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Thoracic Epidural Analgesia with Low Concentration of Bupivacaine Induces Thoracic and Lumbar Sympathetic Block

A Randomized, Double-blind Clinical Trial

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Background: **Clinical benefits of thoracic epidural anesthesia (TEA) are partly ascribed to thoracic sympathetic block. However, data regarding sympathetic activity during TEA are scarce and contradictory. This prospective, randomized, double-blind study evaluated the segmental propagation of sympathetic block after low-concentration, high-volume TEA using digital thermography.**

Methods: **Twenty-four patients were included in the study. Thoracic epidural catheters were placed at a median insertion level of T8–T9. Patients were accommodated for 20 min to the room temperature of 23° ± 0.3°C. Skin temperature was recorded by digital thermography. After baseline measurement of heart rate, arterial pressure, and core body and skin temperature, 10 ml saline (control group) or 10 ml bupivacaine, 0.25% (TEA group), respectively, was administered epidurally. Five minutes (t5) and 20 min (t20) after baseline measurements, hemodynamic parameters and core body temperature were again measured, and sensory block was identified by loss of cold–warm discrimination. In the thumb, the toe, and each thoracic dermatome, difference from baseline temperature was calculated at t5 and t20. Data were analyzed by Mann–Whitney U test.**

Results: **Baseline characteristics did not differ among groups. Median spread of sensory block at t20 was T5–L5. At both t5 and t20, skin temperature decreased more in the control group than in the TEA group in all thoracic dermatomes ($P < 0.05$). Toe temperature increased in the TEA group compared with the control group ($P < 0.05$), whereas thumb temperature remained unchanged.**

Conclusion: **TEA with 10 ml bupivacaine, 0.25%, induced thoracic and lumbar sympathetic block that precedes and exceeds sensory block. Caudal limit of sympathetic block could not be demonstrated in this study.**

MAJOR surgery triggers an organism's response to stress, which is characterized by profound endocrine, metabolic, and hemodynamic alterations.[1,2] The activation of the sympathetic system results in tachycardia and increases myocardial oxygen consumption. It plays a pivotal role in explaining perioperative intestinal hypoperfusion and dysfunction, which is commonly seen after major surgery and is aggravated when opioids for pain therapy are necessary.[3–5]

Currently, continuous thoracic epidural anesthesia (TEA) is established as a key element in perioperative management to optimize pain therapy, minimize the stress response, and improve perioperative recovery and outcome.[2,6–8] The beneficial effects of TEA have been attributed in part to segmental thoracoabdominal sympathetic block.[9–11]

However, both experimental and clinical data regarding the presence of sympathetic block, its extent, and its relation to the extent of sensory block are scarce. Animal studies demonstrated sympathetic block during TEA accompanied by reactively increased sympathetic activity outside the blocked segments.[9,12] However, clinical studies could not consistently show a thoracic sympathetic block within the area of sensory block.[13,14] Furthermore, in humans, the extent of sympathetic block varies with concentration and volume used to induce TEA. High TEA (C7–T3) with 4.2 and 7.9 ml bupivacaine, 0.75%, induced a caudally unrestricted sympathetic block exceeding the sensory block, whereas 4–6 ml bupivacaine, 0.5% (T3–T4), did not change leg sympathetic activity.[13,15,16]

These studies investigated high TEA and used high concentrations and low volumes. However, TEA is frequently used at mid and low thoracic levels for major thoracoabdominal surgery, and higher volumes and lower concentrations of local anesthetics are applied. Information about sympathetic activity in this clinically relevant setting is currently not available.

We therefore conducted a prospective, randomized trial in patients undergoing major abdominal surgery using infrared thermography of the skin to noninvasively evaluate segmental sympathetic activity during TEA using 10 ml bupivacaine, 0.25%.

Our first aim was to test the hypothesis that low-concentration, high-volume TEA induces a sympathetic block in the thoracic and abdominal dermatomes, indicated by altered skin temperature regulation. The sec-

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ondary scope of the study was to evaluate the cranial and caudal limits of the sympathetic block and its correlation to the sensory block.

Materials and Methods

After approval of the ethics and patient safety committee of the University of Muenster, Muenster, Germany (Reg. No. 4VIII Sielen), this prospective, randomized, double-blind study (ClinicalTrials.gov) was performed in adult patients undergoing major elective abdominal and thoracoabdominal surgery during combined general anesthesia and TEA at the University Hospital of Muenster. We did not include patients with obesity (body mass index >30 kg/m^2), a history of relevant cardiovascular afflictions (microangiopathy or macroangiopathy, coronary artery disease), insulin-dependent diabetes mellitus, neurologic disorders of any kind, sepsis, systemic inflammatory response syndrome, or fever. Informed written consent was obtained from all patients.

Patients received 0.3 mg/kg body weight clorazepam the morning before surgery. After connecting standard cardiorespiratory monitoring according to national guidelines, an intravenous saline infusion *via* a peripheral vein of the left arm was started at a rate of 100 ml/h. Noninvasive blood pressure, respiratory rate, electrocardiogram, and pulse oximetry were continuously recorded.

Consecutively, a closed-tip, three-orifice epidural catheter (Perifix; Braun Melsungen, Melsungen, Germany) was placed at the level of T7–T11 according to the requirements of the surgical procedure using a paramedian approach and the loss-of-resistance technique. To avoid potential bias, incremental injection of local anesthetic, epidural sufentanil injection, or application of a test dose containing epinephrine was not applied. Only an aspiration test was performed, which might be, however, related to a higher risk of undetected catheter malposition than the other tests.[17] The catheter was carefully secured by a tape dressing. Thereafter, patients were situated in the supine position, and the right arm was comfortably abducted to 90°. Except for the pubic region, the patients were completely uncovered. The ambient temperature was kept constant at 23° ± 0.3°C and an air change rate of 10/h, light was dimmed, and disturbance by movements and noise was minimized. After 20 min of acclimatization, patients were randomly assigned to a control or TEA group by closed envelopes. Control patients received a bolus of 10 ml saline solution epidurally, and the TEA group received a bolus of 10 ml bupivacaine, 0.25% (AstraZeneca, Wedel, Germany), epidurally. At 5 min (t5) and 20 min (t20) after the study drug was injected, motor block was quantified by the Bromage score, and the level of sensory block was assessed by loss of cold–warm discrimination, tested by cooled, alcohol-based skin-disinfectant, at the left arm, the left midaxillary line, and the left leg.

Temperature Measurement

Thermographic measurements were conducted using infrared thermography before the injection of the study drug (t0) and continuously after epidural injection for 20 min. The infrared radiation of the patient's body was recorded by a liquid nitrogen–cooled infrared sensor camera (Varioscan LW 3011; Infratec, Dresden, Germany). This sensor records wavelengths between 8 and 12 μm, which are the predominant parts of the heat spectrum of human skin. It provides a temperature resolution of 0.03°C without necessitating manipulations or disturbances of the patient. The acquired images were saved by a computer system and evaluated off-line by a blinded investigator using custom-made software (IRBIS plus 2.2; Infratec).

Skin areas representing the segments T1–T12 were defined by the anatomical landmarks for T1, T4, T10, and T12 and an equal division of the skin area between the landmarks. Each skin segment was enclosed by a polygon as demonstrated in figure 1, and the mean skin temperature of each polygon was used for analysis.

Skin temperature difference was calculated at t5 and t20 according to the equation $\Delta T = Tx - T0$, where Tx is the temperature 5 or 20 min after baseline, and T0 equals baseline temperature. Changes in skin temperature were used as a surrogate parameter for sympathetic activity during the study period.

In addition, skin temperature of the right thumb and the right big toe were measured by a fast-response surface thermometer (BAT 10; World Precision Instruments, Berlin, Germany) at t0, t5, and t20. Rectal temperature was continuously recorded.

Statistical Analysis

Group size was estimated using the sample size estimation tool of Sigmastat 3.1 (Systat Software GmbH, Erkrath, Germany) to detect 1°C difference in temperature change assuming an SD of 0.8°C and a power of 0.8. Assumptions were based on temperature changes recorded in previous studies in humans and a thermographic study in rats.[12,13,18] Hemodynamic, respiratory, and temperature data are displayed as mean ± SEM. Sensory block heights are described as median [25–75%]. Data were compared by chi-square test for categorized data, *t* test for vital parameters, and Mann–Whitney U test for temperature differences using Sigmastat 3.1 software. Significance was defined as $P < 0.05$.

Results

Twenty-four patients were included in the protocol from January 2005 to January 2006. In 4 patients, the

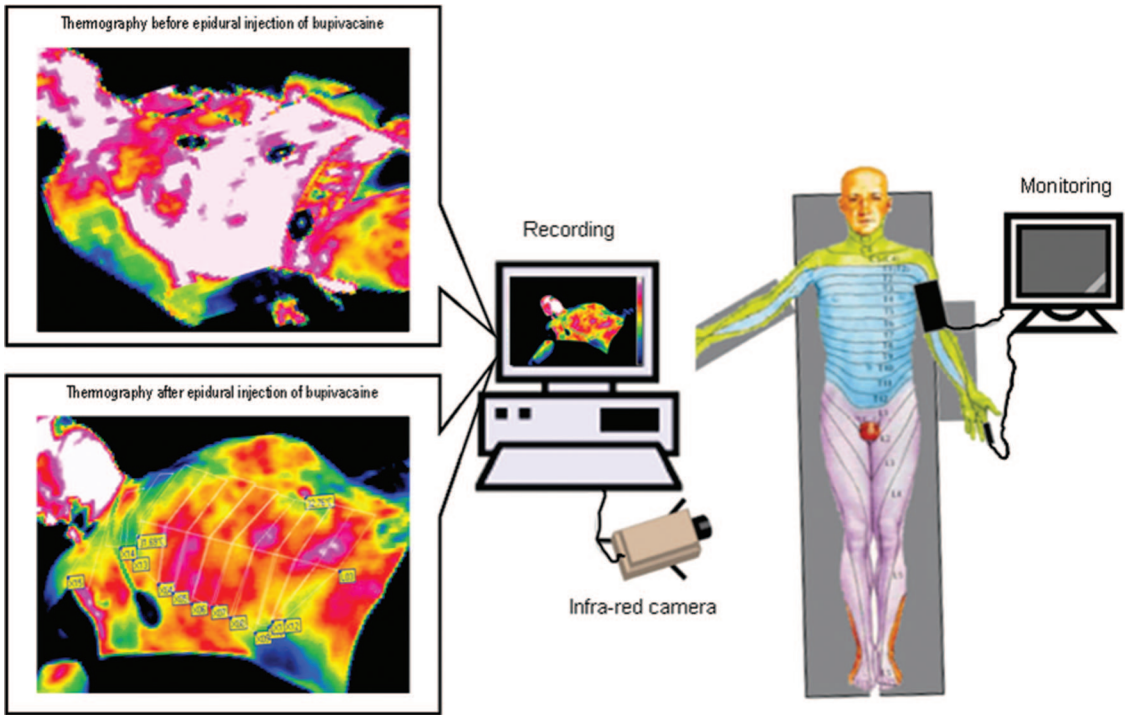

Fig. 1. Experimental setup.

measurements could not be started for organizational reasons. In 1 patient of the control group, the measurements had to be interrupted because of accidental intravascular malposition of the epidural catheter. Hence, the measurements were completed in 10 TEA and 9 control patients.

There was no difference in baseline characteristics such as sex, age, body mass index, preoperative risk index (American Society of Anesthesiologists physical status), and medical history (arterial hypertension, diabetes mellitus, cardiopulmonary afflictions) among groups (table 1).

Table 1. Epidemiologic Characteristics

	TEA	Control
Number (sex)	10 (5 F/5 M)	9 (3 F/6 M)
Age, yr	55.6 ± 13	63.7 ± 11
Weight, kg	72.8 ± 13.6	72.2 ± 10.0
Height, cm	171.7 ± 8.4	172.1 ± 8.3
BMI, kg/m^2	24.6 ± 3.9	24.3 ± 2.0
Body temperature, °C	36.5 ± 0.5	36.1 ± 1.4
ASA physical status	6 ASA II 4 ASA III	8 ASA II 1 ASA I
Relevant comorbidities		
Arterial hypertension	5	3
Diabetes mellitus	2	2
Myocardial afflictions	1	1
Pulmonary afflictions	0	0

Epidemiologic characteristics of the study patients. There was no significant difference between groups.

ASA = American Society of Anesthesiologists; BMI = body mass index; TEA = thoracic epidural anesthesia.

Rectal temperature, systolic and diastolic blood pressure, and heart rate were not significantly affected regarding difference over time and among groups (fig. 2).

In the TEA group, a segmental sensory block developed over time (fig. 3). After 5 min, the median upper limit of sensory block reached T8 [T6–L2]. At this time, however, in all thoracic segments the skin temperature regulation of TEA patients was significantly altered compared with control patients (fig. 4). After 20 min, the area of altered skin temperature regulation still exceeded the sensory block (figs. 3 and 4). Concomitantly, there was no temperature difference among groups on the thumb, indicating that sympathetic block did not reach low cervical segments. However, the skin temperature of the toe was significantly higher in the TEA patients as compared with the control patients, indicating that sympathetic block led to vasodilatation in the leg (fig. 5).

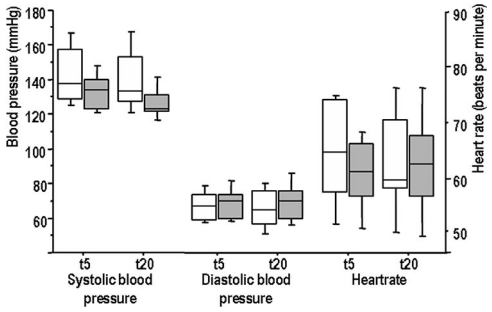

Fig. 2. Hemodynamic parameters. Blood pressure and heart rate at 5 min (t5) and 20 min (t20) after epidural injection in control (*white boxes*) and thoracic epidural anesthesia (*gray boxes*) patients. Data are mean ± SEM. No significant differences were detected among groups or among time points.

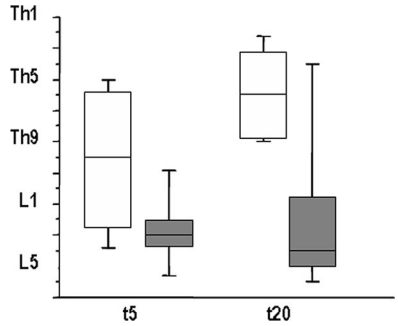

Fig. 3. Sensory block. Median upper (*white boxes*) and lower (*gray boxes*) level of sensory block 5 min (t5) and 20 min (t20) after epidural injection of 0.25% bupivacaine.

Discussion

In this prospective, double-blind, randomized study, an altered skin temperature regulation was demonstrated by infrared thermography during TEA.

Measurement of Sympathetic Activity

There are direct and indirect techniques to record sympathetic nerve activity *in vivo*. The sole direct technique, the microneurography of sympathetic nerves, has been used in both animal experimental and clinical studies of regional anesthesia.[9,16,19–21] This techniques allows continuous and quantitative recording. However, it is invasive and technically complex and has limited spatial resolution. Therefore, its use in clinical research is limited.[21]

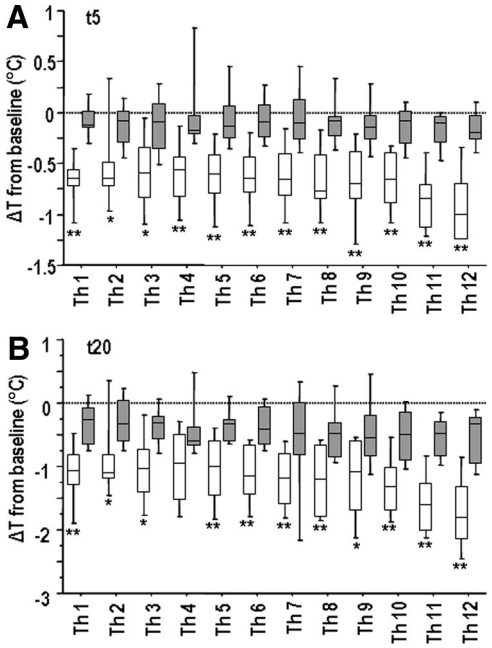

Fig. 4. Thoracic sympathetic block. Mean difference of the skin temperature (ΔT) of the thoracic dermatomes (T1–T12) toward baseline 5 min (*A*) and 20 min (*B*) after epidural injection in control (*white boxes*) and thoracic epidural anesthesia (*gray boxes*) patients. Data are mean ± SEM. * $P < 0.05$, ** $P < 0.01$ *versus* thoracic epidural anesthesia.

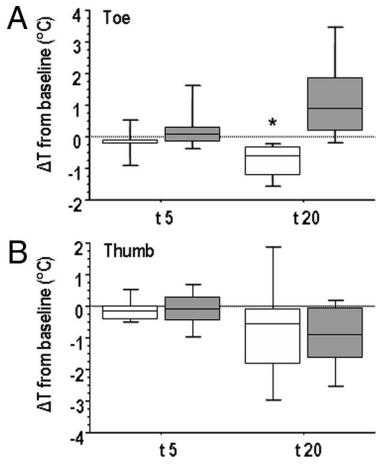

Fig. 5. Lumbar sympathetic block. Toe (*A*) and thumb (*B*) temperature differences (ΔT) *versus* baseline at 5 min (t5) and 20 min (t20) in control (*white boxes*) and thoracic epidural anesthesia (*gray boxes*) patients. Data are mean ± SEM. * $P < 0.05$ *versus* control.

Indirect methods focus on functional changes in effector organs. They include the measurement of skin conductance response[16,22] and heart rate variability.[22,23] Most investigators, however, have focused on measurements of skin perfusion. Heat washout techniques determine cutaneous blood flow by the rate of temperature equilibration.[14] Doppler flow probes have been used to quantify skin perfusion during regional anesthesia or after sympathotomy.[24–26] This is especially suitable in glabrous skin.[25] However, in nonglabrous skin, Doppler measurements may not properly depict vasoregulatory sympathetic nerve activity.[25] Heart rate variability has been used with equivocal results to monitor cardiac sympathetic tone during regional anesthesia.[23,27–30]

Infrared thermography serves as a noninvasive, indirect instrument to evaluate skin sympathetic vasoconstrictive activity. This technique has been validated to quantify a surrogate parameter of sympathetic activity and is used extensively in clinical and experimental studies.[13,18,31–33] Thermography allows a good chronological and spatial resolution of temperature measurement without any manipulation to the patient that might affect sympathetic tone.[34] It permits simultaneous assessment of multiple thoracic segments. Hence, we used thermography to evaluate sympathetic vasoconstrictive activity of nonglabrous skin during TEA.

The activity of the sympathetic nervous system is subjected to rapid regulation in response to cardiac cycle, respiration, environmental and psychic stimuli[16,34,35] that might affect both direct and indirect measurement procedures. To minimize those confounders, all patients participating in our study were placed comfortably in the supine position and were allowed to recover for 20 min after placement of epidural catheters with dimmed light and minimized external stimuli. They reported no discomfort.

The climate conditions were kept stable at 23°C and an air exchange rate of 10/h. Under these conditions, vaso-

constrictive neurons are tonically active to reduce skin perfusion and the resulting heat loss while sudomotor and vasodilative fibers are inactive.[36,37] Therefore, under the given conditions in the current study, skin temperature regulation is presumed to allow valid assessment of sympathetic activity.

Effect of TEA on Sympathetic Activity

Skin temperature regulation was significantly altered by epidural high-volume, low-concentration bupivacaine injected at mid and low thoracic segments. This finding supports the concept of thoracic and abdominal sympathetic block induced by TEA.

Thoracic sympathetic block, however, has not been consistently demonstrated during TEA. High TEA induced by 2 ml lidocaine, 2%, and 3 ml bupivacaine, 0.5%, injected at T3–T4 increased thoracic cutaneous blood flow as assessed by heat washout.[14] In contrast to this, thoracic skin temperature remained unchanged or even decreased in TEA using 4.2 ml bupivacaine, 0.75%, injected at T6–T9.[13]

In both studies, sympathetic nerve activity was assessed by changes in skin perfusion within the area of sensory block in awake patients.[13,14] Differences regarding the patients' thermoregulatory state and the study design might have contributed to the contradictory results. While sympathetic block was demonstrated compared with baseline in patients covered by a blanket,[14] no sympathetic block was shown in uncovered patients compared with a control group.[13]

However, no such differences exist between the latter study and the current study, because study design, ambient conditions, and measurement techniques were similar. Nevertheless, we showed a diminished skin temperature decrease during TEA within the sensory block, suggesting thoracic sympathetic block. There is no obvious reason for the contradictory results. A shorter acclimation period and the measurement of the mean skin temperature of the dermatome instead of a punctual measurement might play a role.

In animal experimental studies, thoracic sympathetic block was demonstrated during TEA in awake rats and cats,[12,20] whereas it was not shown in conscious dogs.[31] In anesthetized rats, thoracoabdominal skin blood flow remained unchanged after TEA, although thermography demonstrated increased intestinal perfusion.[24] This might be related to the use of Doppler flow measurement in nonglabrous skin and the influence of general anesthesia.

It is still unclear whether a segmental sensory block goes along with a segmental sympathetic block during TEA in humans. Two clinical studies used 0.75% bupivacaine to induce segmental thoracic sensory block. Both studies demonstrated a significant temperature elevation in the foot, indicating an unrestricted sympathetic block.[13,15] A spinal block of the lumbosacral sympathetic nerves due to bupivacaine permeating through the dura along the high concentration gradient is discussed to mediate this effect.[16] When a lower concentration of bupivacaine is used at T3, no sympathetic block occurs. Furthermore, a slight, albeit nonsignificant, increase in lumbar sympathetic activity is recorded.[16] This study indicates a segmental sympathetic block with a lower dose and concentration of local anesthetic. These findings are corroborated by animal experimental studies.[12,20]

In the current study, the level of sympathetic block exceeded the sensory block in each patient in the TEA group, suggesting a caudally unrestricted sympathetic block. The sympathetic outflow to the lumbar and sacral dermatomes originates not lower than L3. The median lower limit of sensory block reached L4 in this study. Therefore, the sympathetic activity in the dermatomes below L5 was probably reduced similarly, although skin temperature in the sacral segments was not measured in this study. While in high thoracic TEA with 0.75% bupivacaine spinal mechanisms presumably induce lumbosacral sympathetic block, in this study 0.25% bupivacaine at a mid and low thoracic level exerts its effects most probably on the spinal roots.

A cranial limit of sympathetic block could not be directly detected. However, from the lack of temperature change in the thumb, we conclude that no effect on sympathetic activity occurred at the level of C6. Consequently, a relevant sympathetic activation cranial to the sympathetic block, which has been suggested by animal studies and lumbar epidural anesthesia in human, seems unlikely.[9,13]

Our data challenge the concept of caudally restricted sympathetic block that mediates protective effects related to TEA. However, this study investigated the intraoperative situation after the initial loading dose of local anesthetic and does not allow direct conclusions on sympathetic block during postoperative continuous epidural infusion.

In our study, the sympathetic block not only preceded sensory block but also cranially exceeded it by two to three dermatomes. Five dermatomes cranial of the sensory block, no signs of sympathetic block were recorded after 20 min. These results partly reproduce the findings in spinal anesthesia reporting up to six dermatomes' difference between sensory and sympathetic block.[18] The cranial, cervical, and high thoracic sympathetic innervation leave the spinal cord not higher than T1, and sympathetic fibers originating cranial of T6 take a predominantly ascending course. This anatomical constellation explains the difference in the cranial spread of sensory and sympathetic nerve block.

Cardiac nerves originate from C1 to T4–T5.[38] Occasionally sympathetic fibers originating from T5 to T7 were described.[38] Consequently, sympathetic block including T1 might affect part of the cardiac sympathetic nerves. In this study, cardiac sympathetic activity was

not measured. However, in the TEA group, hemodynamic parameters did not change. In the postoperative period, extended sympathetic block might nevertheless contribute to arterial hypotension.

The completeness of the block cannot be quantified by any indirect method. However, previous reports of lumbar epidural anesthesia using higher concentrations of local anesthetics described temperature increases of 5°–10°C in the great toe.[39–41] Another clinical study comparing high and mid thoracic and lumbar epidural anesthesia using 0.75% bupivacaine revealed a gradual increase of toe skin temperature.[13] The lower increase reported in our study is similar to the toe temperature increase in high and mid thoracic TEA in the latter study. This might suggest an incomplete sympathetic block in the lower extremities. From this study, however, no information about the density of cardiac, thoracic, and abdominal sympathetic block can be derived. Only neurographic measurement would have allowed quantification of sympathetic nerve activity, albeit with limited spatial resolution.

In summary, this study demonstrated that TEA induced by a high volume of low-concentrated bupivacaine elicits an early and extended sympathetic block, including thoracic, abdominal, and all lumbar segments.

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