Thoracic Epidural Anesthesia Attenuates Endotoxin-induced Impairment of Gastrointestinal Organ Perfusion

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ABSTRACT

Background: Systemic inflammation can be associated with a redistribution of organ blood flow and a decrease in gastrointestinal perfusion. Regional sympathetic blockade by means of thoracic epidural anesthesia (TEA) has been shown to improve intestinal microcirculation during systemic inflammation. This study tests the hypothesis that during systemic inflammation, TEA attenuates the impairment of gastrointestinal organ perfusion without compromising blood flow to vital organs.

Methods: Eighteen rats were anesthetized, hemodynamically monitored, and mechanically ventilated with room air. By using fluorescent microspheres, organ perfusion was quantified at baseline, 30 min after the start of epidural infusion of either 2% lidocaine (TEA) or normal saline (control), and after 60 and 120 min of intravenous Escherichia coli lipopolysaccharide infusion in TEA and control animals.

Results: Blood pressure initially was lower in TEA animals, but it was comparable to controls during endotoxemia. Gastrointestinal organ perfusion significantly decreased after 120 min of endotoxemia in the controls but not in the TEA animals (−23 ± 27% vs. −6 ± 26%, mean ± SD, P < 0.05). Perfusion of the vital organs such as the heart, brain, liver, and kidneys was comparable between controls and TEA after 120 min of endotoxemia.

Conclusions: TEA attenuates the impairment of gastrointestinal organ perfusion during endotoxemia. Hence, the protective effects of TEA on intestinal microcirculation during endotoxemia may be due to a higher total organ blood flow compared with endotoxemic control animals. Furthermore, in the course of endotoxemia, TEA provides hemodynamic stability and does not compromise blood flow to vital organs.

What We Already Know about This Topic

❖ Systemic inflammation impairs intestinal microcirculation, and this impairment is attenuated by thoracic epidural anesthesia (TEA)
❖ Whether TEA alters blood flow to the gut and vital organs during systemic inflammation is unknown

What This Article Tells Us That Is New

❖ In rats with systemic inflammation from lipopolysaccharide administration, TEA improved intestinal blood flow without reduction in flow to the brain, heart, liver, or kidneys

SYSTEMIC inflammation is associated with alterations in microvascular blood flow1 and may lead to severe hypoperfusion2 resulting in organ failure. Organ blood flow is regulated by various mechanisms depending on the size of the vessel: microvessels (diameter less than 50 μm) are predominantly influenced by local metabolic and paracrine or autocrine mediators and vascular intrinsic properties, whereas larger vessels or macrovessels are more influenced by central circulatory control, neural, and (neuro-)humoral mediators.3–5 Various experimental animal studies have demonstrated that regional sympathetic blockade by means of thoracic epidural anesthesia (TEA) improves gastrointestinal tract (GIT) microvascular perfusion and function during systemic inflammation.6–11 In rodent models of sepsis, amelioration of perfusion deficits with TEA was demonstrated in the muscularis6 and the mucosal layer8 of the gut. The studies were not designed to elucidate the mechanism behind this phenomenon. Therefore, it remained unclear whether these
effects of TEA were due to a redistribution of blood flow within the intestinal tissue layers or to an increase in total blood flow to the gut. Furthermore, the question of how TEA influences the distribution of blood flow between various organs during systemic inflammation was not addressed.

Therefore, this study tested the hypothesis that TEA improves endotoxin-induced impairment of GIT organ perfusion without compromising blood flow to vital organs. In a rat model of normotensive endotoxemia, we quantified the effects of TEA on regional blood flow by using the microspheres reference sample technique.\[12\]

**Materials and Methods**

**Animals**

Eighteen male Sprague-Dawley rats weighing 320 ± 15 g (mean ± SD) were used in the experiments after approval by the local animal care committee (Berlin, Germany). Animals were handled according to the “science-based guidelines for laboratory animal care” of the National Research Council (2003). The rats were housed in our animal facility and had access to a standard pellet food (Altromin, Lage, Germany) and tap water until the experiment.

**Experimental Protocol**

In all animals, general anesthesia was induced by subcutaneous injection of urethane (99% urethane (N), 1.5 g/kg; Sigma Aldrich Chemie GmbH, Deisenhofen, Germany) and ketamine (Ketavet, 50 mg/kg; Pharmacia & Upjohn GmbH, Erlangen, Germany) with top-up doses of ketamine for approximately every 2 h (15–30 mg/kg). Animals underwent epidural catheterization, tracheotomy, and vascular and left proximal perfusion without compromising blood flow to vital organs. In a rat model of normotensive endotoxemia, we quantified the effects of TEA on regional blood flow by using the microspheres reference sample technique.\[12\]

**Tracheal and Vascular Cannulation**

Tracheostomy allowed mechanical ventilation with room air (Harvard Apparatus, Edenbridge, United Kingdom), which was controlled by expired gas analysis (TSE Technical & Scientific Equipment GmbH, Bad Homburg, Germany). In addition, cannulation of a femoral artery (PE50; Portex, Hythe, United Kingdom) permitted arterial blood gas analysis (Rapidlab 348, Chiron Diagnostics GmbH, Fernwald, Germany) and arterial blood pressure monitoring. The right external jugular vein was cannulated (PE50) for infusion of fluids and central venous pressure monitoring. The left ventricle was cannulated with a polyethylene catheter (PE50) via the right carotid artery. The correct position of the catheter tip in the left ventricle was validated by online pressure curve monitoring and autopsy. Hemodynamic monitoring was performed using a transducer (model p23 ID; Gould-Statham, Hato Rey, Puerto Rico, Spain) connected to arterial and venous lines via three-way cocks. Body temperature was kept at 36°C throughout the experiment using a warming pad.

**Epidural Catheterization**

Epidural catheterization was performed according to a modified method described by Bahar et al.\[13\] A polyethylene catheter of 200-mm length (PE 10; Portex) was armed with a monofilamentous suture (Prolene\[\textsuperscript{®} 4/0; Ethicon Inc., Somerville, NJ) to reduce the dead space of catheter to 5 µl. To ensure catheter placement at a thoracic level of T7, a hub was created 65 mm from the tip using heated glue. The catheter was surgically implanted through a drilled hole in the dorsal lamina of L4 and 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 catheter’s segmental position in the epidural space was assessed by autopsy. Epidural spread of lidocaine was determined in all animals by supplementing the lidocaine with 0.1% methylene blue and assessing the segmental extent of blue stain at autopsy.

**Quantification of Organ Blood Flow**

We determined organ blood flow using the reference withdrawal method\[14\] with fluorescent microspheres. For blood flow measurement, 0.3 ml (approximately 100,000) polystyrene microspheres, each with a diameter of 15 µm, was injected into the left ventricle within 20 s. Subsequently, the catheter was flushed with 0.4 ml warm hydroxyethyl starch. An arterial reference sample was withdrawn into a plastic syringe at a flow rate of 0.63 ml/min. Sampling was started 10 s before and finished 40 s after the injection of microspheres. The organs were harvested, weighed, and conserved in 5% formalin overnight. The following samples were used: right and left hemispheres of the brain, right and left ventricles of the heart, the stomach, the duodenum, a piece of jejunum, a piece of ileum, the colon, the pancreas, the spleen, two liver samples (reflecting hepatic artery blood flow), the upper poles of both kidneys, and right and left ileopsoas muscle. After preservation, the organs and reference samples were collected for quantification of lidocaine and catecholamine plasma concentrations. Then, animals were decapitated, and organs were harvested for the determination of microsphere content.
were kept in specially designed sample processing units consisting of a filter (Filtersystem B0511133), filter holder, and sample tube (Angelika Gaiser, Kunststoff- und Metallprodukte GmbH, Kappel-Grafenhausen, Germany). Fluorescence intensity in the reference samples and organs was determined by an investigator blinded to the experimental protocol using a robot-assisted method. Then, organ blood flow was calculated from the reference sampling flow rate and fluorescence intensity of the organ and reference samples.

**Determination of Plasma Catecholamine Concentrations**

The plasma concentrations of norepinephrine and epinephrine were measured by an investigator blinded to the experimental protocol (F.H.P.) using reversed-phase high-performance liquid chromatography with electrochemical detection by means of a commercially available reagent kit (Bio-Rad, Munich, Germany). In brief, catecholamines were extracted from the plasma samples with alumina using an internal standard for compensation of variable extraction efficiency. Then, catecholamines were reextracted from alumina using diluted phosphoric acid. This extract was injected onto the analytical column. The high-performance liquid chromatography device was composed of an AS-100 autosampler with a cooled sample tray (4°C), a model 1350T pump with SSI LP-21 LO-Pulse pulse damper, a column heater, and a model 1340 electrochemical detector (all instrumentation by Bio-Rad except for the pulse damper: Scientific Systems Inc., State College, PA). The separation was performed at 40°C. Catecholamines were detected amperometrically at a working potential of +0.55 V. Quantification was based on the comparison of the epinephrine/internal standard and norepinephrine/internal standard peak height ratios in the unknown samples to the corresponding ratios in the plasma calibrator. Data acquisition and calculations were carried out using ChemStation software (Rev. A. 06.03; Agilent, Waldbronn, Germany). Interassay coefficients of variation at concentrations between 64 and 1092 ng/l were less than 7% for epinephrine and at concentrations between 188 and 1305 ng/l were less than 8% for norepinephrine.

**Determination of Plasma Lidocaine Concentrations**

Determination of lidocaine plasma concentrations was performed by an investigator blinded to the experimental protocol (Berliner Betrieb für Zentrale Gesundheitsliche Aufgaben, Berlin, Germany). High-performance liquid chromatography was used with a detection limit at 0.02 µg/ml.

**Statistical Analysis**

All tests were performed using Sigma Stat version 3.10 (Systat Software GmbH, Erkrath, Germany). Catecholamine data were analyzed using Student t test for independent variables. To detect significant differences within groups, a Friedman repeated-measures analysis of variance on ranks was performed followed by the Student-Newman-Keuls test to correct for multiple comparisons. Intergroup differences were determined only on time points of microspheres injection using the Mann–Whitney rank sum test. P values were adjusted using the Bonferroni procedure. Statistical testing was two tailed with significance assumed at P < 0.05.

**Results**

In the postmortem examination, the tip of the epidural catheter was localized at the segmental level of T8 (7, 8) (median [quartiles]) with epidural spread of methylene blue from segment T4 (3, 5) to T11 (10, 11). In the TEA group, the plasma concentration of lidocaine at the end of the experimental protocol was 0.33 ± 0.09 µg/ml (mean ± SD). The plasma concentrations of epinephrine measured at the end of the experimental protocol were lower in TEA animals (1340 ± 661 µg/ml, mean ± SD) compared with the controls (2121 ± 355 µg/ml, P = 0.048), whereas the plasma concentrations of norepinephrine were not significantly different between groups (TEA: 1939 ± 1244; control: 1301 ± 231 µg/ml).

**Hemodynamic Variables**

Mean arterial pressure (MAP) remained largely constant throughout the experiment in endotoxemic rats without TEA (fig. 1), whereas MAP decreased temporarily after epidural infusion of lidocaine. The values were comparable in both groups after 60 and 120 min of endotoxemia (fig. 1). Small transient changes in heart rate were seen after epidural bolus infusion of lidocaine. Heart rate increased significantly after 60 and 120 min of endotoxemia in both groups (fig. 1).

**Blood Gas Analysis**

PO2 and PaCO2 were stable throughout the experiments with small intergroup differences in PaCO2. pH and base excess decreased in both groups during endotoxemia with lower pH values in the control animals at all time points. Sodium and potassium values remained virtually unaltered during the experiment. Hematocrit decreased after baseline measurements without intergroup differences.

**Blood Flow to Gastrointestinal Tract Organs**

Blood flow to GIT organs was significantly higher in the TEA compared with the control animals during endotoxemia.

**Blood Flow to the Heart**

Baseline values (ml · 100 g−1 · min−1, median [quartiles]) did not differ between groups (stomach control: 103 [69, 123] vs. TEA: 87 [66, 103]; ileum control: 190 [161, 281] vs. TEA: 186 [149, 205]). Blood flow to GIT organs such as the stomach and ileum showed similar patterns during epidural infusion and endotoxemia, reaching statistical significance in cumulated data of all GIT organs (fig. 2). Epidural infusion of lidocaine increased blood flow to GIT organs such as the ileum (fig. 2). Infusion of lipopolysaccharide decreased GIT organ blood flow in both groups after 120 min. Blood flow to GIT organs was significantly higher in the TEA compared with the control animals during endotoxemia.
Epidural infusion of lidocaine decreased blood flow to the heart significantly (fig. 3). Blood flow to the heart increased with infusion of lipopolysaccharide in both groups but was higher after 60 min of lipopolysaccharide infusion in the control when compared with the TEA animals (fig. 3).

**Blood Flow to Other Organs (Brain, Liver, Spleen, Pancreas, Kidney, and Muscle)**

Blood flow baseline values of the brain were different between group control (ml/100 g/min, median [quartiles] for all values): 189 [124, 196] and TEA: 118, [102, 155] \( P < 0.05 \). Baseline values in other organs did not show intergroup differences (liver control: 41 [29, 63] vs. TEA: 47 [38, 54]; spleen control: 101 [88, 142] vs. TEA: 118 [94, 161]; pancreas control: 72 [48, 119] vs. TEA: 83 [55, 98]; kidneys control: 547 [459, 579] vs. TEA: 500 [409, 569]; muscle control: 8 [6, 15] vs. TEA: 12 [8, 17]). Hepatic blood flow decreased only initially during epidural infusion without significant intergroup differences but was stable in the course of lipopolysaccharide infusion. Splenic blood flow increased during endotoxemia in both groups, whereas pancreatic blood flow decreased after 120 min of lipopolysaccharide infusion. The changes of blood flow to the brain, kidney, and muscle did not differ between groups.

**Discussion**

This study investigated the effects of TEA on organ blood flow in rats before and after the induction of normotensive endotoxemia. We demonstrated that blood flow to GIT organs was higher with TEA compared with endotoxemic controls despite initially decreased MAP. In contrast, blood flow to the heart initially was lower in the TEA animals but was restored in the course of endotoxemia. Cerebral blood flow was altered neither by TEA-induced hypotension nor by endotoxemia.

**Critique of the Method**

A major concern in studies dealing with epidural anesthesia is that the sympathetic blockade may not include the segments innervating the region of interest and that neuronal response to stress stimuli may be bypassed by a humoral stress response. In preceding investigations, we were able to show that epidural application of 30 \( \mu l \) lidocaine, 2%, induces sympathetic blockade encompassing the splanchic region. By adding methylene blue to the local anesthetic, we were able to determine the minimum spread in the epidural space, which in our experiments includes the majority of thoracic segments. As monitoring of heart rate revealed only a short and small decrease after epidural infusion of lidocaine (fig. 1), complete sympathetic blockade of fibers innervating the heart (T1–T4) seems unlikely. To find out whether the sympathetic block includes fibers innervating the adrenal gland (T12–L1), the plasma concentration of catecholamines was determined. The results show that TEA significantly reduced epinephrine but not norepinephrine plasma concentration. Unlike epinephrine, norepinephrine is not solely produced in the adrenal gland. During systemic inflammation tyrosine hydroxylase, the rate-limiting enzyme of norepinephrine synthesis is upregulated, leading to excessive production of norepinephrine in peripheral sympathetic nerve endings. This may be associated with a spillover of norepinephrine in the systemic circulation. Our results, therefore, are consistent with a sympathetic blockade of the adrenal gland assuming neuronal spillover of norepinephrine from sympathetically unblocked regions.

To determine the effects of endotoxin and regional sympathetic blockade on organ blood flow, we used the microsphere reference withdrawal method. This well-accepted and accurate method enabled us to perform repetitive measurements of blood flow to various organs at different time points in every animal. To demonstrate a cumulative effect on the GIT, the values of blood flow of respective organs were summed up. Because absolute values of organ blood flow differ substantially between GIT organs (e.g., stomach: 104 ± 41 vs. duodenum: 436 ± 127 ml/100 g/min) and baseline values were comparable between groups, we used relative values.
Hemodynamic and Systemic Variables

Constant MAP values throughout the experiment were observed in control animals representing normotensive endotoxemia (fig. 1). TEA led to a significant reduction in MAP (fig. 1), which is a common effect of neuraxial blockade because of a decrease in systemic vascular resistance. In the course of endotoxemia, MAP recovered and was then comparable with the control group throughout the further experiment (fig. 1), indicating a similar volume status in both experimental groups. Comparable hematocrit values in both groups (table 1) confirm this notion. Heart rate significantly increased after 1 h of lipopolysaccharide infusion in both groups (fig. 1). This is in line with the findings of Xu et al., who showed an increase in heart rate 1 h after single intraperitoneal lipopolysaccharide injection and were able to correlate this with an increase in cardiac output.

pH and base excess (table 1) decreased in the course of endotoxemia, with significantly lower values in endotoxemic control animals at all time points. Endotoxemia has been shown to cause gut mucosal acidosis, cellular hypoxia, and serum lactate acidosis. Higher pH values in TEA animals do not allow the conclusion that cellular oxygen utilization was superior in TEA animals, as significant differences were also present in baseline values and PaCO₂ values were slightly lower in TEA compared with control animals at baseline and 120 min of endotoxemia.

Regional Blood Flow

Continuous intravenous infusion of lipopolysaccharide decreased (approximately 20–40%) blood flow to GIT organs within 120 min (fig. 2). This observation is supported by other studies investigating acute endotoxin effects on blood flow distribution. There are numerous causes for a reduction in organ blood flow during normotensive endotoxemia. Although microcirculation may be impaired by blood cell adhesion and mediator-induced activation and edema of endothelial cells, larger supplying vessels may be constricted because of activation of the sympathetic nervous system. Although the aim of this study was not to investigate the underlying mechanism, quantification of plasma catecholamines reveals that lipopolysaccharide activated the sympathetic nervous system, a strong contributor to impairment of blood flow. Furthermore, this study demonstrates that endotoxin effects on blood flow differ even between anatomically adjacent organs within the splanchnic circulation (e.g., stomach and spleen). This shows that splanchnic perfusion cannot be measured in one organ and highlights
the need for organ-specific differentiation of splanchnic blood flow.

In other organs such as the liver, kidney, ileopsoas muscle, and brain (table 2), blood flow was not notably influenced by endotoxin. With respect to kidney and muscle blood flows during endotoxemia, the experimental findings are heterogeneous, whereas hepatic arterial blood flow and cerebral perfusion are known to be preserved even in shock states.

Former studies investigating the effects of TEA on splanchnic perfusion in healthy subjects have demonstrated unchanged or even decreased GIT organ blood flow during TEA. Recent studies of TEA during hemorrhagic shock and systemic inflammation, however, reported that TEA significantly attenuated an impairment of intestinal microvascular perfusion. This suggests that the protective effects of TEA on organ perfusion can particularly

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<th>Table 1. Systemic Variables</th>
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<td><strong>Na⁺, mm</strong></td>
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<td><strong>K⁺, mm</strong></td>
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<td><strong>Hct, %</strong></td>
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Data are median (quartiles), n = 9 per group.

* P < 0.05 vs. baseline. † P < 0.05 between groups.

BE = base excess; Hct = hematocrit; LPS = lipopolysaccharide; TEA = thoracic epidural anesthesia.

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<th>Table 2. Organ Blood Flow (% Change)</th>
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<td><strong>Pancreas</strong></td>
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Organ blood flow is expressed as percentage change from baseline values. Data are median (quartiles), n = 9 per group.

* P < 0.05 vs. baseline.

LPS = lipopolysaccharide; TEA = thoracic epidural anesthesia.
be visualized in states of increased sympathetic tone. In this study, sympathetic activation, which contributed to GIT perfusion deficits, was induced by an intravenous administration of lipopolysaccharide. TEA ameliorated the decrease in GIT organ perfusion after 120 min of endotoxia (fig. 2). It seems feasible that by blocking effenter sympathetic nerve fibers, TEA attenuates endotoxin-induced vasoconstriction in GIT vessels and thus decreases vascular resistance. Given that cardiac output and MAP are not altered, GIT organ perfusion should increase. Because heart rate, the main determinant of cardiac output in small rodents, and MAP were comparable between groups at 120 min of endotoxia, it seems plausible that TEA increases GIT organ blood flow by vasodilation of supplying arteries, as demonstrated for the superior mesenteric artery by Vagts et al.19

In a recent study, we found that TEA prevented perfusion deficits in microvessels of the muscularis during rodent endotoxia.6 According to the classification of Gore and Bohlen,31 first-order intestinal arterioles arise from small mesenteric arteries, penetrate the muscle layers, and run into the submucosal layer. From the submucosal layer, blood is distributed into the mucosa via third-order arterioles or into the muscle layers via fourth-order vessels. Because sympathetic nerve fibers have only been identified in the vicinity of muscularis (but not mucosal) microvessels,30 two explanations for the results existed: (1) total blood supply to the gut is not altered but is redistributed into (sympathetically blocked) dilated vessels of the muscularis layer and (2) dilation of mesenteric arteries increases total blood supply to all layers of the gut. This study demonstrates that during endotoxia, supply to GIT organs may be higher with TEA compared with an endotoxemic control, suggesting that an increase in total blood supply may have been responsible for the microcirculatory changes.

Apart from altering organ blood flow, TEA may have influenced microvascular perfusion by affecting adhesion of leukocytes30 or reducing vascular permeability.11 Furthermore, systemic effects of local anesthetics on microvascular blood flow have to be considered.32 Systemic application of lidocaine in a rodent model of endotoxia, when compared with ours, however, did not change intestinal microvascular hemodynamics despite significant effects on leukocyte adhesion and vascular permeability.33

Blood flow to the heart was lower in TEA animals after 30 min of epidural infusion (fig. 3). The heart in our model is outside the sympathetic blockade. Because cardiac sympathetic nerves arise from spinal segments, which are located next to sympathetically blocked segments, enhanced sympathetic activity in these nerve fibers may have led to coronary vasoconstriction and decreased cardiac perfusion.34,35 However, another feasible explanation is that coronary perfusion decreased because of TEA-induced hypotension (fig. 1) and returned to normal values when arterial pressure matched with values of control animals in the course of the endotoxia (fig. 1).

Epidural infusion of lidocaine significantly decreased liver blood flow (table 2). This is in accordance with a variety of studies that investigated the effects of TEA on splanchnic perfusion.36–39 All studies reported a concomitant drop in blood pressure, suggesting a susceptibility of liver blood flow to hypotension. Looking at the results of this study, it has to be stated that perfusion of splanchnic organs differs considerably regarding its dependence on MAP. It is noteworthy that during endotoxia, TEA was associated with stable values of liver blood flow (table 2). In addition, TEA did not influence cerebral perfusion considerably (table 2), implying a safe use during normotensive systemic inflammation in these animals. Furthermore, even the use of TEA during endotoxic shock in sheep did not negatively affect cardiovascular hemodynamics nor global oxygen transport.40,41

Summary and Conclusion

In this study, TEA increased gastrointestinal perfusion and attenuated lipopolysaccharide-induced perfusion deficits. We suggest that the preservation of intestinal microvascular perfusion in systemically inflamed animals with TEA may be due to a higher total blood flow to GIT organs when compared with controls. Blood flow to vital organs, such as the heart, brain, liver, and kidney, was comparable between groups after 120 min of lipopolysaccharide infusion, implying a safe use of this technique in systemically inflamed animals.

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