Thoracic Epidural Anesthesia Attenuates Hemorrhage-induced Impairment of Intestinal Perfusion in Rats

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**Background:** During hemorrhagic hypotension, sympathetic vasoconstriction crucially contributes to gut mucosal damage. Sympathetic blockade by thoracic epidural anesthesia has been shown to increase mucosal microvascular perfusion and to improve survival after severe hemorrhage in laboratory animals. This study investigates the effects of thoracic epidural anesthesia on intestinal microvascular perfusion during hemorrhagic hypotension in rats.

**Methods:** In 32 anesthetized Sprague-Dawley rats either lidocaine 2% (thoracic epidural anesthesia) or normal saline (control) was infused via thoracic epidural catheters. Hemorrhagic hypotension (mean arterial pressure 30 mmHg for 60 min) was induced by withdrawal of blood, which was subsequently retransfused for resuscitation. Functional capillary density and erythrocyte velocity in the mucosa and muscularis were determined by intravital microscopy. Leukocyte–endothelium interaction was studied in postcapillary venules and sympathetic nerve fibers of the intestinal wall were identified by immunohistochemistry.

**Results:** During hypotension functional capillary density was significantly (P < 0.001) lower in the muscularis of the control group (median [25/75 percentile]: −46.5% [−59.6/−20.8%] change from baseline) as compared with animals that received thoracic epidural anesthesia (−6.1% [−13.4/4.1%]). There were no differences in erythrocyte velocity between groups throughout the experiment. Leukocyte rolling increased significantly (P < 0.001) after resuscitation in control (12 [6/15] vs. baseline 2.5 [1/8]) but not in thoracic epidural anesthesia (4 [2.3/7] vs. baseline: 5 [3/15.5]). Sympathetic nerve fibers were identified in the muscularis and submucosa but not in the mucosa.

**Conclusions:** During hemorrhagic hypotension and after resuscitation, thoracic epidural anesthesia has beneficial effects on intestinal microvascular perfusion. Because of blockade of sympathetic nerves, thoracic epidural anesthesia prevents perfusion impairment of the muscularis during hypotension and attenuates leukocyte rolling after resuscitation.


**Materials and Methods**

**Animals**

Male Sprague-Dawley rats weighing 250–300 g were used in all experiments. All animals were housed in our animal facility and supplied with a standard diet and tap water ad libitum until the experiment. The study was approved by the local animal care committee (Berlin, Germany; permit No. G0021/01).

**Epidural Catheterization**

Epidural catheters were prepared according to the slightly modified method of Bahar et al.12 Briefly, a 200-mm-long polyethylene catheter (PE 10, Portex, Hythe,
UK) was armed with a monofilamentous suture (Prolene® 4/0, Ethicon Inc., Somerville, NJ) to reduce catheter dead space to 5 μl. To ensure catheter placement at a thoracic level of T11/12, a hub was created 40 mm from the tip using heated glue (LT110, UHU GmbH, Bühl, Germany). A sagittal midline incision along the spinal processes of L2–S1 was made during general anesthesia. The spinal process of L5 was removed and a hole was drilled in the dorsal lamina of L4. The catheter was introduced to the point where the hub reached the drilling hole. Subsequent suture and tape fixation prevented displacement of the catheter. After each experiment, the correct position of the catheter in the epidural space was confirmed by autopsy. Epidural spread of lidocaine was tested with equivalent doses of methylene blue solution 1% (n = 6). Plasma lidocaine concentrations at the end of the experiment were determined by gas chromatography (n = 5).

**Experimental Protocol**

Animals were allocated to four groups (table 1). Anesthesia was provided by subcutaneous urethane (1.5 g/kg) and intramuscular ketamine (50 mg/kg). Ketamine was supplemented between the measurements, if necessary. An epidural catheter was inserted as described in the previous section. A tracheostomy was performed and animals were mechanically ventilated with room air using a small-animal ventilator (Harvard Apparatus, Edenbridge, UK). The right and left carotid artery were cannulated using polyethylene catheters (PE 50, Portex) for continuous monitoring of MAP and heart rate (HR) and withdrawal of blood. The right external jugular vein was cannulated for continuous infusion of normal saline (3 ml/h) to ensure normovolemia. Arterial blood was analyzed for blood gases, hematocrit and acid–base status repeatedly (Rapidlab 348, Chiron Diagnostics GmbH, Fernwald, Germany). If necessary, ventilation was adjusted to maintain arterial Pco₂ within the normal range (40 ± 5 mmHg). During the hypotensive period metabolic acidemia required hyperventilation to a mean Pco₂ of 26.4 ± 2.4 (SD). Body temperature was kept constant at 37°C throughout the whole experiment using a warming pad and a rectal temperature probe linked with a control unit (Harvard Electronics, Edenbridge, UK).

A segment of distal ileum was prepared for intravital microscopy and rats were allowed to stabilize for 30 min. All animals received an intravenous bolus injection of normal saline (1 or 2 ml) to hold initial hematocrit within the range of 35–55%. After intravenous injection of 0.2 ml 5% fluorescein isothiocyanate-labeled dextran (molecular weight 150,000; FD 150S, Sigma Aldrich, Deisenhofen, Germany), baseline recordings from 10 randomly chosen mucosal villi (group I and II) and 10 regions of muscularis (group III and IV) were obtained. Subsequently, an epidural injection of lidocaine 2% (30 μl) was administered in group I and III over a period of 15 min. A continuous epidural infusion of lidocaine 2%, with an infusion rate of 100 μl/h (Infusion pump, Harvard Apparatus, South Natick, MA), was started to sustain the level of sympathetic blockade. Control groups (II and IV) received normal saline in a corresponding regimen. 30 min after the start of the epidural infusion a second set of recordings was obtained. Hemorrhagic hypotension was induced within 15 min by incremental withdrawal of blood into a heparinized plastic syringe to a MAP of 30 mmHg. MAP was maintained at this level for 60 min by further withdrawal or transfusion of blood (constant pressure model). At the end of the hypotension period, another set of images was recorded to study the impact of hemorrhagic hypotension on ileal perfusion with or without epidural sympathetic blockade. For resuscitation, the entire volume of withdrawn blood was transfused within 15 min. A final set of images was obtained 60 min after resuscitation. On completion of the experiment, the animals were killed by an intravenous injection of pentobarbital (200 mg/kg).

**Immunohistochemistry**

Six rats were anesthetized with halothane and transcardially perfused with 100 ml of phosphate-buffered saline (pH 7.4) and 300 ml of cold phosphate-buffered saline containing 4% paraformaldehyde (pH 7.4, fixative solution). The terminal ileum was removed, postfixed at 4°C for 30 min in the fixative solution, and cryoprotected at 4°C overnight in phosphate-buffered saline containing 10% sucrose. The tissues were then embedded in tissue-Tek compound (O.C.T., Miles Inc., Elkhart, IN) and frozen at −20°C. Ten-micrometer-thick sections prepared on a cryostat were mounted onto gelatin-coated slides. Immunofluorescence staining of the sections was performed as described previously. Unless otherwise stated, all incubations were done at room temperature and phosphate-buffered saline was used for washing (three times for 10 min) after each step. The sections were first incubated for 60 min in block solution (phosphate-buffered saline containing 0.3% Triton X-100, 1% bovine serum albumin, 4% goat serum, and 4% horse serum), then overnight at 4°C with mouse antirat tyrosine hydroxylase antibodies (1:1000, Incstar, Minneapolis, MN). This was followed by 1-h incubation with fluorescein isothiocyanate-conjugated horse antimouse secondary antibody (Vector Laboratories, Burlingame, CA). After final washings, the sections were mounted in Vectashield (Vector Laboratories) and analyzed under a

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**Table 1. Experimental Groups**

<table>
<thead>
<tr>
<th>Group (n = 8)</th>
<th>Layer Investigated</th>
<th>Epidural Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Mucosa</td>
<td>Lidocaine 2% (TEA)</td>
</tr>
<tr>
<td>II</td>
<td>Mucosa</td>
<td>Normal saline (CTRL)</td>
</tr>
<tr>
<td>III</td>
<td>Muscularis</td>
<td>Lidocaine 2% (TEA)</td>
</tr>
<tr>
<td>IV</td>
<td>Muscularis</td>
<td>Normal saline (CTRL)</td>
</tr>
</tbody>
</table>

CTRL = control; TEA = thoracic epidural anesthesia.
fluorescence microscope (Zeiss, Jena, Germany) with appropriate filters. To demonstrate specificity of staining, either the primary or the secondary antibodies were omitted. These control experiments did not show tryosine hydroxylase staining. For histologic assessment, ileal tissue sections were stained by hematoxylin and eosin.

Preparation of the Ileum
A loop of the terminal ileum was exteriorized through an abdominal midline incision and positioned on an adjustable platform. This experimental setup ensured permanent visualization of mesenteric vessels and prevention of accidental compression and vascular stasis. Separating the intestinal loop from the abdominal wall avoided the transmission of respiratory movements and improved the quality of in vivo imaging. For visualization of the mucosa, the ileal segment was opened along its antimesenteric border over a distance of 3 or 4 cm using electrocautery. Subsequently, it was gently cleaned its antimesenteric border over a distance of 3 or 4 cm

In Vivo Microscopy
Microscopy was performed using a Leitz microscope (Leitz, Wetzlar, Germany) equipped with a 150-W xenon lamp (XBO 150 W/1, Osram, München, Germany) and attached to a Ploemo-Pak illuminator (Leitz) with an I2 (excitation: 450–490 nm, more than 515-nm emission) filter block for epifluorescence illumination. With a ×10 water-immersion objective, the technique allowed for a magnification of approximately ×600. The microscopic picture was transferred to a monitor (Sony, Cologne, Germany) by a low-light camera (CF8/4 FMC C, KAPPA opto-electronics GmbH, Gleichen, Germany) and videotaped (RTV-950, Blaupunkt, Hildesheim, Germany) for off-line analysis.

Microcirculatory Analysis
An investigator who was blinded to the study design performed microcirculatory off-line analysis using a personal computer equipped with a real-time image-processing board. A specially designed software package (Vision3D, Vmorph, Pries AR, Drüsedow S, Berlin, Germany, 1998) was used to determine capillary density and erythrocyte velocity in the mucosa and the muscularis as well as main villus arteriole diameters. Capillaries were manually redrawn on a transparent sheet from subsequent frozen video images (fig. 1). This allowed us to reproduce the complete microvascular network despite temporary blurring of the picture due to gut motility.

Perfused and nonperfused capillaries were determined separately. Using Vision3D, the network was transferred to the computer to obtain capillary lengths (computer-assisted calculation). Observation areas were defined as the boundaries of the villus for the mucosa (fig. 1) and the boundaries of the monitor screen for the muscularis. Functional capillary density (FCD) was defined as the length of erythrocyte-perfused capillaries (cm−1) per observation area. Nonperfused capillary density was defined as the length of capillaries without erythrocyte perfusion over the observation period of 60 s per observation area. The values for FCD and nonperfused capillary density were added to obtain the total capillary density. To obtain one value for capillary density per rat and time point, the capillary lengths of 6–10 regions were added and divided by the sum of the corresponding areas. Erythrocyte velocity was determined using the frame-by-frame method. The distance a fluorescent plasma gap covered over the time of 2–10 frames (40 ms each) was measured and divided by the time. Three values were determined in each observation area and data of 6–10 regions then were averaged. Mucosal erythrocyte velocity was determined in the terminal feeding arterioles (fig. 1). FCD and erythrocyte velocity are reported as percentage change from baseline values. The diameter of the main villus arteriole was assessed at three different segments of the vessel. The three values were averaged to give one value for each individual villus arteriole, and the median value of 10 arterioles was calculated to give one diameter per measurement.

Leukocyte-Endothelium Interaction
To assess leukocyte–endothelium interaction, white blood cells were stained by an intravenous injection of rhodamine 6G (0.1 ml of a 0.2% solution). Using a N2.1 filter block (excitation: 515–560 nm, more than 580-nm emission), leukocytes were visualized in submucosal post-capillary venules of 100 ± 14.2 μm diameter. Leukocytes...
moving along the vessel wall at a velocity well below that of other blood cells were defined as rolling leukocytes. Focus was set on the vessel wall at its circumference and leukocytes were counted along a vessel length of 100 μm for 60 s. Three venules were examined in each animal (n = 6 per group) at baseline and 60 min after resuscitation.

Statistical Analysis
All tests were performed using Sigma Stat 2.03 software (SPSS Inc., Erkrath, Germany). Nonparametric data are displayed as medians and quartiles [25th, 75th percentiles]. All values in tables are presented as mean ± SD. Blood-loss was compared using paired t test. Two-way repeated measures analysis of variance was applied to all other data. Nonparametric data were ranked before analysis. Student-Newman-Keuls test was used for multiple comparisons. For all statistical tests, significance was assumed at the P < 0.05 level.

Results
Epidural spread of lidocaine was tested with analogous doses of methylene blue solution 1% and reached from T6 to L4 (n = 6). Mean ± SD lidocaine plasma concentration in TEA animals at the end of the experiment was 0.54 ± 0.15 μg/ml (n = 5).

Hemodynamic Data
Table 2 shows hemodynamic data, which are comparable at baseline values in all groups. TEA decreased MAP significantly only in group III. During hypotension, HR decreased in TEA animals but not in controls. After resuscitation, MAP and HR were lower in the TEA group than in the respective controls. Hematocrit was significantly lower in control group IV during hypotension. In all groups hematocrit was restored into the normal range (36–54%) after retransfusion of shed blood. During hemorrhage, blood loss was comparable in all groups (group I: 2.0 ± 0.2, group II: 2.2 ± 0.1, group III: 1.9 ± 0.1, group IV: 2.2 ± 0.1 ml/100 g).

Acid–Base Status
Table 3 shows pH and base-excess data in TEA and control groups. Besides an increase in pH after epidural infusion of lidocaine 2%, TEA prevents a severe decrease

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>30 min after Epidural Infusion</th>
<th>After 60 min of Hypotension</th>
<th>60 min after Resuscitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I (TEA)</td>
<td>115 ± 9</td>
<td>106 ± 16</td>
<td>30 ± 0</td>
<td>51 ± 11*</td>
</tr>
<tr>
<td>II (CTRL)</td>
<td>109 ± 13</td>
<td>115 ± 19</td>
<td>30 ± 0</td>
<td>72 ± 23</td>
</tr>
<tr>
<td>III (TEA)</td>
<td>123 ± 6</td>
<td>104 ± 16†</td>
<td>30 ± 0</td>
<td>92 ± 22*</td>
</tr>
<tr>
<td>IV (CTRL)</td>
<td>118 ± 18</td>
<td>118 ± 13</td>
<td>30 ± 0</td>
<td>121 ± 11</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I (TEA)</td>
<td>344 ± 58</td>
<td>347 ± 67</td>
<td>297 ± 55†</td>
<td>301 ± 59†</td>
</tr>
<tr>
<td>II (CTRL)</td>
<td>375 ± 53</td>
<td>395 ± 30</td>
<td>368 ± 39</td>
<td>389 ± 47</td>
</tr>
<tr>
<td>III (TEA)</td>
<td>389 ± 35</td>
<td>335 ± 56</td>
<td>294 ± 40*</td>
<td>341 ± 69*</td>
</tr>
<tr>
<td>IV (CTRL)</td>
<td>388 ± 48</td>
<td>376 ± 19</td>
<td>366 ± 22</td>
<td>436 ± 31</td>
</tr>
<tr>
<td>Hct (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I (TEA)</td>
<td>47.4 ± 4.6</td>
<td>41.6 ± 3.0</td>
<td>29.6 ± 4.3</td>
<td>35.5 ± 4.1</td>
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<tr>
<td>II (CTRL)</td>
<td>44.9 ± 4.4</td>
<td>42.4 ± 5.7</td>
<td>26.7 ± 4.1</td>
<td>36.1 ± 7.9</td>
</tr>
<tr>
<td>III (TEA)</td>
<td>50.4 ± 3.3</td>
<td>45.6 ± 4.2</td>
<td>31.9 ± 5.0</td>
<td>38.8 ± 3.7</td>
</tr>
<tr>
<td>IV (CTRL)</td>
<td>50.4 ± 3.5</td>
<td>47.9 ± 3.9</td>
<td>24.9 ± 6.9†</td>
<td>42.6 ± 2.8</td>
</tr>
</tbody>
</table>

Data are mean ± SD.
* P < 0.05 vs. control group; † P < 0.01 vs. TEA group.
BE = base excess; CTRL = control; TEA = thoracic epidural anesthesia.

Table 2. Mean Arterial Pressure, Heart Rate, and Hematocrit

Table 3. Acid–Base Status
in pH and base excess during hypotension. Mean ± SD pH of the blood after 1 h of storage was 7.19 ± 0.05.

**Microvascular Perfusion of the Terminal Ileum**

Values for total capillary density were comparable between groups, indicating equivalent microvascular conditions after tissue preparation (group I: 505.4 ± 70.6, group II: 555.1 ± 156.3, group III: 310.3 ± 19.8, group IV: 299.5 ± mm⁻¹). Figure 2 shows the change of functional capillary density from baseline values in the mucosa and the muscularis. In the mucosa, no significant changes were seen during the experiment. In the muscularis, hemorrhagic hypotension significantly impaired capillary perfusion in the control group but not in the TEA group.

Figure 3 shows the change in erythrocyte velocity during the experiment. Epidural infusion of lidocaine 2% or normal saline had no significant effect on erythrocyte velocity. During hypotension velocity is reduced in the muscularis only. After resuscitation erythrocyte velocity is restored. No differences between groups could be seen in either layer throughout the experiment. In both groups, diameters of main villus arterioles did not vary significantly during the experiment (CTRL: 10.4 ± 1.8, 9.3 ± 1.4, 10.6 ± 1.4, 10.1 ± 1.3 μm; TEA: 11.4 ± 1.6, 10.1 ± 2, 9.9 ± 1.3, 10.2 ± 1.5 μm).

**Immunohistochemistry**

Figure 4 shows hematoxylin-eosin staining (A) and immunohistochemistry (B–D) of the terminal ileum. Perivascular tyrosine hydroxylase-immunoreactive nerve fibers were abundant in the muscularis (B and C) and submucosa (D), but were not detected in the mucosa (D) of the rat terminal ileum.

**Leukocyte-Endothelium Interaction**

Figure 5 shows that leukocyte rolling increased significantly in the control group after resuscitation but...
remained unchanged in the TEA group. Diameters of postcapillary venules did not differ between groups at baseline and after resuscitation (CTRL: 99.8 ± 14.1, 101.8 ± 14.2 μm; TEA: 102.1 ± 10.9, 105.2 ± 17.1 μm).

**Discussion**

The principal findings of this study are that (1) hemorrhagic hypotension distinctly affects ileal microvascular perfusion, and the capillary perfusion deficit is limited to the muscularis; (2) sympathetic innervation of vessels was detected in all layers of the gut except the mucosa; (3) TEA blocks sympathetic activation and thus inhibits hypotension-induced impairment of capillary perfusion in the muscularis despite a decrease in MAP; (4) TEA prevents systemic acidemia and a severe decrease in base excess during hypotension; and (5) TEA inhibits the increase of rolling leukocytes after hypotension and resuscitation.

To quantitatively assess the effects of hemorrhagic hypotension, TEA, and the combination of both on the transmural microvascular perfusion of the gut, we determined FCD and erythrocyte velocity of both the mucosa and muscularis in rats. Apart from the fact that tissue supply with oxygen also takes place by transmural oxygen loss through precapillary microvessels, FCD and blood flow represent major parameters of tissue oxygenation.
Hemodynamic Data

During the constant-pressure hypotension period, HR was significantly lower in TEA animals (table 2). Sixty minutes after resuscitation, MAP and HR were significantly altered between groups, and differences in MAP and HR seen with TEA are most likely due to sympathetic blockade of nerve fibers innervating resistance vessels and the heart, respectively. Because methylene blue staining has revealed epidural spread to a thoracic level of T6, we speculate that the local anesthetic effect exceeds the upper level of the dye, a finding that has been described previously.16

Hematocrit in group IV was slightly but significantly lower compared to other groups during hemorrhage. Hemodilution studies in rats have shown that the critical hematocrit for intestinal oxygen supply is approximately 16%,17 which is far lower than the value reached in group IV (24.9%). Also, hemodilution to a hematocrit of 25% does not affect the ability of the gut to maintain oxygen consumption during hypotension (MAP 42 mmHg). 30 Moreover, a decrease in tissue oxygenation should cause an increase in capillary exchange surface and blood flow than a decrease. This implies that the decrease in FCD (fig. 2, right) is due to an alteration in perfusion pressure rather than an alteration in hematocrit.

Intestinal Microvascular Perfusion during Hypotension and after Resuscitation.

The decrease in erythrocyte velocity observed during hemorrhage in the ileal muscularis (fig. 3) is in agreement with the common finding of splanchnic hypoperfusion as a regulatory response to systemic hypotension.19,20 Our results further show that during hemorrhagic hypotension capillary perfusion is reduced in the muscularis but not in the mucosa. This transmural redistribution is in line with the results of studies that found a shift of blood flow towards the more vulnerable mucosa when perfusion pressure is decreased.21-23

Although multiple factors regulate intestinal blood flow, we hypothesize that the redistribution of intestinal capillary perfusion in favor of the mucosa during hemorrhage is mainly due to sympathetically mediated vasoconstriction. This hypothesis is supported by our immunohistologic findings (fig. 4), which show rich sympathetic innervation in vessels of the submucosa and muscularis but not of the mucosa. Accordingly, the mucosa is far less affected by sympathetic stimulation as compared to the muscularis.24 During sympathetically mediated vasoconstriction of large submucosal arterioles, mucosal arterioles may even dilate as a result of an autoregulatory escape.25,26

Effects of Thoracic Epidural Anesthesia on Intestinal Microvascular Perfusion

Under baseline hemodynamic conditions, TEA did not notably alter mucosal FCD (fig. 2, left). Accordingly, Sielenkämper et al.8 reported that epidural bupivacaine had no significant effect on total intercapillary area size, an analogous value for FCD. They described, however, an increase in erythrocyte velocity and a considerable shift from intermittent to continuous perfusion of mucosal capillaries. Both effects could not be confirmed in our experiments (perfusion data not shown). During subsequent hemorrhagic hypotension, TEA completely prevented the decrease in FCD in the muscularis. Because TEA did not notably alter erythrocyte velocity but led to a significant increase of perfused capillaries during hypotension, an overall increase in blood flow to the intestine must be postulated.

Diameters of the main villus arteriole were not considerably altered by epidural lidocaine. Congruent with our results, neither epidural bupivacaine8 nor surgical denervation of major mesenteric vessels27 had an effect on the diameter of the villus arteriole. This finding again is explained by scarce adrenergic innervation of the ileal mucosa shown in our immunohistochimical studies. Possible sites for the neural control of intestinal blood flow are parallel (muscularis) and serially connected upstream arterioles (submucosa, mesenterium). Indeed, vasoconstriction of large supplying mesenteric arterioles was observed during hemorrhagic hypotension.26,28,29

Effects of Epidural Lidocaine on Systemic pH and Base Excess

Severe metabolic derangements are often seen with hemorrhagic shock in laboratory animals.30-32 As shown in table 3, TEA prevents metabolic acidemia and reduces the dramatic decrease in base excess during hypotension. Although these values are restored in controls after resuscitation, they represent important prognostic factors for survival after hemorrhagic shock.31 A reduction of gastric and intestinal pH by means of TEA has been demonstrated by others.7,53-55 Whether alterations in systemic acid-base status are based on changes in gastrointestinal pH cannot be stated.

Leukocyte-Endothelium Interaction

Leukocyte–endothelium interaction after ischemia/reperfusion is a well-described phenomenon that contributes to posts ischemic tissue injury.36,37 Prevention of leukocyte rolling, the first step of the inflammatory reaction to low-flow states, attenuates reperfusion injury38 and increases survival after hemorrhagic hypotension in rats.39 We examined the influence of TEA on posthemorrhage leukocyte–endothelium interaction. We chose submucosal postcapillary venules for assessment of leukocyte rolling because these vessels drain blood from muscularis and mucosa. Figure 5 shows that epidural lidocaine prevented the rise in the number of rolling leukocytes after hemorrhage and resuscitation observed in control animals. Although a systemic effect of lidocaine cannot be completely excluded, a mean plasma concentration of 0.51 μg/ml seems to be too low to influence leukocyte trafficking. Effect on superoxide anion release of neutrophils is re-
ported at plasma levels of 1.0–5.6 μg/ml in humans.\textsuperscript{40} In a rabbit model of hydrochloric acid aspiration, lung leuko-
questration was reduced at lidocaine plasma concentra-
tions of 1.2–2.5 μg/ml.\textsuperscript{41}

Because venule diameters and arteriolar blood cell velocity are not altered by TEA, an augmentation of venular hemodynamic forces as a possible explanation for decreased leukocyte rolling with TEA is unlikely. We therefore postulate that by improving tissue oxygenation in the intestine during hypotension, TEA reduces activation of endothelium and leukocytes.

In conclusion, this study shows that TEA, despite its depressant effect on HR and MAP, improves microvas-
cular perfusion of the small intestine during acute hem-
orrhagic hypotension in rats. During hemorrhage, TEA preserves capillary perfusion of the muscularis, most likely due to effects on upstream arterioles and arteries. Furthermore, TEA prevents severe systemic acidosis and inhibits intestinal leukocyte rolling, both important fac-
tors for survival after hemorrhagic shock. The specific effect of TEA on microvascular perfusion of the muscu-
laris is in accordance with the lack of sympathetic nerve fibers within the mucosa. Further investigations are needed to assess the effects of regional sympathetic blockade on mesenteric arterioles and blood flow distribu-
tion to other organs during hemorrhage.

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