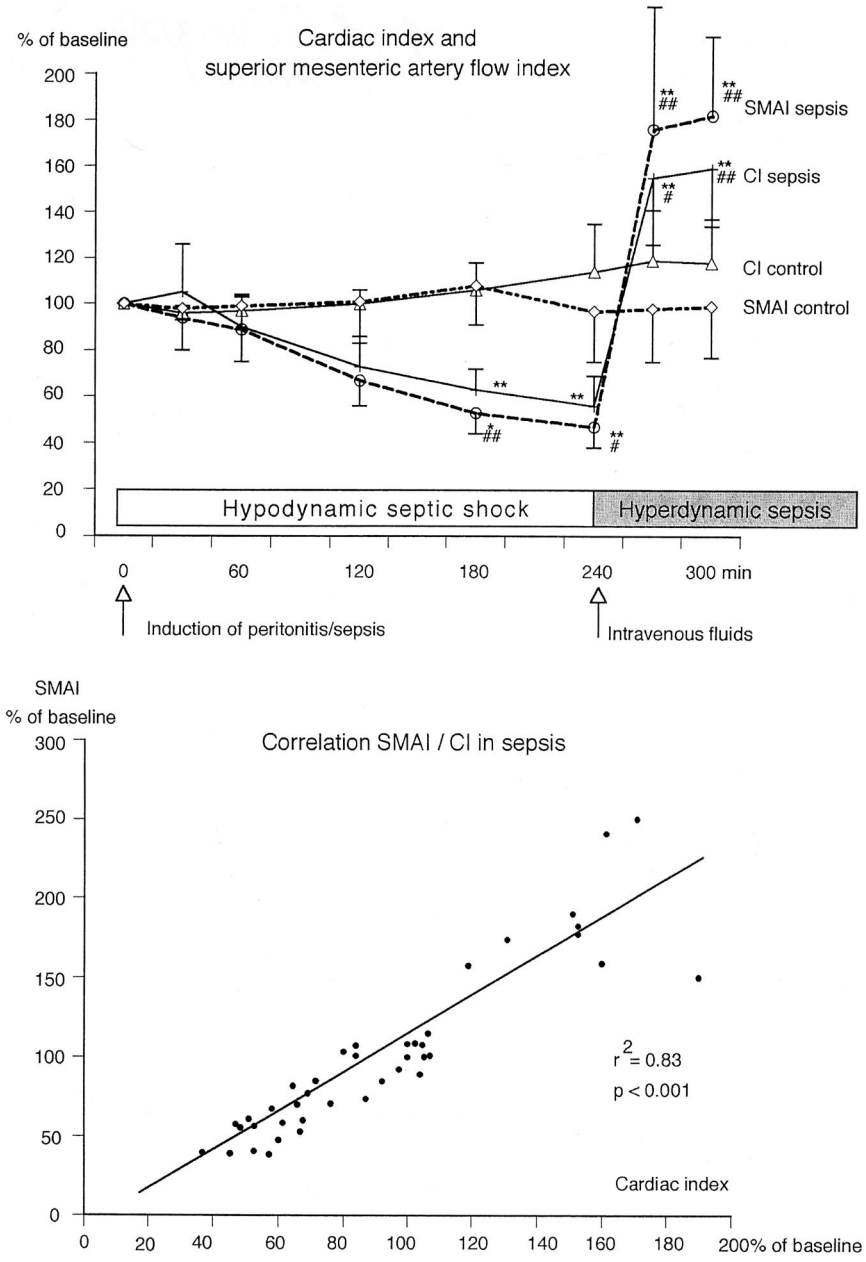

Fig. 1. (*A*) Relative changes (percent of baseline; mean ± SD) in cardiac index (CI; continuous line) and superior mesenteric artery blood flow index (SMAI flow; dotted line) in the controls and in the septic animals. In the septic group, peritonitis/sepsis was induced at t = 0, and at t = 240, intravenous fluids were administered to alter hypodynamic septic shock to hyperdynamic sepsis. The controls were neither exposed to sepsis at t = 0 nor to infusion of intravenous fluid load at t = 240 min. *$P < 0.05$, **$P < 0.01$ as compared with baseline. #$P < 0.05$, ##$P < 0.01$ compared with the control group. (*B*) Correlation analysis between CI and SMAI for the sepsis group. $r^2 = 0.83$, $P < 0.001$.

cluded because of technical problems (no tracing). All other results were included in the final data analysis. In the septic group, microcirculatory blood flow in the mucosa of the stomach decreased by 40 ± 20% ($P < 0.001$) in parallel with CI ($r^2 = 0.54$; $P < 0.001$). Interestingly, microcirculatory blood flow in the jejunal and colonic mucosa remained virtually unchanged during hypodynamic sepsis despite marked reduction in CO and SMA flow. In fact, compared to CO, there was a relative increase in microcirculatory blood flow in the jejunal and colonic mucosa at 240 min (fig. 4; $P < 0.001$). During hypodynamic sepsis, blood flow in the muscularis decreased by 55 ± 20% in the stomach ($P < 0.001$), 64 ± 17% in the jejunum ($P < 0.001$), and 70 ± 13% in the colon ($P < 0.001$; fig. 3). Microcirculatory blood flow in the muscularis of the jejunum and colon decreased significantly more than systemic flow ($P < 0.001$; fig. 4). Intravenous fluid administration increased microcirculatory blood flow in the mucosa of the stomach, jejunum, and colon to 22%, 24%, and 31% above baseline, respectively. However, when indexed to systemic flow, the mucosa perfusion in all three parts of the gastrointestinal tract was slightly reduced (fig. 4). During the hyperdynamic phase, microcirculatory blood flow in the muscularis increased substantially only in the stomach (by 48 ± 54%; $P < 0.01$; fig. 3), while in the jejunum and colon, there was no significant change (fig. 3), and compared to systemic flow, microcirculation deteriorated even further (fig. 4).

pHi in the mucosa of the stomach and jejunum de-

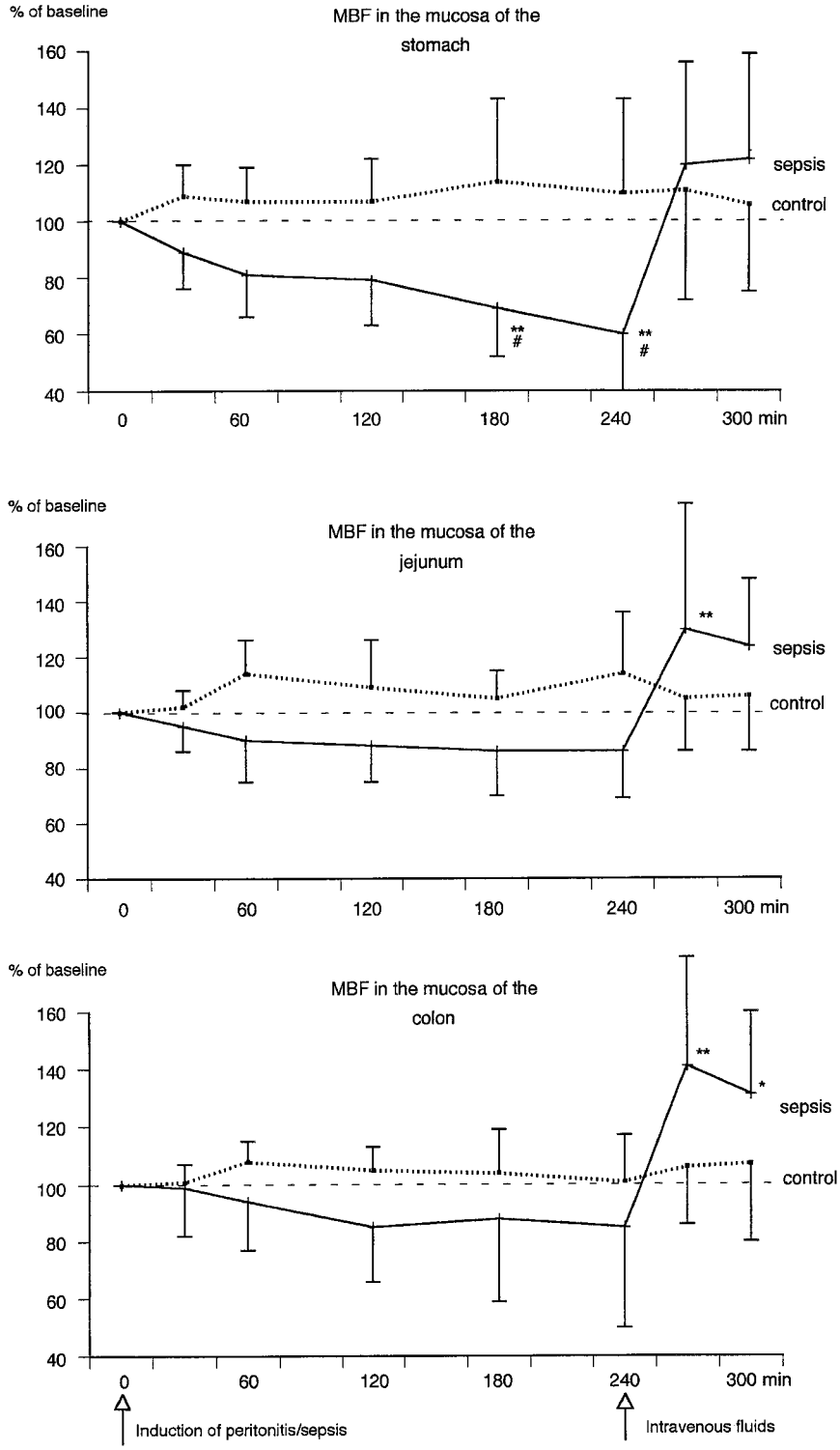

Fig. 2. Relative changes (percent of baseline; mean ± SD) in microcirculatory blood flow (MBF) in the mucosa of the stomach, jejunum, and colon in the septic group (continuous line) and in the control group (dotted line). In the septic group, peritonitis/sepsis was induced at t = 0, and at t = 240, intravenous fluids were administered to convert hypodynamic septic shock to hyperdynamic sepsis. The controls were neither exposed to sepsis at t = 0 nor to infusion of intravenous fluids at t = 240 min. *$P < 0.05$, **$P < 0.01$ compared with baseline. #$P < 0.05$, ##$P < 0.01$ compared with the control group.

creased in parallel ($r^2 = 0.67$) during hypodynamic septic shock. During hyperdynamic sepsis, pHi in both the stomach and jejunum increased significantly but remained significantly below baseline ($P < 0.001$; fig. 5).

The systemic oxygen extraction ratio increased from 35% at baseline to 53% ($P < 0.001$) during hypodynamic septic shock (fig. 6). During the same time, the mesenteric extraction ratio increased from 30% to 65% ($P < 0.001$). Both systemic and mesenteric extraction decreased with intravenous fluid administration, to 30% and 19%, respectively (fig. 6). Arterial and mesenteric lactate levels both increased significantly during the development of septic shock (fig. 6).

Hemoglobin, acid–base, and metabolic variables from the two groups are summarized in table 2.

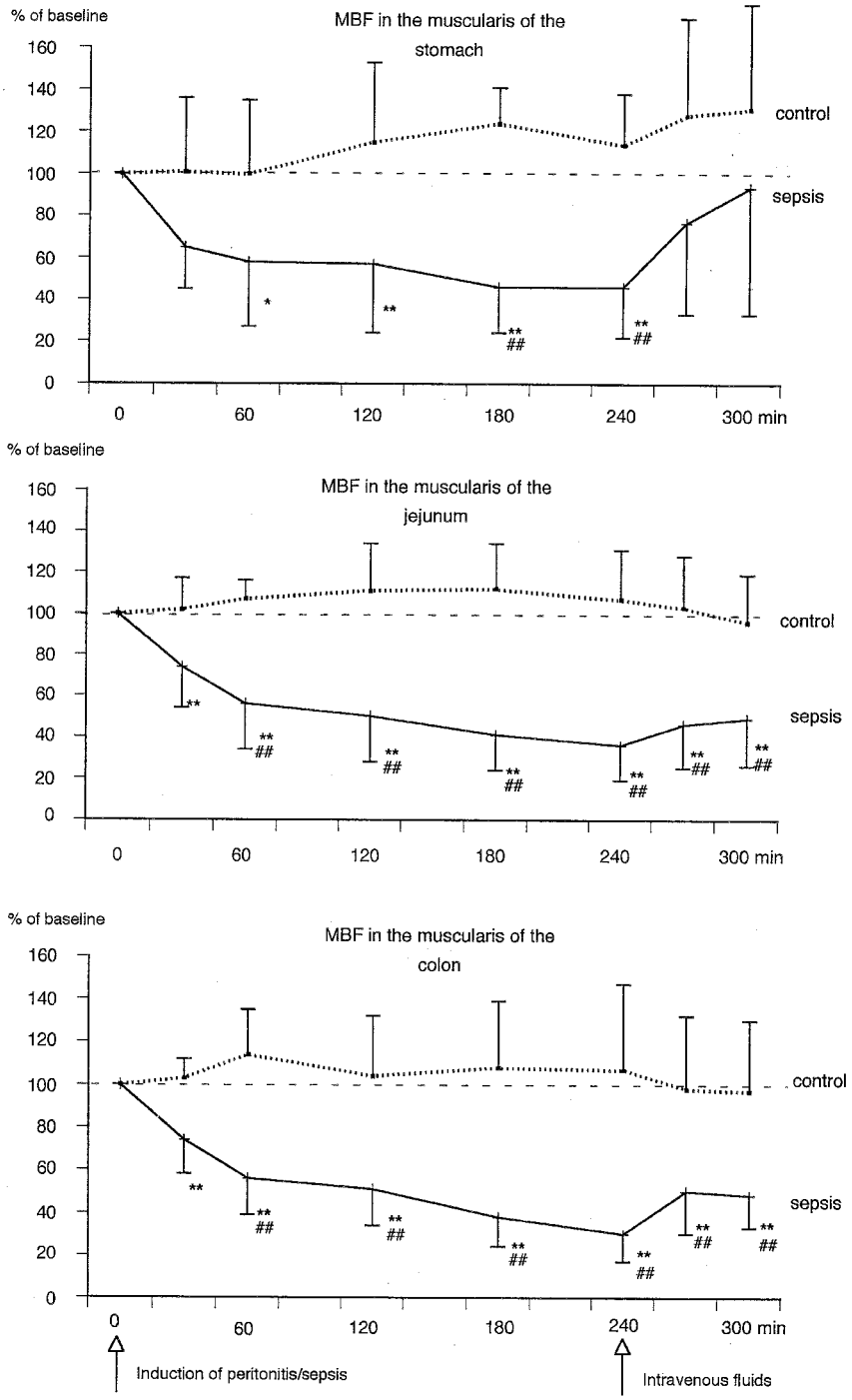

Fig. 3. Relative changes (percent of baseline; mean ± SD) in microcirculatory blood flow (MBF) in the muscularis of the stomach, jejunum, and colon in the septic group (continuous line) and in the control group (dotted line). In the septic group, peritonitis/sepsis was induced at t = 0, and at t = 240, intravenous fluids were administered to convert hypodynamic septic shock to hyperdynamic sepsis. The controls were neither exposed to sepsis at t = 0 nor to infusion of intravenous fluids at t = 240 min. *$P < 0.05$, **$P < 0.01$ compared with baseline. #$P < 0.05$, ##$P < 0.01$ compared with the control group.

Discussion

In the current study, changes in regional blood flow, as reflected by SMA blood flow, were closely correlated to changes in systemic flow in the septic animals (fig. 1). This suggests that there was no compensatory shift of flow, away from the gastrointestinal tract, to the systemic circulation, despite a significant decrease in CO. It can be speculated whether this lack of redistribution was due to effects of general anesthesia or whether it was caused by other factors, such as local or regional effects of the intraabdominal infection. It is well known that volatile anesthetics interfere with vasoregulation and therefore with redistribution of flow during reduced systemic blood flow.[35,36] To minimize the influence of anesthesia on circulatory control, the current study was performed using intravenous anesthesia alone, which has been shown to have fewer effects on systemic hemodynamics.[37,38] Macrocirculatory and microcirculatory data from in the controls also remained quite stable throughout the study (figs. 1–3). On the other hand, it

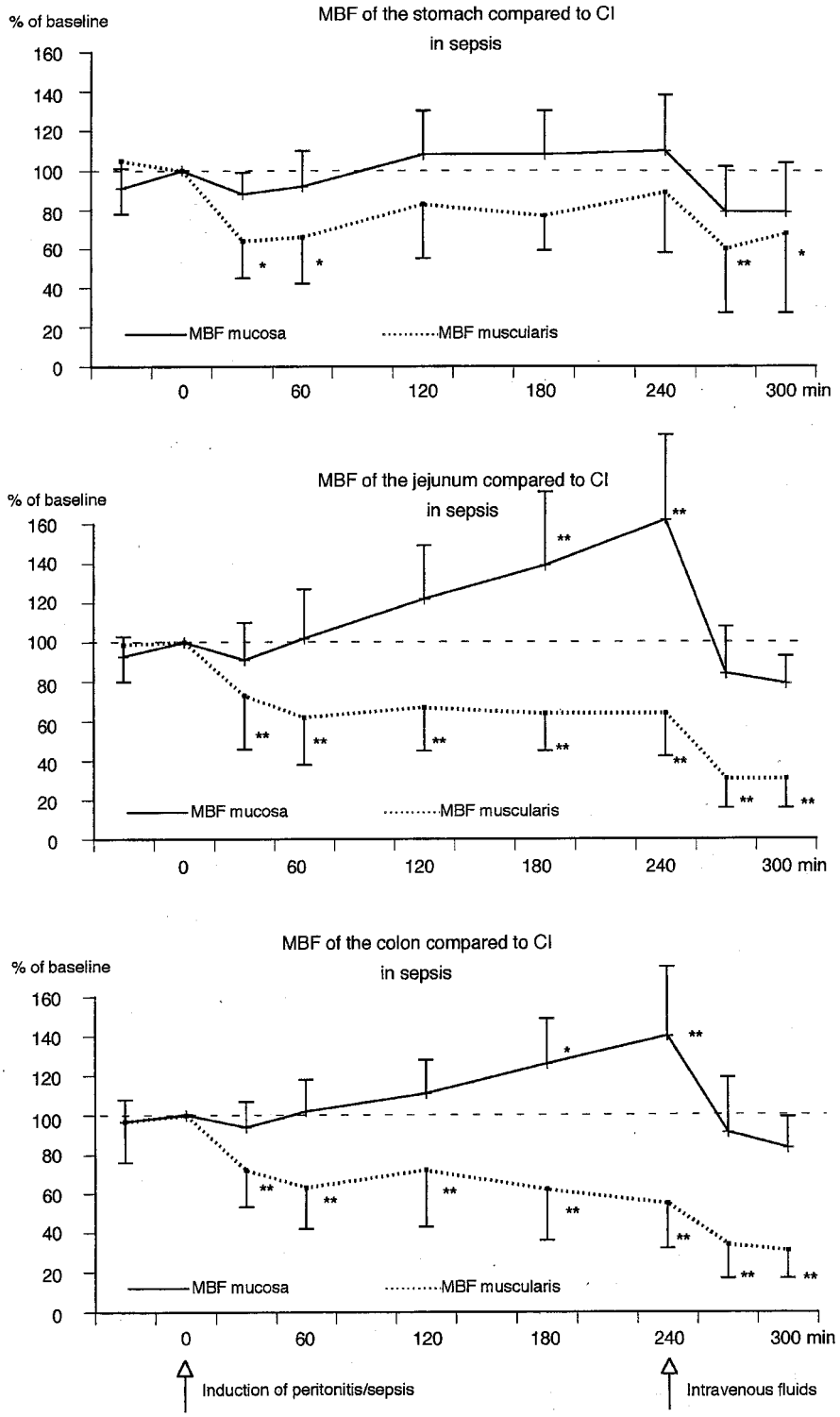

Fig. 4. Changes in microcirculatory blood flow (MBF) compared with systemic flow (cardiac index; CI) in the septic animals. The ratio between MBF and CI at t = 0 was set at 100%. MBF in the gastric mucosa decreased similarly to CI (ratio virtually constant during hypodynamic septic shock). In the jejunal and colonic mucosa, MBF increased significantly compared to CI (ratios 1.6 and 1.4, respectively, at t = 240 min). MBF in the muscularis decreased in all parts of the gastrointestinal tract during hypodynamic septic shock, and during hyperdynamic sepsis, it decreased even further. *$P < 0.05$, **$P < 0.01$ compared with baseline.

has been shown that in early generalized peritonitis, splanchnic oxygen consumption may be increased,[34] perhaps as a consequence of a generalized inflammation in the splanchnic bed. In the present study, a trend toward an increased oxygen consumption in the splanchnic bed was recorded in the animals in which mesenteric oxygen consumption was measured. Thus, increased local or regional oxygen demand in the splanchnic region may have prevented shift in blood flow away from the splanchnic bed.

The most important result of the current study is perhaps that mucosal blood flow in the small intestine and colon remained virtually unchanged (maximum decrease, approximately 10–15%) during the hypodynamic phase of septic shock, despite a 50% decrease in both SMA flow and in CI. These results can only be explained

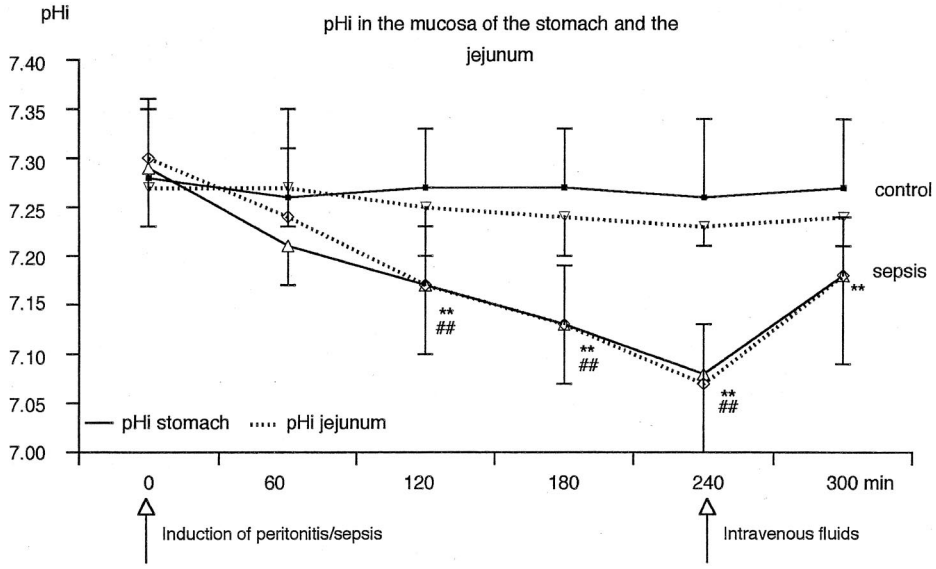

Fig. 5. Changes in pHi in the stomach (continuous line) and the jejunum (dotted line). For the sepsis group, at t = 0, pHi was 7.29 in the stomach mucosa (which is reported to be normal for pigs[43]) and 7.30 in the jejunal mucosa. The decrease in pHi during hypodynamic septic shock to 7.07 in the jejunum and 7.08 in the stomach, as well as the increase during hyperdynamic sepsis (after intravenous fluid load at 240 min), were virtually in parallel. For the controls, pHi in both stomach (continuous line) and in the jejunum (dotted line) were quite stable. *$P < 0.05$, **$P < 0.01$ compared with baseline. #$P < 0.05$, ##$P < 0.01$ compared with the control group.

if mucosal autoregulation was, at least in part, functional in early septic shock. Maintenance of adequate blood flow to the tip of the mucosal villi is crucial to protect the mucosal barrier function and prevent bacterial translocation. It has been shown that in nonseptic animals, blood flow to the tip of the villi is maintained down to a perfusion pressure of 30 mmHg or when total blood flow is reduced by 50%.[39] It can, therefore, be assumed that because of severely reduced regional perfusion during early sepsis, as seen in our study, there was vasodilatation in the mucosa and a vasoconstriction in the muscularis, which diverted flow away from the muscularis to the mucosal layer. This hypothesis is supported by the work of Connolly *et al.*,[40] who have shown that the small intestinal mucosa has an immense ability to match microcirculatory oxygen delivery with metabolic needs during low flow states. As soon as systemic oxygen delivery is reduced, multiple reflexes react to augment vasoconstriction and maintain blood pressure. This response contributes to redistribution of blood flow to tissues with higher metabolic oxygen demand and allows an increased oxygen extraction within the tissues.[40,41] Considering the proportionally high oxygen requirements in the metabolically active mucosa, it is more than likely that microcirculatory blood flow in the intestine is regulated by oxygen demand. This diversion of flow can be interpreted as redistribution of flow away from the "less important" muscularis layer toward the vital mucosal layer of the intestine. The purpose of such a mechanism could be preservation of mucosa functional integrity. The extent of the decrease in microcirculatory flow in the muscularis layer was, however, somewhat unexpected because it significantly exceeds the already marked decrease in systemic and regional flow (fig. 3).

Although it may appear logical to assume that the shift in blood flow from the muscularis to the mucosa was a mechanism to preserve blood flow to the mucosa during low-flow state, it is possible that other factors contributed as well. The reduction in perfusion of the muscularis layer, as seen in this study, can perhaps be seen as the result of a physiologic response to the severe intraabdominal bacterial infection *i.e.*, a defense mechanism to reduce uptake and systemic spread of endotoxin and bacteria from the abdominal cavity.

Although there was a significant redistribution of flow in favor of the intestinal mucosa, it was apparently not sufficient to meet the mucosal oxygen demand. At least the increase in mesenteric serum lactate (fig. 6) and decrease in intramucosal pHi (fig. 5) suggest that oxygen requirements of the intestinal wall were not fully met despite maintained microcirculatory flow in the mucosa. Furthermore, during the hypodynamic phase of septic shock, we recorded a significant compensatory increase in oxygen extraction in the splanchnic region (fig. 6). The magnitude of the oxygen extraction reached levels usually seen only when oxygen consumption becomes dependent on oxygen delivery.[42] Interestingly, pHi in the gastric mucosa, where microcirculatory blood flow decreased significantly, and pHi in the jejunal mucosa, where microcirculatory blood flow remained virtually constant, decreased in parallel ($r^2 = 0.66$; fig. 5). This is in accordance with data published by Montgomery *et al.*[43] showing that gastric mucosal pHi correlates signif-

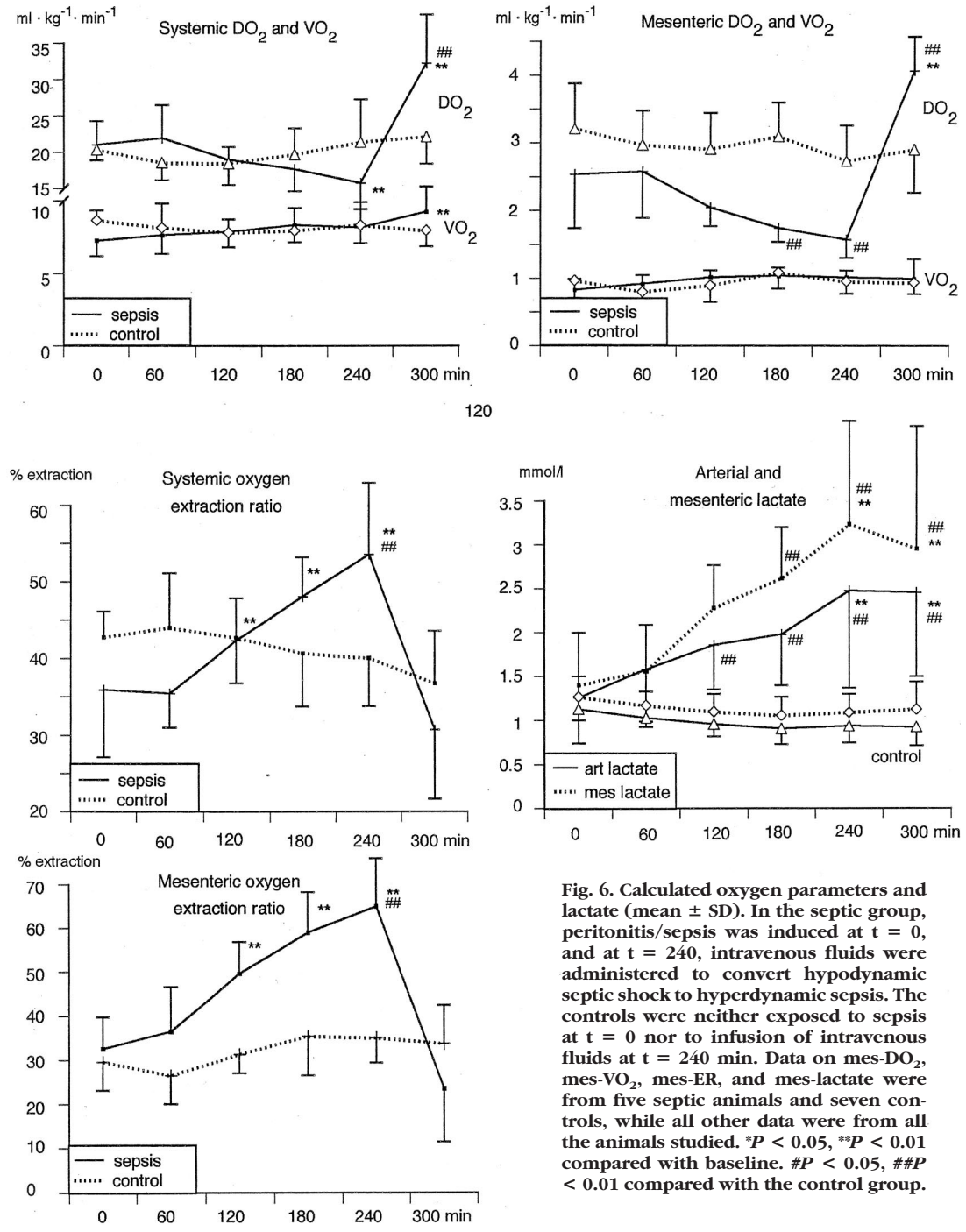

Fig. 6. Calculated oxygen parameters and lactate (mean ± SD). In the septic group, peritonitis/sepsis was induced at t = 0, and at t = 240, intravenous fluids were administered to convert hypodynamic septic shock to hyperdynamic sepsis. The controls were neither exposed to sepsis at t = 0 nor to infusion of intravenous fluids at t = 240 min. Data on mes-DO_2, mes-VO_2, mes-ER, and mes-lactate were from five septic animals and seven controls, while all other data were from all the animals studied. *$P < 0.05$, **$P < 0.01$ compared with baseline. #$P < 0.05$, ##$P < 0.01$ compared with the control group.

icantly with pHi in the small and large intestine in a porcine model of hemorrhage. On the other hand, when the different behavior of microcirculatory flow in the mucosa of the stomach and the small intestine is considered, these findings are intriguing. Also, when bearing in mind that the mucosal blood flow in the jejunum remained virtually constant during the hypodynamic phase of septic shock, it is tempting to assume that the oxygen delivery of the mucosa in the small intestine was sufficient. The fact that the splanchnic oxygen consumption remained constant or showed a trend to increase supports that assumption. This does not, however, explain the development of mucosal acidosis in the jejunum. Gastric and intestinal tonometry are generally believed to reflect the metabolic state of the mucosa during low-flow states. Whereas the carbon dioxide diffuses readily through tissues, the carbon dioxide measured by tonometry may originate in other tissues, such as the intestinal muscularis, which was, in contrast to the mucosa, markedly hypoperfused (figs. 3 and 4).[18] In other words, it may be suggested that mucosal acidosis in the stomach was predominantly caused by hypoperfusion of the gas-

Table 2. Acid–base and Metabolic Variables during Septic Shock

	Pao_2, mmHg		$Paco_2$, mmHg		pHa		SvO_2, %		HCO_3^-, mM		Arterial Hematocrit, %	
Min	Control	Sepsis	Control	Sepsis	Control	Sepsis	Control	Sepsis	Control	Sepsis	Control	Sepsis
0	142 ± 9	144 ± 10	41 ± 1	40 ± 2	7.482 ± 0.02	7.465 ± 0.03	58 ± 4	62 ± 7	29. ± 1.8	28.1 ± 1.5‡	29.4 ± 4.4	31.9 ± 2.5
60	138 ± 16	140 ± 15	41 ± 2	43 ± 2	7.479 ± 0.02	7.417 ± 0.04§	57 ± 6	62 ± 4‡	29.4 ± 1.7	26.3 ± 1.6§	25.4 ± 4.0	36.6 ± 2†§
120	134 ± 16	137 ± 11	41 ± 1	43 ± 2	7.471 ± 0.02	7.392 ± 0.04†§	58 ± 5	54 ± 5*	28.8 ± 1.4	24.8 ± 1.8†§	25 ± 4.5	39.4 ± 2.8†§
180	133 ± 18	133 ± 15	42 ± 1	44 ± 2*	7.461 ± 0.02†	7.365 ± 0.03†§	59 ± 7	49 ± 4†	28.4 ± 1.7	24 ± 1.7†§	25.8 ± 4.3	42.6 ± 3.4†§
240	131 ± 13	131 ± 14†	42 ± 2	45 ± 2†	7.454 ± 0.02†	7.326 ± 0.05†§	59 ± 5	44 ± 8†§	28 ± 1.6	22.2 ± 2.2†§	25.4 ± 4.1	43.2 ± 4.2†§
300	128 ± 12*	122 ± 20†	42 ± 1	43 ± 3	7.45 ± 0.02†	7.367 ± 0.04†§	64 ± 6	67 ± 5	28.2 ± 1.5	23.5 ± 2.2†§	26.1 ± 4.4	31.2 ± 4.2‡

Data shown as mean ± SD.

HCO_3^-, arterial bicarbonate; $Paco_2$, arterial carbon dioxide tension; Pao_2, arterial oxygen tension; pHa, arterial pH; SvO_2, mixed venous oxygen saturation.

*$P < 0.05$, †$P < 0.01$ compared with baseline.

‡$P < 0.05$, §$P < 0.01$ compared with the control group.

tric mucosa, while acidosis in the mucosa of the small bowel may have been caused by hypoperfusion of the muscularis. However, this hypothesis will have to be tested in another study.

Other possible mechanisms that may have caused this mucosal acidosis would be microvascular dysfunction, caused by decreased capillary density, which can occur despite that flow remains unchanged[14] or it may have been caused by cytopathic hypoxia, a sepsis related defect in oxygen utilization.[17]

In conclusion, this study has shown that microcirculatory blood flow in the mucosa of the small and large intestine remained virtually constant during hypodynamic septic shock despite considerable reduction in regional blood flow. It appears that redistribution of microcirculatory blood flow away from the muscularis layer toward the mucosa is an important regulatory mechanism to maintain blood flow to the intestinal mucosa during hypodynamic septic shock. These findings suggest a largely intact autoregulation of blood flow in the intestinal wall in early septic shock.

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