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Thoracic Epidural Anesthesia Increases Mucosal Perfusion in Ileum of Rats

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Background: **Previous studies reported that thoracic epidural anesthesia (TEA) protected against a decrease in gastric intramucosal pH, suggesting that TEA increased gut mucosal perfusion. The current study examines the effects of TEA on ileal mucosa using intravital microscopy in anesthetized rats.**

Methods: **Nineteen rats were equipped with epidural catheters, with the tip placed at T7 through T9. Rats were anesthetized and mechanically ventilated. After midline abdominal incision, the ileum was prepared for intravital microscopy. Videomicroscopy on the ileal mucosa was performed before and after epidural infusion of 20 μl of bupivacaine 0.4% (TEA group, n = 11 rats) or normal saline (control group, n = 8 rats). Microvascular blood flow in ileum mucosa was assessed offline using computerized image analysis.**

Results: **Control rats exhibited unchanged mean arterial pressure and microvascular perfusion. During TEA, mean arterial pressure was decreased compared with the control group (93 ± 10 *vs.* 105 ± 9 mmHg; $P < 0.05$). Epidural bupivacaine increased red cell velocity in terminal arterioles from 888 ± 202 to 1,215 ± 268 μm/s (control, 793 ± 250 to 741 ± 195 μm/s; $P < 0.001$ between groups). Because arteriolar diameter was not affected, this increase in red cell velocity may represent an increase in arteriolar blood flow. Total intercapillary area (inversely related to perfused capillary density) was unchanged, but for the TEA group the difference between total intercapillary area and the intercapillary area calculated for continuously perfused capillaries was decreased compared with the control group (16 ± 12 *vs.* 40 ± 19%; $P < 0.001$), indicating a decrease in intermittent (stop-and-go) blood flow in the villus microcirculation.**

Conclusion: **Thoracic epidural anesthesia increased gut mucosal blood flow and reduced intermittent flow in the villus microcirculation in the presence of a decreased perfusion pressure. (Key words: Bupivacaine; gut; intravital microscopy; microcirculation.)**

GASTROINTESTINAL hypoperfusion may occur during surgical interventions, especially during major abdominal surgery[1] or if the procedure involves cardiopulmonary bypass.[2,3] Gastrointestinal hypoperfusion is regarded as an important factor in the pathophysiology of the so-called surgical stress response and is thought to be related to postoperative complications such as intestinal paralysis and loss of gut barrier function.[4,5] Splanchnic hypoperfusion may be associated with increased mortality rates in critically ill patients.[6,7]

Thoracic epidural anesthesia (TEA) has been shown to attenuate surgery-related injuries to the gastrointestinal system. Experimental and clinical work demonstrated that epidural anesthesia decreases the time of intestinal paralysis after laparotomy or abdominal surgery,[8–10] an effect that was explained by the blockade of sympathetic efferent nerves.[9] Also, clinical studies demonstrated that TEA prevented a decrease in gastric intramucosal *p*H (pH_i) in patients undergoing major abdominal surgery.[11,12] Gastric pH_i, a surrogate marker for the adequacy of intestinal perfusion, is a determinant of outcome in surgical patients.[7]

It has been postulated that the observed effect of TEA preventing a decrease in gastric pH_i are related to sympathetic nerve blockade, similar to the effects on intestinal paralysis.[11] For example, sympathetic nerve blockade could result in a decrease of metabolic demands or, alternatively, in improved tissue oxygen delivery as a result of either an increase or a beneficial redistribution of gut mucosal blood flow.

Because the effects of TEA on the gastrointestinal microcirculation are unclear, we designed a study to describe the effect of TEA on gut mucosal blood flow.

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Specifically, our hypothesis was that infusion of epidural bupivacaine would increase mucosal blood flow in the ileum of isoflurane-anesthetized rats. In rats equipped with an epidural catheter at the thoracic level, we used intravital microscopy to determine the effect of epidural bupivacaine on arteriolar and capillary blood flow in the ileum mucosa.

Methods

Animals

Approval from the Animal Care Committee of the District Government of Münster was obtained to perform the described experiments. Male Sprague–Dawley rats, weighing 320–380 g, were used after a 1-week acclimatization period in our laboratory. For the recovery period after implantation of an epidural catheter, the animals were housed individually in standard living cages with food and water *ad libitum*.

Epidural Catheterization

For epidural catheterization, we used the method previously described by Grouls *et al.*[13] with slight modifications. Anesthesia was induced and maintained by isoflurane inhalation. A polyethylene catheter (PE10) was introduced into the epidural space through a hole drilled in the fourth lumbar vertebra. The catheter was threaded cephalad to place the tip between T7 and T9, a distance of about 60–65 mm.

On fixation of the catheter to the fourth lumbar vertebra, the proximal end was tunneled subcutaneously to the posterior cervical area. The animals were allowed 24 hours to recover from anesthesia and surgery. Animals showing any sign of neurologic damage were discarded. On completion of the experiment, the rats were killed and the position of the catheter tip was verified after injection of Evans blue solution. Animals with catheter tips located intrathecally or outside the level of T7 through T9 also were excluded from the study.

Muscle Tone

Muscle tone was scored by manual inspection and visual observation according to the Bromage score for humans, which was modified for rats as described by Grouls *et al.*:[13] 0 = normal tone, free movement of the hind limbs; −1 = weak hypotonia of the hind limbs and body posture; −2 = moderate hypotonia of the hind limbs and body posture; −3 = inability to support the body on the hind limbs and flat body posture.

Experimental Protocol

Twenty-four hours after placement of the epidural catheter, the rats received an injection of 20 μl 0.4% bupivacaine *via* the epidural route. Muscle tone was scored for 30 min to determine duration and quality of the motor blockade in the absence of general anesthesia. Another 24 h later, rats were anesthetized again using isoflurane inhalation. A tracheotomy was performed and the animal was ventilated mechanically using a rodent ventilator pump (55-3428; Harvard Apparatus, Holliston, MA) and receiving an isoflurane-O_2-N_2 mixture (fraction of inspired oxygen = 0.5). Catheters were advanced into the superior vena cava and left carotid artery, and a small midline laparotomy was performed. After completion of the surgical procedures, the isoflurane concentration was adjusted at 1.5% volume for the remainder of the experiment, and the animal was placed on the microscope stage. Normal saline was infused continuously (2 ml per 100 g per hour, intravenously). Blood gases were analyzed with a gas analyzer (ABL 3, Radiometer, Copenhagen, Denmark) to ensure sufficient oxygenation (arterial oxygen saturation > 93%) and to adjust ventilation to maintain a partial pressure of carbon dioxide of 35–45 mmHg. Arterial blood pressure and body temperature were measured continuously. Body temperature was kept at approximately 36°C using an infrared heat lamp.

Next, a segment of distal ileum was prepared for intravital microscopy. After bowel preparation, images from 4–10 villi of ileal mucosa were recorded after a 20-min stabilization period from the time the gut preparation was completed (baseline 1). The animals then received an injection of 20 μl of either bupivacain 0.4% (TEA group, n = 11 rats) or normal saline (control group, n = 8) through the epidural catheter. A second set of recordings from the mucosa was obtained starting 3–5 min later, to allow sufficient time for hemodynamic stabilization for those rats that received bupivacaine infusion. Recordings were completed within 20 min from the time of bupivacaine or placebo infusion. Thirty-five to fifty-five minutes after bupivacaine infusion (15–35 minutes after resolution of TEA according to the duration of TEA as estimated from the experiments in the awake state) a final set of images was recorded in rats that had received bupivacaine (baseline 2). The purpose of these additional recordings was to study if changes in mucosal perfusion caused by infusion of epidural bupivacaine were reversed after resolution of epidural anesthesia (baseline 2).

Before the experiment was started, pilot series were

conducted to confirm that the animal model was technically possible and to identify the time available for intravital microscopy during TEA. Additional experiments were performed in awake rats equipped with an epidural catheter, to exclude the possibility that epidural infusion of normal saline would affect hind limb motility (n = 4).

Tissue Preparation

Intravital microscopy (Eclipse TE 300 microscope; Nikon, Düsseldorf, Germany) was performed according to a previously standardized methodology.[14,15] Prior to intravital microscopy, animals were given intravenous boluses of fluoroisothiocyanate bovine albumin (15–20 mg/ml) to enhance contrast between red cells and plasma. After placement of the animal onto the microscope and midline laparotomy, the ileum was identified and a 3- to 4-cm length of distal ileum, located more than 5 cm proximal to the ileocecal valve, was placed gently onto the stage. The exposed abdominal contents were irrigated intermittently with warmed normal saline.

Using unipolar cautery and fine surgical scissors, two small incisions were made into the bowel lumen on the antimesenteric border, one proximal and one distal to the area to be studied. Polyethylene tubes then were inserted to drain bowel contents. Between the two incisions and along the antimesenteric border, the bowel was opened over a distance of 2–3 cm. Bowel contents were removed gently from the surface of the mucosa using saline-wetted cotton swabs. The ileum then was inverted so that the mucosal surface was facing down on the stage. The tissue was weighted down from the serosal surface outside the immediate area of investigation using cotton swabs and two microscope slides. The temperature of the preparation was measured using a thermocouple probe. With warmed saline the temperature of the preparation was kept between 34 and 36°C.

Recordings and Data Aquisition

Videomicroscopy was performed on 4–10 villi of ileal mucosa for one individual measurement. The fluoroisothiocyanate albumin was visualized using a B2 light filter (excitation filter 450–490 nm, absorption filter 520 nm, 510 dichroic mirror). A 20× objective lens (740× actual magnification) was used. Images were recorded onto videotape using a charge-coupled device camera (HV-C20; Hitachi, Tokyo, Japan) connected in series to a videotape recorder equipped with a time–date generator (AG-TL 700; Panasonic, Hamburg, Germany) and a monitor (Panasonic BT-H1490Y). Each villus was recorded twice for 30 s, interrupted for 30 s to avoid damage of the preparation by fluorescence light. For recordings after the interventions, we studied the same region that was used initially to obtain images. Approximately 50–60% of the initially recorded villi were reidentified during the subsequent measurements and used for true paired comparisons. Minor movements of the bowel (*e.g.*, peristalsis) or local mucus production often prevented optimal visualization of previously recorded villi or rendered a reidentification impossible. Thus other randomly chosen villi in this region were studied as well.

Mean arterial pressure was measured with transducers and a Sirecust 404 monitor (Siemens AG, Munich, Germany). To determine blood pressure for an observation period, three values obtained in 5-min intervals were averaged.

Data Analysis

Image analysis from the video recordings was performed by an investigator who was not involved in the experimental procedures and completely blinded to the experimental design. Microvascular perfusion was analyzed for the capillary networks and the terminal (main) arterioles of the villi. For all measurements that involved computerized analysis, Sigma Scan software (SPSS, Chicago, IL) was used. To obtain absolute values, measurements were calibrated to a standard image of a taped microscope graticule.

Capillary Networks. The recorded images were played on a monitor and the vessel network of each individual villi traced onto a transparent sheet. Perfused capillaries were identified by observing at least one erythrocyte passing through during the 1 min of recording. For some capillaries, the central arteriole or a venule formed one of the boundaries for the purpose of determining the intercapillary area (ICA, inversely related to capillary density). The tracings were scanned into a computer and the images analyzed for ICA. The data for ICA over each villi were averaged, and the average ICA (ICA_{TOT}, in square micrometers) of all villi recorded at a particular time point (baseline 1, TEA, and baseline 2) were averaged again to give one measurement. To assess the quality of capillary perfusion, those segments of capillaries with stop-and-go flow periods (*e.g.*, intermittent flow) then were discarded. The ICA was analyzed again to receive an estimate of the continuously perfused capillary density (ICA_{CONT}). The percent difference between ICA_{TOT} and ICA_{CONT} was used to quantify intermittent flow.

Terminal Arterioles. Red blood cell velocity (V_{RBC}, in μm/s) in terminal feeding arterioles was measured using frame-by-frame analysis. The terminal arteriole of a single villus was identified by observing the direction of flow, the diameter of the vessel, and the characteristic branching into subepithelial capillaries. The average distance of red blood cell flow over time then was determined using 3 to 12 frames differing by 40 ms in time. Between two single frames, the distance that red blood cells had traveled was determined using plasma gaps, which provided contrast between RBCs. The V_{RBC} was determined by dividing the average distance of red blood cell flow over all frames for the flow in a single arteriole by the frame interval (40 ms). To determine the diameter of the arteriole the video was played directly on a computer. The arteriolar diameter then was determined at five different locations at 0, 25, 50, 75, and 100% of the visible segment of the vessel. The average of these five measurements was taken to provide an estimate for the mean diameter of the vessel. Intermittent flow was considered to be present if the arteriole exhibited stop-and-go flow with at least one stop of 1 s or longer during the observation period (1 min). The presence and the duration of intermittent flow was determined for each studied arteriole. Data for V_{RBC}, diameter, and intermittent flow were averaged for all arterioles taped at a particular time point.

To receive an estimate for the spatial heterogeneity of arteriolar perfusion (between villi), the coefficient of variation for the average V_{RBC} between the arterioles at one particular time point was calculated and averaged for each animal. This parameter is regarded as a measure of the heterogeneity of blood flow between villi.

Statistical Analysis

For statistical analysis, Sigma Stat 2.03 software (SPSS) was used. To determine the effects of epidural bupivacaine *versus* placebo infusion, an analysis was performed appropriate for a two-way repeated-measures design. To analyze the effect of epidural bupivacaine on hind limb motility and to assess whether changes in mucosal perfusion were reversed after the resolution of TEA in animals treated with epidural bupivacaine, a one-way repeated analysis of variance was performed. For *post hoc* comparisons, Student *t* tests with correction for multiple comparisons (Bonferroni's method) were used. For all statistical tests, significance was assumed at $P < 0.05$. Data are presented as the mean ± SD.

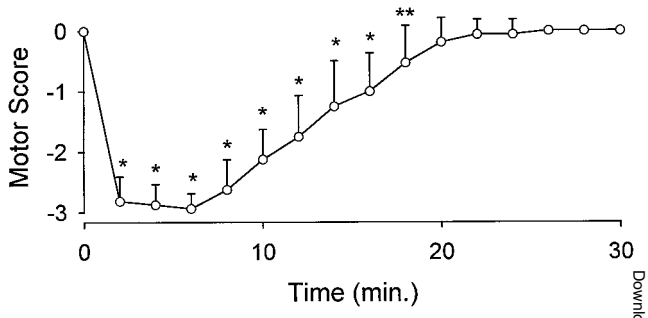

Fig. 1. Time course of changes in motor score (hind limb motility) after epidural administration of 20 μl bupivacaine, 0.4% in awake rats. Values are given as mean ± SD. *$P < 0.001$ *versus* baseline; **$P < 0.01$ *versus* baseline.

Results

Hind limb motility was not affected in four experiments in which conscious rats received a placebo epidural injection of normal saline (motility score = 0 points at all times over 30 min). Figure 1 demonstrates that epidural bupivacaine infusion induced a complete block of hind limb motility in conscious rats, with an onset time of less than 2 min. Motility recovered completely within 18–22 min after infusion in all animals.

During intravital microscopy, epidural infusion of bupivacaine in anesthetized rats resulted in an decrease in mean arterial pressure from 108 ± 9 mmHg at baseline 1 to a nadir of 62 ± 10 mmHg within the first 60 s from the time of infusion (control, 107 ± 7 to 104 ± 10 mmHg; $P < 0.001$ between groups), followed by hemodynamic stabilization within the next 1–4 min. Video recordings to assess the effects of epidural bupivacaine were made after hemodynamics had stabilized, during moderate hypotension (mean arterial pressure = 93 ± 10 *vs.* 105 ± 9 mmHg in control group; $P < 0.05$). At baseline 2, mean arterial pressure had recovered completely in the TEA group (106 ± 12 mmHg).

Diffusion distance in the ileum mucosa, as estimated by ICA_{TOT}, was not altered by epidural bupivacaine (fig. 2). ICA_{CONT} was decreased, however, after epidural bupivacaine, compared with the control group (944 ± 382 *vs.* 1,316 ± 298 μm^2; $P < 0.05$; fig. 3), indicating a transition of intermittent flow to full-time flow in many capillaries. Also, the difference between ICA_{TOT} and ICA_{CONT} was decreased during TEA compared with the control group (TEA, 23 ± 14 to 16 ± 12%; control, 32 ± 7 to 40 ± 19%; $P < 0.001$ between groups), confirming a proportional decrease in intermittent flow in the villus microcirculation. In arterioles, intermittent flow occurred only sporadically (<3% of all studied arterioles)

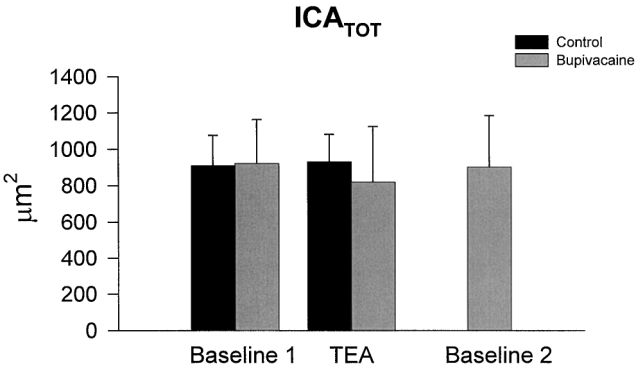

Fig. 2. Effects of epidural bupivacaine on total intercapillary area size (ICA_{TOT}) in gut mucosa. Values are given as mean ± SD. TEA = thoracic epidural anesthesia.

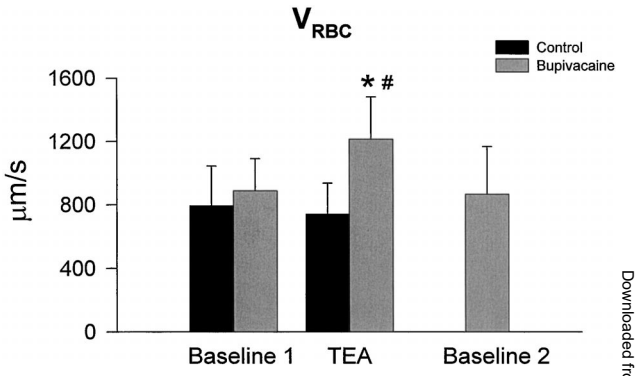

Fig. 4. Effect of epidural bupivacaine on red blood cell velocity (V_{RBC}) in terminal arterioles of gut mucosa. Values are given as mean ± SD. *P < 0.001 *versus* baseline 1; #P < 0.001 *versus* control group. TEA = thoracic epidural anesthesia.

independent of the presence or absence of TEA. V_{RBC} in arterioles increased from 888 ± 202 to 1,215 ± 268 µm/s after bupivacaine administration ($P < 0.001$ between groups; fig. 4); arteriolar diameter was not altered (fig. 5). Spatial heterogeneity of arteriolar blood flow, as estimated by the coefficient of variation for V_{RBC}, remained unchanged after bupivacaine infusion (coefficient of variation = 24.3 ± 7 to 20.1 ± 11.9%, TEA; 26.8 ± 7.8 to 30.8 ± 4.8%, control group). If determined after resolution of TEA (baseline 2), microvascular perfusion was comparable to baseline 1 (figs. 2–5).

Discussion

The main finding of this study was that under isoflurane anesthesia, TEA increased V_{RBC} in terminal arterioles of gut mucosa by 37% despite a mild decrease in arterial perfusion pressure. Because arteriolar diameters were unchanged, this increase in V_{RBC} indicates an increase in gut mucosal blood flow. Simultaneously, the density of continuously perfused capillaries increased and the extent of intermittent flow in the capillary networks of the villus microcirculation decreased, indicating a transition from intermittent flow to full-time flow in many capillaries during TEA. The observed increase in mucosal blood flow may help to explain recent observations of an increased pH_i during TEA in patients undergoing major abdominal surgery.[11]

In this experiment it was important to verify a correct position of the epidural catheter. This was done both prior to intravital microscopy, by determination of the quality and duration of the motor blockade after infusion of bupivacaine, and by *post mortem* examination. The observation of a complete motor block shortly after epidural administration of 80 µg bupivacaine and the results of the post-mortem examinations confirmed a correct position of the epidural catheter in all rats. In

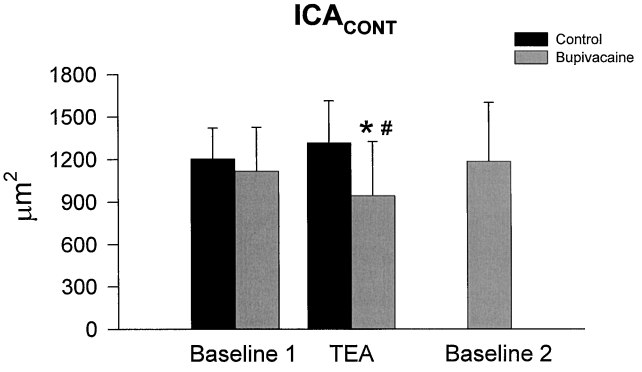

Fig. 3. Effects of epidural bupivacaine on the intercapillary area size calculated for continuously flowing capillaries (ICA_{CONT}) in gut mucosa. Values are given as mean ± SD. *P < 0.05 *versus* baseline 1; #P < 0.05 *versus* control group. TEA = thoracic epidural anesthesia.

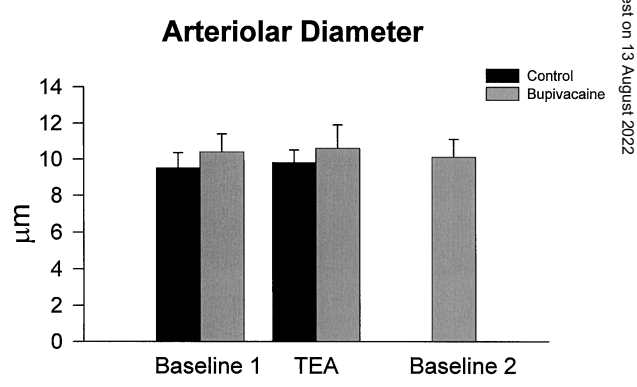

Fig. 5. Effect of epidural bupivacaine on diameter of terminal arterioles in gut mucosa. Values are given as mean ± SD. TEA = thoracic epidural anesthesia.

respect to quality and duration of the motor block, our results exactly reproduced the findings of a previous study where the effect of different doses of bupivacaine were tested using the same score.[13]

Although there are a variety of techniques to measure microcirculatory blood flow, microsphere injection and intravital microscopy are most commonly used to explicitly study microcirculatory flow in experimental settings. While microsphere injection is especially useful to study the distribution of blood flow between tissues and to quantify organ blood flow, intravital microscopy is superior in the measurement of important hemodynamic parameters within the microcirculation, including capillary hemodynamics.[16] Since our objective was to determine, in detail, the effects of epidural anesthesia on mucosal perfusion in a single organ, we therefore chose to use intravital microscopy for this experiment.

Intravital microscopy on the ileum mucosa was performed using a previously standardized methodology, with slight modifications.[14,15] All measurements were obtained in anesthetized, mechanically ventilated rats that underwent laparotomy to obtain access to the ileum. This experimental setup might have been advantageous, because it provided conditions similar to the clinical situation that we meant to address. Isoflurane was chosen as the general anesthetic because it exhibits less influence on the microcirculation than other commonly used anesthetic agents.[17,18] A limitation of this work, however, is that it was not possible to study the influence of TEA on mucosal blood flow in the absence of a general anesthetic. On the other hand, in clinical situations a combination of TEA and general anesthesia is common practice.

Mean arterial blood pressure decreased moderately during TEA, which may be attributed to reduced activity of sympathetic efferent nerves, followed by a decrease in vascular resistance.[19,20] Possible mechanisms for improved gut mucosal blood flow in the presence of sympathetic blockade include a reflex increase in cardiac output in response to TEA-induced vasodilatation and redistribution of blood flow toward the mucosa. The current literature does not support the existence of a reflex increase in cardiac output during TEA. In contrast, TEA was found to depress cardiac output and ventricular contractility in experimental studies in dogs.[21,22] In a clinical study in patients undergoing coronary bypass graft surgery, TEA also decreased cardiac output slightly.[23]

A redistribution of blood flows toward the gut mucosa despite unchanged systemic blood flow may occur as a result of changes in interorgan or within-organ blood flow distribution. Clinical observations using Doppler flow measurements in patients undergoing major abdominal surgery suggested that epidural anesthesia increases gut blood flow.[24] Others demonstrated that, in contrast to TEA, sympathetic efferent nerve activity to mesenteric vessels increases during lumbar epidural anesthesia, leading to mesenteric venoconstriction.[25] Conversely, TEA may be followed by increased sympathetic activity and vasoconstriction in organs away from the anesthetized area, causing a redistribution of blood flow toward the intestine. This mechanism would be supported by a simultaneous decrease in vascular resistance in the areas of sympathetic block, after an increase in arteriolar diameters. Surprisingly, arteriolar diameters in gut mucosa were not altered in this study, despite an apparent increase in mucosal blood flow during TEA. It is possible that changes in arteriolar diameter took place mainly in larger parent arterioles, outside the area of investigation.

The effect of TEA on blood flow distribution within the gut (*e.g.*, away from the muscularis and toward the mucosa) is subject to speculation only, because no data are available on this issue. It has been noted previously, however, that in endotoxic shock, a condition that also is associated with compromise of vascular tone, increases in mucosal blood flow are balanced by a decrease in blood flow to the muscularis, with total mesenteric flow remaining unchanged.[26] It is likely that a redistribution of blood flow from the muscularis to the mucosa during TEA would protect the gut against injury because the mucosa represents the part of the gut that is most vulnerable to decreases in blood flow, with very low oxygen tensions at the tip of the villus.[27]

In a recent study on the effects of a limited upper thoracic epidural block on splanchnic perfusion in lambs, sympathetic efferent nerve blockade, in contrast to the current study, was restricted to T1 through T5. During such block, splanchnic perfusion, as determined using colored microspheres, remained unchanged.[28] Although this study did not allow conclusions about changes in within-organ blood flow distribution, it appears that to influence gut blood flow using TEA, the level of the sympathetic blockade may have to include those efferent sympathetic nerves that supply the gut.

During epidural use of local anesthetics, significant systemic absorption occurs.[29,30] Therefore, systemic effects of the local anesthetic bupivacaine also could be responsible for the observed effects of TEA to improve gut microvascular perfusion. Recent data suggested that intravenous lidocaine, similar to epidural administration,

decreased the time of intestinal paralysis in surgical patients.[31] Experimental studies in rabbits, however, demonstrated that to alter vascular tone in mesenteric veins, very high levels of circulating local anesthetics are required.[20]

During TEA, both an increase in arteriolar V_{RBC} and decreased intermittent flow in the capillary networks of the villus microcirculation were noted. The spatial heterogeneity of arteriolar blood flow (*e.g.*, heterogeneity of flow between arterioles) was unchanged. It appears that blood supply to the mucosa was not generally less heterogeneous, despite a more constant blood flow pattern in the capillary networks. A possible explanation for this observation is that the decrease in intermittent flow was a consequence of the increase in arteriolar V_{RBC}. This interpretation is consistent with earlier reports that the degree of heterogeneity in capillary perfusion depends on V_{RBC}, such that increases in V_{RBC} cause a reduction in the heterogeneity of capillary blood flow.[32]

Assuming an unchanged microvascular hematocrit, the observed increase in V_{RBC} (and in blood flow, because of unchanged arteriolar diameters), may indicate an increase in mucosal tissue oxygen delivery during TEA. Earlier studies reported that in clinical settings, TEA prevented a decrease in gastric pH_i during major abdominal surgery.[11,12] The data in the current study explain these findings and may suggest that pharmacologic suppression of efferent sympathetic nerve activity could be useful to manipulate gut mucosal perfusion.

This study describes changes in gut mucosal perfusion during TEA. In the ileum of anesthetized rats, TEA increased mucosal blood flow and lessened the extent of intermittent flow in the presence of mild hypotension. It is likely that the observed increase in gut mucosal blood flow was the result of sympathetic nerve blockade, followed by a beneficial interorgan or within-organ redistribution of blood flow.

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