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Region of Epidural Blockade Determines Sympathetic and Mesenteric Capacitance Effects in Rabbits

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Background: The mechanisms producing hemodynamic changes during epidural anesthesia are incompletely understood. The role of capacitance changes in the splanchnic venous bed can be clarified by comparing blocks of differing segmental distributions. Specifically, we speculated that blocks that include the innervation to the mesenteric circulation alter hemodynamics, sympathetic activity, and venous capacitance to a greater extent than blocks without blockade of sympathetic nerves to this critical vascular bed.

Methods: Rabbits were studied during α-chloralose anesthesia and mechanical ventilation. Sympathetic efferent nerve activity to the mesenteric vessels was measured by surgically placed electrodes, and mesenteric vein diameter was measured by videomicroscopy. Heart rate and mean arterial pressure were monitored by intraarterial cannulation. Responses were compared after administration of epidural lidocaine using a dose and catheter level that limited anesthetic to lumbar levels (lumbar group) or thoracic levels (thoracic group). In addition, hemodynamic responses were recorded after thoracolumbar block in animals receiving α-chloralose but breathing spontaneously (spontaneous ventilation group) and in awake animals (awake group).

Results: Mean arterial pressure decreased 38.3 ± 5.8% in the thoracic group but only 16.5 ± 2.8 in the lumbar group. Sympathetic efferent nerve activity decreased in the thoracic group but increased in the lumbar group. An increase in vein diameter followed thoracic epidural anesthesia, but venoconstriction was observed after lumbar epidural block. The addition of intravenous sedation with α-chloralose did not increase the hypotensive effect of epidural anesthesia in this model.

Conclusions: Block of sympathetic fibers to the splanchnic circulation with thoracic epidural lidocaine produces mesenteric venodilatation that contributes to hypotension in rabbits. A lesser decrease in blood pressure follows blocks limited to lower segments, because baroreceptor stimulation produces increased splanchnic sympathetic activity and mesenteric venoconstriction. Responses in this model are comparable with and without general anesthesia and mechanical ventilation. To minimize hemodynamic consequences, epidural blockade should ideally be confined to the fewest necessary segments, avoiding splanchnic innervation if possible. (Key words: Anesthetics, local: lidocaine. Anesthetic techniques: epidural. Blood vessels: venous capacitance. Sympathetic nervous system: efferent nerve activity.)

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CIRCULATORY changes during epidural anesthesia are related to the extent of blockade, but not in a simple way. Lumbar injections with interruption of sympathetic fibers originating in spinal segments T10 and below typically produce minimal hemodynamic alterations.[1] Capacitance changes are minor with these lower extremity blocks because veins in skeletal muscle have negligible baseline sympathetic activity and so are unaffected by sympathetic withdrawal.[2] Also, arteriolar dilatation in the blocked segments is balanced by increased resistance in unblocked areas.[3] Anesthesia limited to segments providing cardiac innervation (T1–T5) similarly causes only slight blood pressure and heart rate (HR) changes[4–7] because cardiac performance at rest is not dependent on sympathetic tone, and because the block affects sympathetic nerves to only a small perfusion bed. In contrast, extensive thoracolumbar anesthesia interferes with nearly all sympathetic outflow and often results in hypotension[8–10] because complete sympathetic block produces the

most extensive arteriolar dilatation and little area for compensatory changes. In addition, epidural blockade of thoracic neural segments may produce mesenteric venodilatation[11] that contributes to hypotension by decreasing venous return. The importance of splanchnic venous dilatation during epidural anesthesia in general is uncertain because contributions of this mechanism have been observed only in humans after extensive blockade[11] and in rabbits after full thoracolumbar epidural anesthesia.[12]

Although widely differing segmental regions of epidural blockade are used clinically, splanchnic venous changes during segmental blocks of thoracic or lumbar neural outflow have not been investigated. We speculate that inclusion of segments in the block that contribute preganglionic fibers to the mesenteric bed amplifies hemodynamic depression during epidural anesthesia by decreasing mesenteric sympathetic activity and thereby increasing mesenteric venous capacitance. Using a rabbit model comparable to that used in a previous study of extensive thoracolumbar blockade,[12] the current study examined the effects of lumbar and thoracic segmental epidural anesthesia on directly measured sympathetic activity and mesenteric venous capacitance. In addition, to determine more carefully the relevance of findings with this preparation to clinical situations, we also examined the influence of background systemic anesthesia and mechanical ventilation.

Materials and Methods

Preparation

The preparation was similar to one that we have previously reported.[12] In brief, after approval by the Animal Care Committee, anesthesia was induced in male New Zealand White rabbits (1–2 kg) with thiamylal (10–25 mg/kg) *via* an ear vein. Lidocaine (5 mg/kg) was used for local infiltration of the surgical sites. An epidural catheter was placed by removing the first or sixth lumbar spinous process. The ligamentum flavum was exposed and dissected in the midline, and a catheter (0.965 mm OD) was inserted gently through the gap so as not to puncture the dura and was advanced 1 cm into the spinal canal. The trachea, femoral artery and femoral vein were cannulated for ventilation, blood pressure and HR measurement and blood sampling, and administration of fluids and drugs, respectively. Systemic mean arterial pressure (MAP) was measured with the femoral arterial catheter, and HR was determined

from the arterial pressure signal. A midline laparotomy was made and a postganglionic splanchnic nerve was dissected from the adjacent tissue maintaining continuity proximally and distally. A bipolar recording electrode, composed of two single-strand coated stainless steel wires (0.25 mm OD) in silicone elastomer tubing, was fixed to the nerve with Silgel (tissue-inert silicone polymer; Wacker-Chemie, Munich, Germany) for direct measurement of sympathetic efferent nerve activity (SENA).[13]

Rabbits were placed on a specially constructed transparent and movable microscope stage. A 13-cm loop of ileum was externalized through the laparotomy and mounted in a temperature-regulated plastic chamber. The ileum and associated mesentery were superfused continuously with physiologic salt solution formulated to simulate peritoneal fluid.[14] This solution was maintained at 37°C and pH between 7.35 and 7.45, and continuously aerated with a gas mixture of 5% O_2, 5% CO_2, and 90% N_2. The mesentery was pinned to the Silastic floor of the chamber and *in situ* segments of mesenteric vein 500–800 μm in diameter were cleared of excess fat tissue if their margins were not clearly visible to prepare them for vein diameter (VD) measurement. An on-line videomicroscopy system provided a continuous measurement of mesenteric VD.[15] To verify an adequate preparation of the vessel and nerve, the animals were exposed to hypoxia (fraction of inspired O_2 = 0 for 40 s)[16] before and after the protocol. Data were included only for studies in which SENA and VD were confirmed to be responsive to hypoxia both before and after the full protocol. Rectal temperature was measured continuously by a thermistor probe and maintained between 36.5°C and 37.5°C by a warming pad.

Experimental Protocol

Before the protocol was begun, an interval of at least 1 h followed the preparation of the animal to minimize the effect of the initial thiamylal administration and to allow stabilization of body temperature and measured parameters. Warmed (37°C) normal saline 25 ml/kg was administered intravenously over 10 min. Five minutes later, lidocaine was injected epidurally. Normal saline (30 μl) was injected to flush the catheter. Blood pressure, HR, VD, and SENA measurements were collected for 1 h after the lidocaine injection. Sampled blood was replaced by twice as much normal saline. The ganglionic blocker hexamethonium (10 mg/kg intravenously) was injected at the end of the protocol to

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produce complete sympathetic blockade, confirming postganglionic site of monitoring.[17] SENA measurements were made in reference to the baseline established after hexamethonium administration.

The rabbits were divided into four groups that differed in the sites and doses of lidocaine injection and concurrent systemic medication and ventilation. In two groups, saline 0.4 ml/kg was injected intramuscularly (for comparability with previously studied control groups), and lidocaine 1.0% was injected epidurally in doses and at sites determined in preliminary tests to produce a desired epidural distribution of injectate: thoracic block was produced by injection of 0.2 ml/kg through an epidural catheter inserted at the T12–L1 interspace (thoracic group, n = 6); and lumbar block was produced by the injection of 0.2 ml/kg through a catheter inserted at the L5–L6 interspace (lumbar group, n = 6). Rabbits in these groups had general anesthesia maintained by infusion of α-chloralose (25 mg/h) and vecuronium ($0.3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$). Ventilation was controlled with an animal respirator (655, Harvard Apparatus, South Natick, MA). Normal arterial CO_2 tension (35–40 mmHg) and pH (7.35–7.45) were maintained by ventilator adjustments and $NaHCO_3$ administration guided by arterial blood gas determination (ABL 1, Radiometer Copenhagen, Copenhagen, Denmark) every 15 min and by the continuous monitoring of end-tidal CO_2 tension (1100, Perkin-Elmer, Norwalk, CT).

Two other groups were studied to investigate the effects of mechanical ventilation and general anesthesia during thoracolumbar epidural anesthesia (lidocaine 1%, 0.4 ml/kg, injected at the thoracolumbar junction). General anesthesia was maintained in one group by the infusion of α-chloralose (25 mg/h) as in the other groups, but no vecuronium was administered and the animals breathed spontaneously (spontaneous ventilation group, n = 8). Reliable measurements of nerve activity and VD were not possible because of electrical interference from diaphragmatic activity and movement artifact in the spontaneously breathing animals. Finally, in another group, neither vecuronium nor α-chloralose were administered, and epidural anesthesia was induced only after the animals had fully awakened from the thiamylal anesthesia used during surgical preparation (awake group, n = 6). The animals were loosely confined in a box just small enough to prevent turning and also breathed spontaneously but had no tracheostomy or laparotomy incisions. In the awake and spontaneous ventilation groups, respiratory rate and arterial

blood gases were measured before and 10 min after epidural injection. To examine further the contribution of mechanical ventilation to circulatory changes, MAP, HR, and VD were monitored during brief (15-s) mechanical ventilation imposed on the spontaneous ventilation group during epidural blockade.

At the completion of each experiment, the rabbit was killed with intravenous thiamylal and the spine dissected to confirm that the catheter was properly placed in the epidural space. The extent of epidural solution spread was identified by the stain of ink (particulate black, 25 μl) included with the injectate, and the segmental level of the tip of the catheter was located. Spread within the epidural space was confirmed by ink staining the canal but not the spinal cord.

Statistics

HR, MAP, SENA, and VD were measured from the printed record at 0, 2, 5, 10 and 15 min, and every 15min thereafter. Data were evaluated by multiple analysis of variance for repeated measures comparing least-squares means (Super ANOVA, Abacus, Berkeley, CA). Results are reported as means ± standard error. Findings are considered significant if $P \leq 0.05$.

Results

There were no differences between groups in $NaHCO_3$ administration. Maximum changes in HR, MAP, SENA, and VD for each group are listed in table 1. Percentage changes over time are illustrated in figure 1, which compares lumbar and thoracic groups, and in figure 2, which compares the spontaneous ventilation and awake groups.

Extent of Injectate Spread

On average, the catheter tip was located at the L4/L5 disc in the lumbar group and at the T11/T12 disc in the others. Thr median segmental extent of solution distribution within the vertebral canal (fig. 3) was T11 to L7 for the lumbar group (range T7–T12 cephalad, L6–L7 caudad), T4 to L1 for the thoracic group (range T1–T6 cephalad, T12 to L2 caudad), and T1 to L4 for the spontaneous ventilation and awake groups (range T1–T2 cephalad and L3–L5 caudad).

Mean Arterial Pressure

MAP decreased after lidocaine administration in all groups. Recovery was complete by 60 min. There was

Table 1. Maximum Percentile Changes of Measured Parameters after Lidocaine Injection

	MAP	HR	SENA	VD
Lumbar	−16.5 ± 2.8*	−3.5 ± 2.2	23.0 ± 13.0*	−5.3 ± 2.3*
Thoracic	−38.3 ± 5.8*	3.9 ± 3.6	−47.3 ± 18.7*	8.6 ± 3.6*
Spontaneous ventilation	−48.0 ± 5.0*	−14.2 ± 4.2*		
Awake	−41.3 ± 8.4*	−8.0 ± 6.7*		
IM	−6.9 ± 3.2	4.1 ± 2.3	−6.6 ± 6.7	−1.2 ± 2.0
Thoracolumbar	−56.9 ± 4.3*	−13.1 ± 4.3*	−82.6 ± 14.1*	7.5 ± 1.8*

The bottom two rows present data for comparison from a previous study with an identical preparation, including mechanical ventilation and α-chloralose sedation.[12] In the IM group (n = 7), lidocaine 1.5% 0.4 ml/kg was injected intramuscularly. In the thoracolumbar group (n = 8), lidocaine 1.0% 0.4 ml/kg was injected at the T12/L1 interspace to produce full thoracolumbar blockade.

* $P < 0.05$ versus baseline measurement.

a significantly greater pressure decrease in the thoracic group than in the lumbar group. No difference was noted between spontaneous ventilation and awake groups.

Heart Rate

HR decreased only in the animals receiving thoracolumbar epidural anesthesia (spontaneous ventilation and awake groups). The decrease was significantly less in the awake group at 10 min.

Sympathetic Efferent Nerve Activity

A marked decrease followed injection in the thoracic group. SENA increased at the onset of lumbar epidural anesthesia.

Vein Diameter

VD increased in the thoracic group. Venoconstriction accompanied lumbar epidural lidocaine injection.

Ventilatory Changes

In both the spontaneous ventilation and awake groups, respiratory rate, and arterial CO_2 tension did not change with epidural blockade (spontaneous ventilation: 50.0 ± 4.3 s^{-1} and 32.5 ± 2.6 mmHg before block, 49.1 ± 3.5 s^{-1} and 33.6 ± 4.2 mmHg after; awake: 90.3 ± 13.1 s^{-1} and 25.5 ± 1.8 mmHg before block, 89.0 ± 12.4 s^{-1} and 23.5 ± 0.7 mmHg after). Brief mechanical ventilation imposed on spontaneous ventilation group animals had no effect on HR, MAP, or VD (data not shown).

Discussion

Studies in humans have documented greater hemodynamic consequences of extensive epidural anesthesia compared with more limited neuraxial blockade.[3,18,19] It is well accepted that hemodynamic changes with spinal and epidural anesthesia are influenced by the extent of sympathetic blockade produced by the block. However, attempts to delineate this relation have been limited by a lack of consistent evidence on the extent and intensity of sympathetic blockade when various measures of sympathetic activity are used. Skin blood flow may increase in areas more extensive than the sensory blockade,[20] or may increase with a limited segmental distribution and even paradoxically decrease in the center of thoracic segmental blocks.[21] Elimination of the skin conduction response is unpredictable and incomplete.[22] Global norepinephrine production decreases partially[23] or not at all[24] with extensive block. Not only do these observations fail to produce a clear picture of sympathetic blockade with spinal and epidural anesthesia, but the sites of measurement may not be those important to hemodynamic changes. Sympathetic system activity is heterogeneous and fibers to different tissues exhibit specific patterns of basal and reflex activity.[25,26] Because neuraxial blockade is an incomplete process,[22,27] uniform effects on sympathetic activity to various organs can not be assumed. Changes in skin blood flow, circulating norepinephrine,[28] and sweat gland function have minimal influence on hemodynamics, giving impetus to direct measurement of activity in sympathetic fibers supplying large vascular beds. Microneurographic monitoring of sympathetic fibers to lower extremity muscle vasculature has shown prompt and complete termination of activity with onset of epidural anesthesia in humans.[29,30]

We monitored the sympathetic innervation of the splanchnic circulation because of the unique role of splanchnic veins in regulating circulatory capacitance.[31,32] The importance of these vessels during spinal
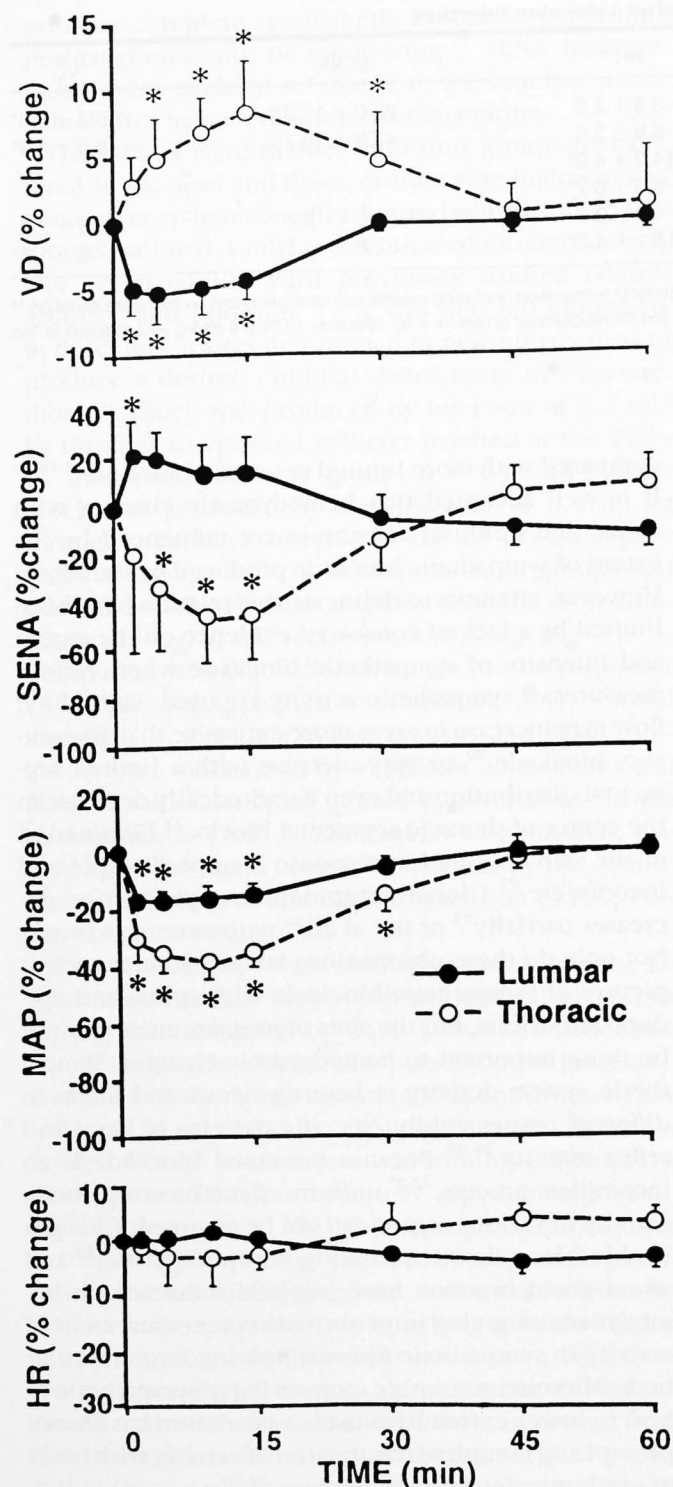
Fig. 1. Responses in heart rate (HR), mean arterial pressure (MAP), sympathetic efferent nerve activity (SENA), and vein diameter (VD) to lidocaine injected at 0 min in the thoracic and lumbar epidural block groups. *Significant change from baseline.

and epidural anesthesia is supported by abrupt hemodynamic collapse in humans when abdominal vasodilatation accompanies the onset of epidural anesthesia.[11] We have found that extensive epidural anesthesia in rabbits produces hypotension and splanchnic venodilatation.[12] These changes are concurrent with ablation of sympathetic activity to the splanchnic bed, and are not explained by direct effects of local anesthetic on the vessels, altered circulating catecholamine concentrations, or by passive response to increased transmural pressure.[33] Systemic local anesthetic has been shown to produce minimal circulatory changes in this model.[12]

The spread of ink, which was used as an indication of bulk flow of injectate within the epidural space, slightly underestimates the extent of anesthetic effect.[34] Decrease in SENA was in fact observed after two of the lumbar injections. A greater extent of anesthetic effect would act to diminish the distinction between lumbar and thoracic groups, so the observed differences in physiologic parameters may underestimate the contribution of splanchnic mechanisms.

The current study shows that epidural anesthetic effects on the veins and nerves of the splanchnic circu-
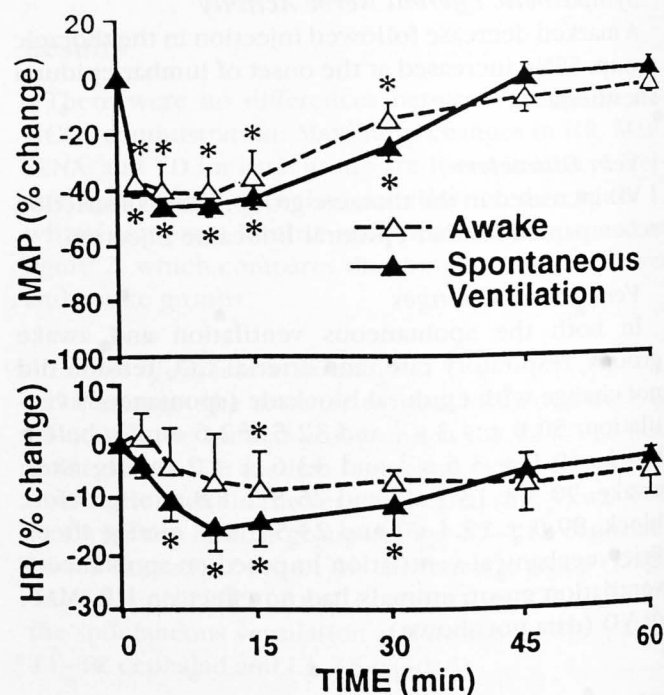
Fig. 2. Responses in heart rate (HR) and mean arterial pressure (MAP) to epidural lidocaine injected at 0 min in the spontaneous ventilation and awake groups. *Significant change from baseline.

Fig. 3. Median segmental spread of thoracic and lumbar blocks. The segmental origin of splanchnic sympathetic fibers is al...

lation are sensitive to the distr... the thoracic group, blockade i... origins of preganglionic fibers s... circulation,[35] reflected in dec... turn caused increased VD. The... in the thoracic group is somet... ously studied mechanically v... thoracolumbar blockade (see... son),[12] probably because of th... culatory beds for compensator... imals with the more extensive...

The importance of splanchn... in the diminished hypotension... blockade. Without pregangl... baroreceptor driven increased... to the splanchnic bed. In the... enteric venoconstriction may... namic changes from blocked... Although these changes are co... cannot be proved with these... that, independent of capacita...

Fig. 3. Median segmental spread of epidural injectate for thoracic and lumbar blocks. The segmental origin of preganglionic splanchnic sympathetic fibers is also shown.

lation are sensitive to the distribution of blockade. In the thoracic group, blockade included the segmental origins of preganglion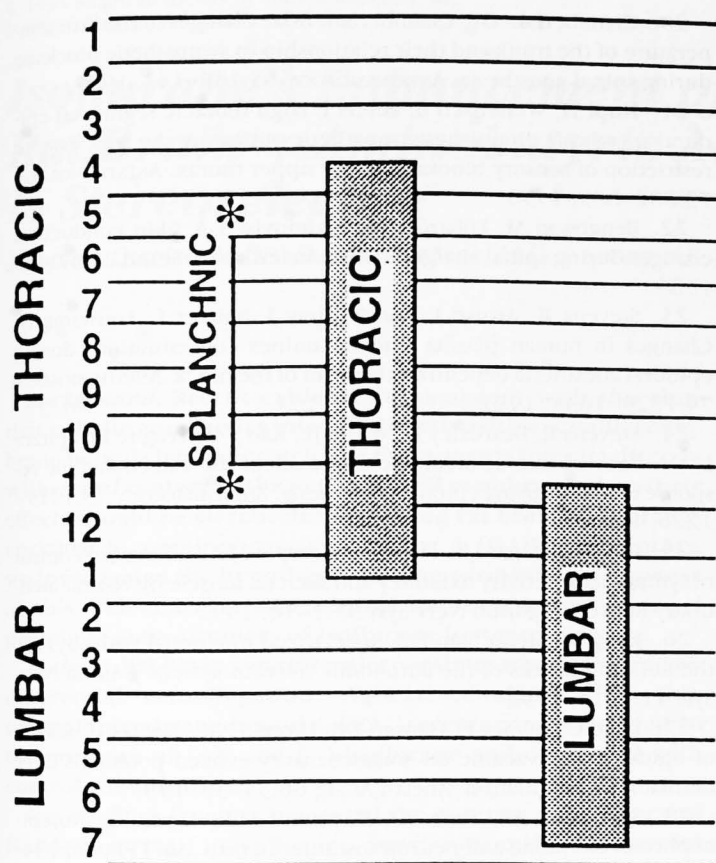ic fibers supplying the splanchnic circulation,[35] reflected in decreased SENA, which in turn caused increased VD. The hypotension observed in the thoracic group is somewhat less than in previously studied mechanically ventilated animals with thoracolumbar blockade (see table 1 for comparison),[12] probably because of the lack of responsive circulatory beds for compensatory vasoconstriction in animals with the more extensive, nonsegmental blocks.

The importance of splanchnic innervation is evident in the diminished hypotension during lumbar epidural blockade. Without preganglionic neural blockade, baroreceptor driven increased SENA is revealed in fibers to the splanchnic bed. In these animals, reflect mesenteric venoconstriction may have buffered hemodynamic changes from blocked regional vascular beds. Although these changes are correlated, a causal relation cannot be proved with these data. It is also possible that, independent of capacitance changes, the degree

of hypotension in the various groups reflects in part the relative amount of denervated arterioles and resulting resistance changes.

In this and an earlier study,[12] hypotension during epidural anesthesia was more dependent on the extent of blockade than on concurrent general anesthesia, mechanical ventilation, or the presence of neck and laparotomy incisions. The MAP decrease previously observed in mechanically ventilated animals with thoracolumbar blockade was somewhat greater than in the current awake or spontaneous ventilation groups (table 1). This difference is likely due to the circulatory depressant consequences of mechanical ventilation, although brief mechanical ventilation imposed on spontaneously breathing animals had no easily identifiable effects in isolation. A more extensive abdominal surgical preparation in the mechanically ventilated animals (including electrode insertion) also may have contributed to greater hypotension. Decreased HR observed in the groups receiving the most extensive blocks (awake, spontaneous ventilation, and previous mechanically ventilated thoracolumbar blocks) may result from more complete cardiac denervation. Because the group receiving thoracic blockade did not show any HR change, a more likely explanation for bradycardia in the groups with more extensive block is vagal increase caused by reflexes initiated by low cardiac filling pressures.[36,37]

We conclude that different regions of epidural blockade produce graded effects on blood pressure but divergent effects on splanchnic sympathetic activity and VD. Blockade that interrupts the sympathetic innervation to the abdominal vasculature produces mesenteric venodilatation and more pronounced decrease in blood pressure. This indicates that splanchnic venous capacitance plays a pivotal role in determining hemodynamic responses to epidural anesthesia in rabbits. Humans have a proportionately greater lower extremity mass, so a rabbit model may overestimate the importance of abdominal vascular changes. The current results suggest, however, that when possible, blocks for surgery or pain control should be limited to the involved area in cases in which it is desirable to limit hemodynamic consequences.

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Isoflurane's Enha
Rat Brain γ-Amin
Is Stereoselective

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Background: Recent evidence is co
that volatile anesthetics interact direc
brane-bound channel proteins. If thes
with chiral centers in the neuronal ce
effects should be stereoselective. Usi
enriched in γ-aminobutyric acid typ
we investigated the hypothesis that th
of this well-characterized central n
protein to stereoisomers of isofluran

Methods: Rat brain synaptic microv
differential centrifugation. Agonist
through membrane-bound GABA$_A$ r
the presence of (+)- and (−)-isoflur
control conditions.

Results: Both isomers increased th
GABA; however, (+)-isoflurane was s
and efficacious than the (−)-isomer.
ner (140 μM) reduced the median e
GABA from 12.7 ± 1.0 to 5.4 ± 0.5 μM
reduced it to 9.6 ± 1.0 μM (P < 0.001)
1.6 times as potent as the (−)-isomer
gated flux (79 ± 11 vs. 130 ± 17 μM,
addition, the (+)-isomer produced s
imal enhancement of flux (9.8 ± 0.4
s^{-1}; P < 0.001).

Conclusions: Isoflurane's effects on
were stereoselective. This result su