

Effects of Epidural and Systemic Lidocaine on Sympathetic Activity and Mesenteric Circulation in Rabbits

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Background: The mechanisms producing hemodynamic changes during epidural anesthesia are incompletely understood. This study examines the sympathetic block and splanchnic venodilatation that result from extensive thoracolumbar epidural anesthesia in rabbits using direct measurements of sympathetic efferent nerve activity (SENA) and mesenteric vein diameter (VD).

Methods: Epidural catheters were inserted in rabbits anesthetized with α -chloralose, paralyzed with vecuronium, and receiving mechanical ventilation. Arterial pressure was monitored with a femoral cannula, heart rate was determined from the pressure signal, SENA was measured from a postganglionic splanchnic nerve, and VD was measured from segments of ileum externalized *in situ*. Epidural anesthesia was induced with 0.4 ml/kg lidocaine, using concentrations of either 0.5, 1, or 1.5%. Control animals received intramuscular lidocaine in a dose of either 6 or 15 mg/kg. After recovery from epidural anesthesia, complete sympathetic blockade was induced by systemic administration of the ganglionic blocker hexamethonium (HX). Individual groups included from five to eight animals.

Results: A mild decrease in arterial pressure and SENA followed the larger dose of intramuscular lidocaine, but no changes occurred in VD in the control animals exposed to

systemic lidocaine at levels comparable to that in the epidural groups (0.96–3.58 μ g/ml). Epidural injectate extended from T2 to L5. All concentrations of epidural lidocaine produced comparable degrees of hypotension (–53.5 to –61.4%), decreased SENA (–82.6 to –95.5%), and increased VD (7.5 to 10.2%). The duration of the changes was greater with more concentrated lidocaine. Hexamethonium produced changes in arterial pressure and VD comparable to those evoked by epidural anesthesia.

Conclusions: Epidural anesthesia increases splanchnic venous capacitance by markedly decreasing splanchnic sympathetic nerve activity. (Key words: Anesthetics, local; lidocaine. Anesthetic techniques; epidural. Sympathetic nervous system: efferent nerve activity; venous capacitance.)

THE hemodynamic changes that accompany extensive neural blockade by spinal and epidural anesthesia are a major limiting factor in the safe use of these techniques. Despite the frequency and occasional severity of systemic hypotension, the mechanism is not clearly established. It is accepted that blockade of sympathetic outflow is the predominant cause of hemodynamic alterations induced by epidural block, but investigation has been impeded by the lack of direct measurement of sympathetic activity. Studies using indirect measures report a variable extent and intensity of sympathetic blockade. Some reports demonstrate a limited sympathetic blockade during epidural anesthesia. For example, monitoring sympathogalvanic response¹ or toe pulse amplitude² indicates a sympathetic block much more limited than sensory or motor changes. Thermographic measurements reflecting skin blood flow show changes restricted to the distal extremities, even during extensive blocks.³ Epinephrine levels are usually unchanged, and norepinephrine levels may decrease by only 47%, despite epidural block of all thoracolumbar segments.⁴ Other reports show consistently prompt and intense sympathetic interruption from epidural local anesthetics. After small epidural doses of local anesthetic in humans, skin blood flow measured by laser Doppler increases before sensory changes.⁵ The

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only studies using direct measurement of sympathetic activity recorded impulses in the postganglionic fibers to the skin and muscle of the leg, and showed complete elimination of spontaneous and induced sympathetic activity after induction of epidural anesthesia.^{6,7} The influence of local anesthetic concentration on the intensity of sympathetic blockade has not been examined.

One proposed mechanism by which sympathetic blockade causes decreased cardiac output and blood pressure during epidural anesthesia is increased venous capacitance.⁸ Veins in skeletal muscle have little or no sympathetic innervation,⁹ and the circulation of the limbs contribute minimally to the active control of capacitance.¹⁰ For these reasons, epidural blockade produces no increase in venous capacitance of the extremities.^{11,12} However, the splanchnic veins, which contain 25% of the total blood volume, are richly supplied with sympathetic nerves,¹³ and the resting tone in splanchnic veins is dependent on tonic sympathetic neural activity.¹⁴ The splanchnic bed accounts for almost all of the reflex capacitance response that buffers systemic circulatory volume changes.^{10,15} These features indicate that splanchnic sympathetic blockade can result in important capacitance increases, which would be poorly buffered by reflex venoconstriction in non-splanchnic beds. This mechanism may contribute to hypotension when epidural anesthesia extends to the spinal segments providing preganglionic fibers to the splanchnic sympathetics (T5–T11).¹⁶

In this study, we examine the hypothesis that sympathetic blockade and splanchnic venodilatation contribute to hypotension during epidural anesthesia by using simultaneous direct measurement of both sympathetic activity and mesenteric vein diameter (VD). We also compare the responses from graded concentrations of epidural lidocaine to responses from systemic lidocaine. To avoid the influence of variable extent of blockade, a large injectate volume is used to expose the full thoracolumbar range of preganglionic sympathetic fibers to the epidural solution.

Materials and Methods

Preparation

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 and maintained by α -chloralose (25 mg/h). Lidocaine (5 mg/kg) was used for local infiltration of the surgical sites. An epidural catheter was placed by removing the first 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 advanced 1 cm into the spinal canal.

Other instrumentation of the rabbits was comparable to that reported previously.¹⁷ The trachea, femoral artery, and femoral vein were cannulated for ventilation, blood pressure determination and blood sampling, and administration of fluids and drugs, respectively. A midline laparotomy was made and a postganglionic splanchnic nerve was isolated 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 Silastic tubing, was fixed to the nerve with Wacker silgel (Wacker-Chemie, Munich, Germany) for sympathetic efferent nerve activity (SENA) recording. The study was performed during the infusion of vecuronium ($0.3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$), and ventilation was controlled with a Harvard animal respirator (model 655; Harvard Apparatus, South Natick, MA). Normal P_{CO_2} (35–40 mmHg) and pH (7.35–7.45) were maintained by ventilator adjustments, and NaHCO_3 administration was guided by arterial blood gas determination (Model ABL 1; Radiometer Copenhagen, Copenhagen, Denmark) every 15 min and by the continuous monitoring of end-tidal P_{CO_2} (model 1100; Perkin-Elmer, Norwalk, CT). Rectal temperature was measured continuously by a thermistor probe and maintained between 36.5 and 37.5°C by a warming pad.

The rabbits were placed on a specially constructed transparent and movable microscope stage (fig. 1). An approximately 13-cm loop of ileum was externalized through the laparotomy and mounted in a temperature-regulated plastic chamber. The mesentery was pinned to the Silastic floor of the chamber and *in situ* segments of 500–800 μm diameter mesenteric vein were cleared of excess fat tissue if their margins were not clearly visible, to prepare them for VD measurement. To verify an adequate preparation of the vessel and nerve, the animals were exposed to a hypoxic stress ($F_{\text{I}_{\text{O}_2}} = 0$ for 40 s)¹⁸ before and after the protocol. Data were included only for studies in which SENA and VD were confirmed to be responsive to hypoxic stress both before and after the full protocol; in about 30% of the

||Hainsworth R: The importance of vascular capacitance in cardiovascular control. *News in Physiological Sciences* 5:250–254, 1990

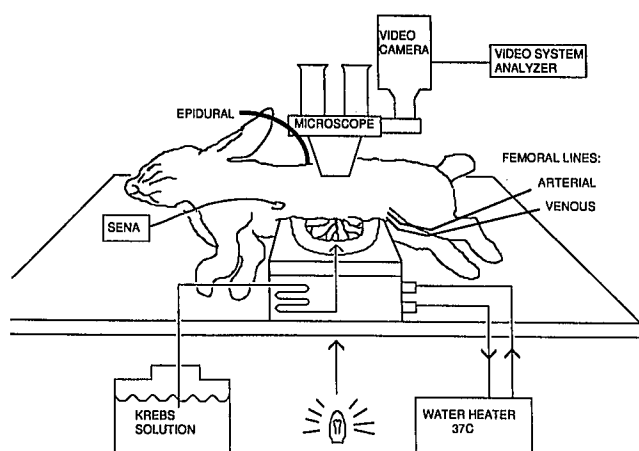


Fig. 1. Experimental setup *in situ* study of vein diameter and sympathetic efferent nerve activity (SENA) in rabbits during epidural anesthesia.

animals, the first vein prepared was not suitable. The ileum and associated mesentery were superfused continuously with physiologic salt solution formulated to simulate peritoneal fluid.¹⁹ This solution was maintained at 37° C and pH between 7.35 and 7.45, and continuously bubbled with a gas mixture of 5% O₂, 5% CO₂, and 90% N₂.

At the completion of the study of each animal, the rabbit was killed with thiamylal and the spine dissected to confirm that the catheter was properly placed in the epidural space, and to determine the extent of epidural solution spread by the stain of ink included with the injectate. Epidural spread was evident when ink stained the canal but not the spinal cord, and intrathecal placement was evident if the cord was stained and not the canal wall.

Measurements

All devices were calibrated before the study of each animal. Systemic mean arterial pressure (MAP) was measured *via* the femoral arterial line, and the heart rate (HR) was determined from the arterial pressure signal. An on-line videomicrometer system provided a continuous measurement of mesenteric vein diameter. This reproducibly ($r \geq 0.999$) measures diameters as small as 200 μm .²⁰ The vessel of interest was contrasted from the background by intense back lighting and monitored by a camera mounted on a dissecting microscope, producing a horizontal dark image. A comparator signal was derived from the filtered video signal,

and its duration was determined by an eight-bit timer module with a digital-to-analog converter to produce an analog signal proportional to the vessel diameter. The directly measured nerve activity was amplified 40,000 \times and passband filtered between 0.1–2 kHz. A fourth-order Bessel filter and a moving time averager with a digital-to-analog converter using 200-ms time increments produced an analog output proportional to SENA.²¹ The data were printed on an eight-channel recorder (Astro-Med model 9500; Astro-Med, West Warwick, RI). Serum lidocaine levels were determined by fluorescent polarization immunoassay (TDX system, Abbott, North Chicago, IL) with a standard deviation for repeated determinations of 4% of the measured level in the range relevant to this study. NaHCO₃ administration per kilogram of body weight was calculated for each animal.

Experimental Protocol

The reversibility and extent of blockade were examined by preliminary study of six rabbits, in which the preparation consisted of only epidural cannulation, after which the rabbits were allowed to awaken. Either 1 or 1.5% lidocaine, in volumes of 0.15–0.35 ml/kg, was then injected epidurally. Sensory and motor function were monitored by evaluating the flexion of the hind legs against gravity while the rabbit was held upright, the ability to ambulate normally, the withdrawal of extremities to a forceps pinch on the fore and hind paw pad, and a flinch response to a forceps pinch in the midportion of the back adjacent to the epidural insertion site.

Thirty-six rabbits were studied using hemodynamic, SENA, and VD monitoring. An interval of at least 1 h followed the preparation of the animal before starting the protocol, 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 then administered intravenously over 10 min. Five minutes later, epidural anesthesia was induced using 0.4 ml/kg lidocaine in concentrations of either 0.5, 1, or 1.5%. Normal saline (30 μl) was injected to flush the catheter. In control rabbits, 1.5% lidocaine was injected intramuscularly in the thigh on the side without femoral cannulae, in doses of 6 mg/kg (0.4 ml/kg) or 15 mg/kg (1 ml/kg), and 0.4 ml/kg normal saline was injected epidurally. Groups included five to eight rabbits. Animals were allotted to groups on an alternating basis. Data were collected for 2 h after the lidocaine injection. Arterial

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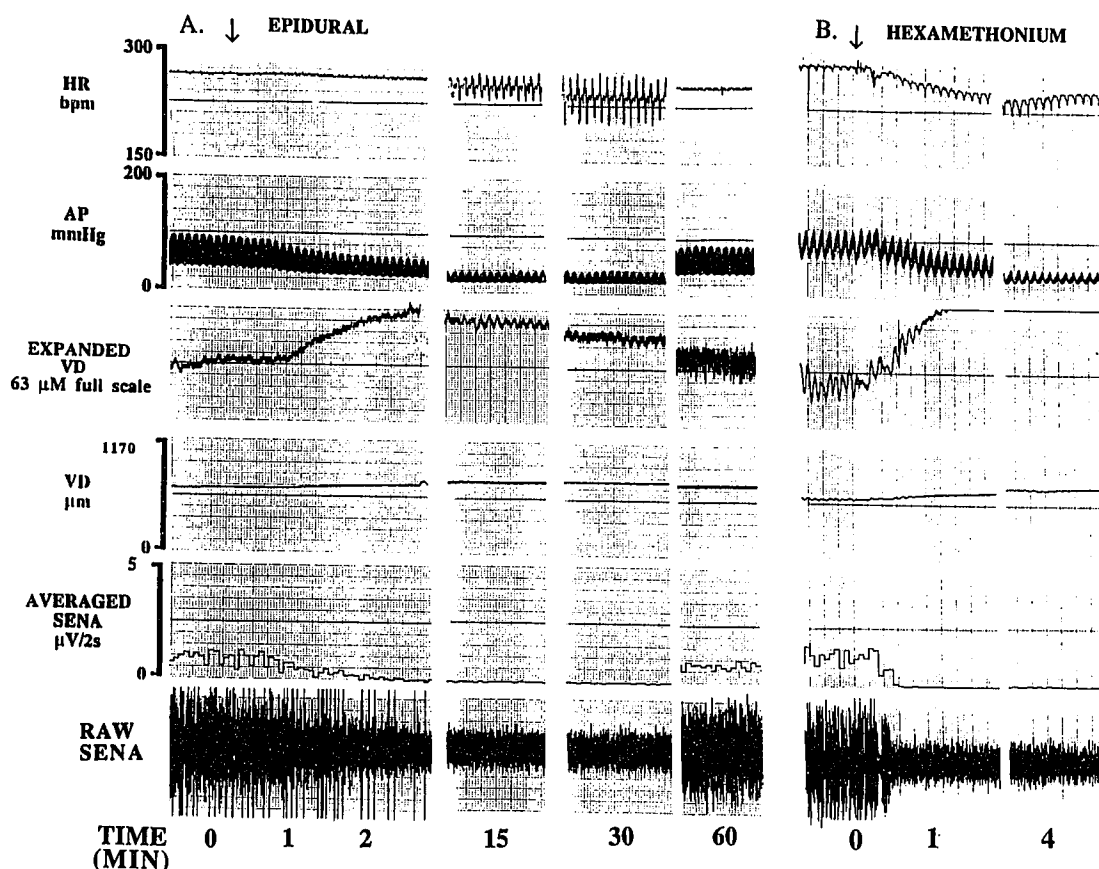


Fig. 2. (A) Typical traces at baseline, response to epidural lidocaine 1%, and recovery, demonstrating decreased heart rate (HR), decreased arterial pressure (AP), increased mesenteric vein diameter (VD), and decreased sympathetic efferent nerve activity (SENA) during epidural blockade. (B) Response to 10 mg/kg intravenous hexamethonium, demonstrating prompt cessation of SENA and mesenteric venodilation.

blood (1 ml) was sampled for the determination of lidocaine levels before epidural or intramuscular injection (time 0) and at 15, 30, and 120 min afterward. Sampled blood was replaced by twice as much normal saline. The ganglionic blocker hexamethonium (HX; 10 mg/kg intravenously) was injected at the end of the protocol to produce complete sympathetic blockade.²² Measurements of SENA were made in reference to the baseline established after HX administration.

Statistics

Heart rate, MAP, SENA, and VD were measured from the printed record at 0, 2, 5, 10, and 15 min, and every 15 min thereafter. Data were evaluated by multiple ANOVA for repeated measures with individual contrasts (Super ANOVA; Abacus, Berkeley, CA), comparing measurements to baseline and comparing values at each

time among the five study groups. Before analysis, arc-sine transformations were performed on all percentage changes to assure normal distribution of the values.²³ Results are reported as mean \pm SEM. Findings are considered significant if $P < 0.05$.

Results

There was no difference in body weight between groups. Typical responses of MAP, SENA, and VD to the induction of epidural anesthesia and to HX are illustrated in figure 2. Maximal changes from baseline for MAP, SENA, VD, and serum lidocaine levels are listed in table 1. For comparisons with controls, epidural groups were matched to the control group with similar serum lidocaine levels: the 0.5% epidural lidocaine group was compared with the low-dose control, and

Table 1. Maximum Changes

Lidocaine Route and Dose	HR (% change)	MAP (% change)	SENA (% change)	VD (% change)	Serum Lidocaine ($\mu\text{g/ml}$)	Administered NaHCO_3
IM 6 mg/kg (n = 7)	4.1 \pm 2.3	-8.4 \pm 4.0	-21.4 \pm 10.6	2.3 \pm 3.5	1.1 \pm 0.4*	3.9 \pm 0.5
IM 15 mg/kg (n = 5)	-3.8 \pm 1.5	-13.4 \pm 4.1*	-25.9 \pm 6.4*	-4.1 \pm 2.3	3.6 \pm 0.4*	4.5 \pm 0.8
Epidural 0.5% 0.4 ml/kg (n = 5)	-6.2 \pm 3.3*	-53.5 \pm 4.9*	-85.9 \pm 8.2*	10.2 \pm 1.9*	1.0 \pm 0.1*	2.7 \pm 0.3
Epidural 1.0% 0.4 ml/kg (n = 8)	-13.1 \pm 4.2*	-56.9 \pm 4.3*	-82.6 \pm 14.1*	7.5 \pm 1.8*	2.1 \pm 0.1*	3.8 \pm 0.4
Epidural 1.5% 0.4 ml/kg (n = 7)	-8.6 \pm 5.4*	-61.4 \pm 3.6*	-95.5 \pm 1.9*	9.4 \pm 1.8*	2.7 \pm 0.2*	3.3 \pm 0.3

Values are mean \pm SEM.

HR = heart rate; MAP = mean arterial blood pressure; SENA = sympathetic efferent nerve activity; VD = mesenteric vein diameter; IM = intramuscular.

* $P < 0.05$ versus baseline.

the 1 and 1.5% epidural lidocaine groups were compared with the high-dose intramuscular control group.

Epidural Catheterization

Autopsy examination of the spinal canal revealed that two epidural catheters had entered the dural sack, one had entered a vein, and one produced an epidural hematoma; the data from these four studies were not included in the analysis. Six epidural catheters were initially intravascular, as was evident by the aspiration of blood, and required reinsertion; no hemorrhage was evident by autopsy. In awake rabbits, hind leg flexion against gravity was blocked for 18–31 min; ambulation returned after 20–40 min; hindleg withdrawal in 0–26 min, and back sensation in 29–44 min. There was no evidence of forelimb motor or sensory blockade, and all animals recovered completely. Injections produced no pain behavior or change in alertness. In the rabbits studied invasively, solution was distributed in the epidural space from a median of T2 (range T1–T4) to L5 (range L2–L6), with no significant differences between groups. Epidural spread covered the segments at which preganglionic innervation to the mesentery originates (T5–T11) in all animals.

Lidocaine, NaHCO_3 , and Hexamethonium

Serum lidocaine levels of the two control groups encompassed the levels generated by epidural administration (fig. 3). Levels were maximum at 15 min. The

maximum serum level after epidural 1.5% lidocaine was significantly higher than an equal dose (6 mg/kg) intramuscularly. There were no differences in NaHCO_3 administration per kilogram between groups.

Hemodynamics

One animal that received 1.5% lidocaine died 3 min after the epidural injection. The data from this animal are not included in the group analysis, and are discussed separately below. Initial MAP group averages ranged from 70.2 ± 6.2 to 88.9 ± 5.5 mmHg,

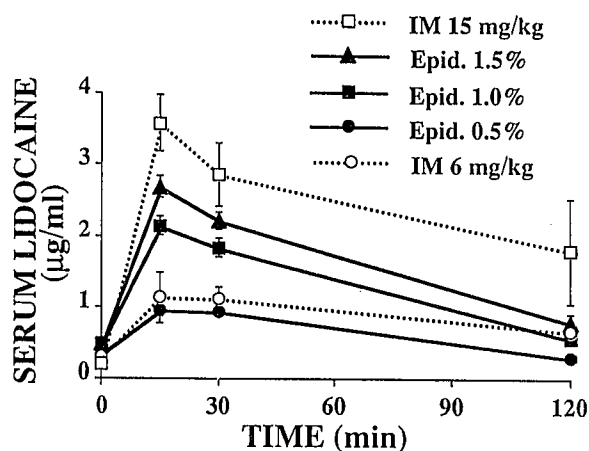


Fig. 3. Serum lidocaine levels during epidural and intramuscular lidocaine.

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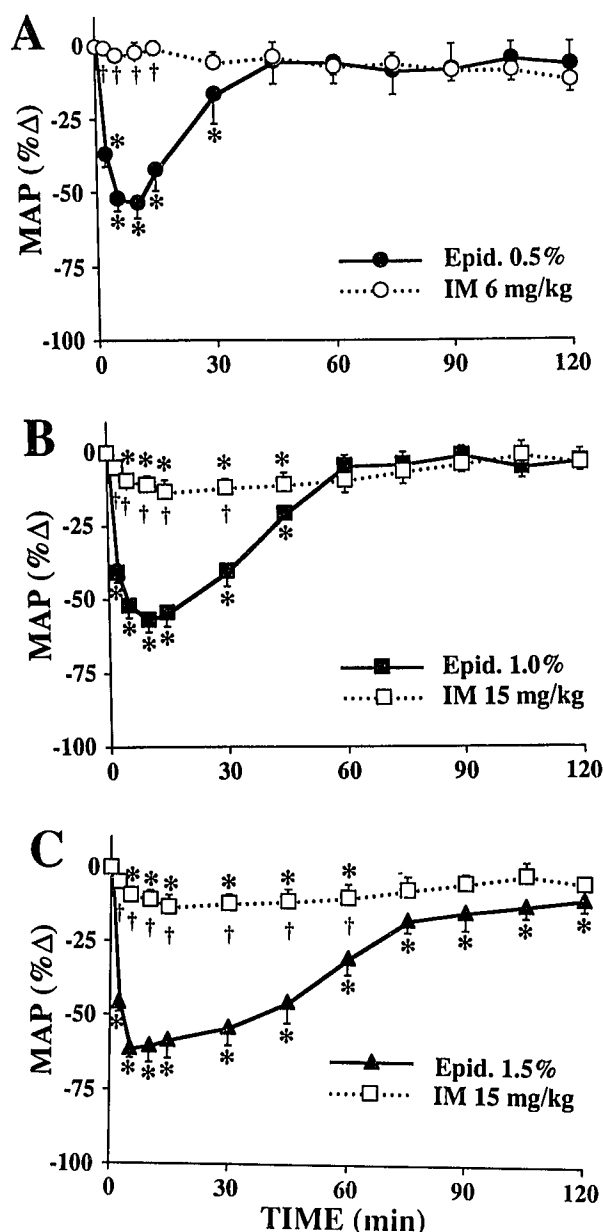


Fig. 4. Changes in mean arterial pressure (MAP) during (A) epidural lidocaine 0.5% and 6 mg/kg intramuscular lidocaine, (B) epidural lidocaine 1% and 15 mg/kg intramuscular lidocaine, and (C) epidural lidocaine 1.5% and 15 mg/kg intramuscular lidocaine. Values are mean \pm SEM. * $P < 0.05$ compared with baseline (time = 0); † $P < 0.05$ comparing the epidural to intramuscular value at that time point.

with no significant differences between groups. Mean arterial pressure (fig. 4) decreased in the animals receiving intramuscular lidocaine only at the larger dose, by a maximum of $13.4 \pm 4.1\%$. In the epidural

anesthesia groups, MAP decreased by a maximum of $53.5 \pm 4.9\%$ (0.5% lidocaine), $56.9 \pm 4.3\%$ (1% lidocaine), and $61.4 \pm 3.6\%$ (1.5% lidocaine); the differences between these maximal changes were not significant. The depression of MAP was longer with higher concentrations of lidocaine; MAP was lower than baseline for 30 min in the 0.5% lidocaine group, 45 min in the 1% lidocaine group, and throughout the study period in the 1.5% lidocaine group. Hexamethonium produced a significant decrease in MAP of $52.1 \pm 2.4\%$.

Initial HR group averages ranged from 253 ± 13 to $293 \pm 10 \text{ s}^{-1}$, with no significant differences between groups. There were no significant HR changes from baseline in the control groups or epidural 0.5% lidocaine group (fig. 5). Heart rate decreased by a maximum of $13.1 \pm 4.2\%$ with epidural 1% lidocaine and $8.6 \pm 5.4\%$ with epidural 1.5% lidocaine.

Sympathetic Efferent Nerve Activity

Sympathetic efferent nerve activity did not significantly change from baseline in the 6-mg/kg intramuscular lidocaine group (fig. 6), and decreased in the 15-mg/kg intramuscular lidocaine group only at 15 min, by $25.9 \pm 6.4\%$ ($P = 0.045$). Sympathetic efferent nerve activity was significantly depressed in all epidural anesthesia groups. The maximum decreases in the 0.5, 1, and 1.5% epidural lidocaine groups were 85.9 ± 8.2 , 82.6 ± 14.1 , and $95.5 \pm 1.91\%$, respectively (not significantly different). Sympathetic efferent nerve activity was significantly lower than baseline for 30 min in the 0.5 and 1% epidural lidocaine groups, and for

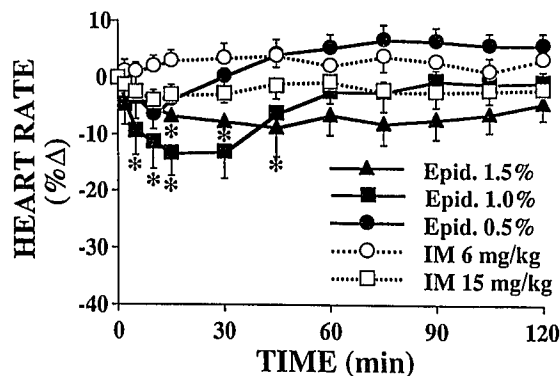


Fig. 5. Time-dependent changes in heart rate during epidural and intramuscular lidocaine. Values are mean \pm SEM. * $P < 0.05$ compared with baseline (time = 0).

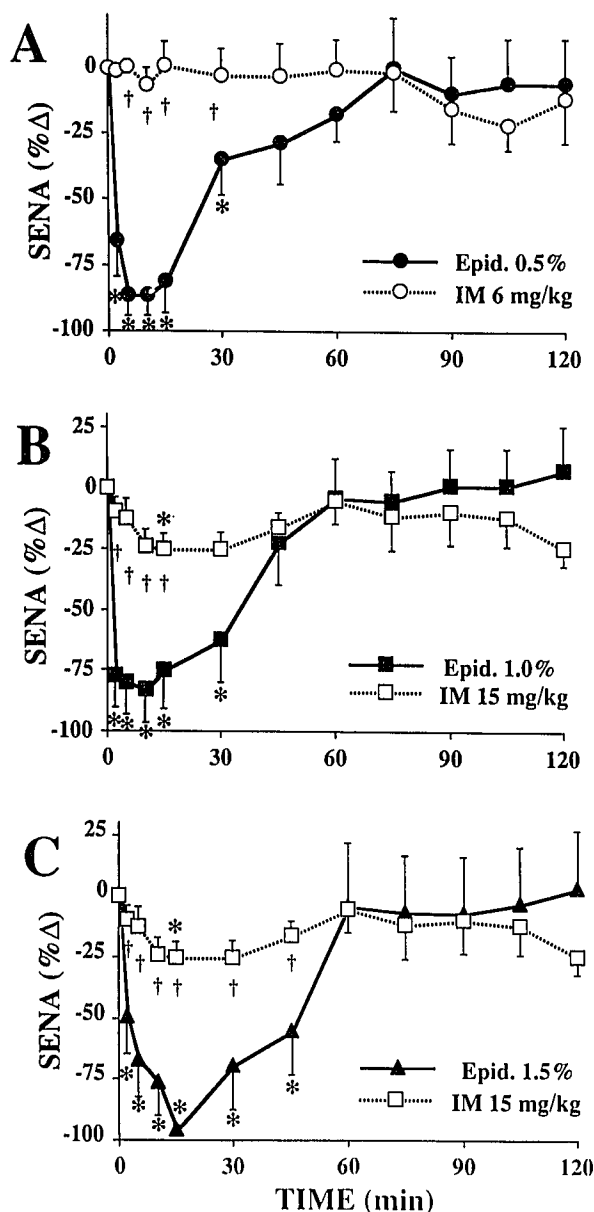


Fig. 6. Changes in sympathetic efferent nerve activity (SENA) over 2 h during (A) epidural lidocaine 0.5% and 6 mg/kg intramuscular lidocaine, (B) epidural lidocaine 1% and 15 mg/kg intramuscular lidocaine, and (C) epidural lidocaine 1.5% and 15 mg/kg intramuscular lidocaine. Values are mean \pm SEM. * $P < 0.05$ compared with baseline (time = 0); † $P < 0.05$ comparing the epidural to intramuscular value at that time point.

45 min in the 1.5% epidural lidocaine group. Hexamethonium immediately depressed SENA in all animals, demonstrating that the monitored nerve was a postganglionic sympathetic nerve.

Vein Diameter

Initial VD group averages ranged from 687 ± 40 to $832 \pm 81 \mu$, with no significant differences between groups. There were no VD changes from baseline in the control groups (fig. 7). Vein diameter significantly increased in all epidural anesthesia groups, and each animal receiving epidural lidocaine showed an increase in VD within 10 min of injection. The maximum increases of VD in the 0.5, 1, and 1.5% epidural groups were 10.2 ± 1.9 , 7.5 ± 1.8 , and $9.4 \pm 1.8\%$, respectively (not significantly different from each other). Vein diameter was significantly greater than baseline for 30 min in the 0.5 and 1% epidural lidocaine group, and for 45 min in the 1.5% lidocaine group with a somewhat variable baseline after 60 min. Hexamethonium produced a significant increase in VD of $10.1 \pm 1.7\%$.

Death After Epidural Lidocaine 1.5%

A 1.7-kg rabbit died within 3 min of the epidural injection of 1.5% lidocaine. The preceding surgical preparation and medication were unremarkable, and stable, normal baseline values had been achieved. Before the epidural injection, however, the animal demonstrated an extreme response to the hypoxic stress used to assure responsive VD and SENA before initiating the protocol; although a VD decrease of 15–30% is typical with hypoxia in this model,¹⁹ the vein vasoconstricted by 40% in this animal. In the first 3 min after injection of the epidural lidocaine, VD increased by 19%, the SENA decreased 100%, the HR decreased by 25%, and the MAP decreased from 80 to 20 mmHg with a flat arterial wave form. Autopsy showed the epidural catheter to be properly placed and ink distribution to span from T2 to L5.

Discussion

We have described a reliable and reversible acute small animal model of epidural anesthesia. The principal findings of this study are: 1) an increase in directly measured splanchnic VD during epidural anesthesia; 2) a decrease in directly measured SENA during epidural anesthesia; 3) a time course of SENA and VD changes that matches MAP changes; 4) a potency of 0.5% lidocaine comparable with more concentrated solutions in producing sympathetic blockade; and 5) mild SENA and no VD changes in response to systemic lidocaine.

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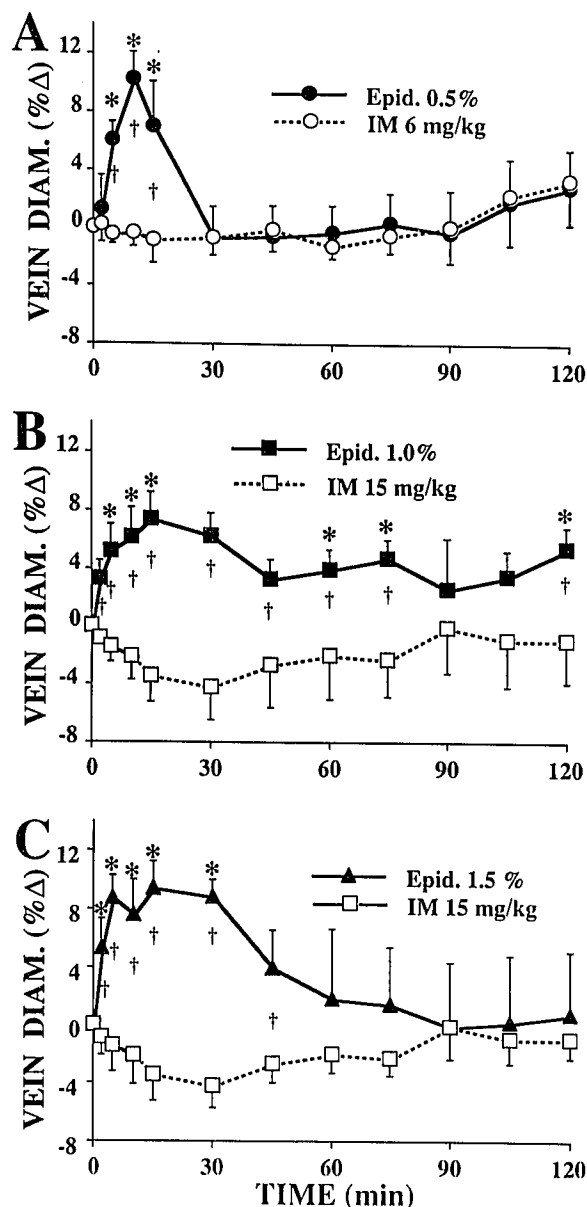


Fig. 7. Changes in vein diameter during (A) epidural lidocaine 0.5% and 6 mg/kg intramuscular lidocaine, (B) epidural lidocaine 1% and 15 mg/kg intramuscular lidocaine, and (C) epidural lidocaine 1.5% and 15 mg/kg intramuscular lidocaine. Values are mean \pm SEM. * $P < 0.05$ compared with baseline (time = 0); † $P < 0.05$ comparing the epidural to intramuscular value at that time point.

Preparation

In the invasively monitored rabbits receiving α -chloralose, it was not proved that the epidural injection of lidocaine produced anesthesia, because sensory and

motor testing was not done in these animals. However, the injection of smaller doses in awake animals produced clear evidence of anesthetic effect. Also, the epidural delivery of the solution was documented by autopsy. The spread of solution in the epidural space is, typically, more limited than the segmental spread of anesthetic effect.²⁴ After a long stable baseline, the monitored values promptly changed after epidural lidocaine injection, and changes were minimal after systemic administration. Because of these considerations, it is reasonable to attribute the responses to the onset of epidural anesthesia. It is possible that the observed changes are caused by the analgesic effect of the epidural blockade, producing a central decrease in sympathetic tone, rather than peripheral blockade of preganglionic fibers. However, a lack of response of MAP, SENA, or VD to epidural or systemic fentanyl in identically prepared animals in our lab (unreported data) argues against this mechanism.

Hemodynamics

The HR was highly variable between animals, perhaps because of differences in baseline autonomic status or response to thiamylal and α -chloralose. The HR decrease in the 1 and 1.5% epidural lidocaine groups may indicate a more extensive or intense blockade of cardioaccelerator fibers in the upper thoracic segments.

Hemodynamic responses to systemic lidocaine are influenced by concurrent general anesthesia.²⁵ The slightly decreased MAP with the larger dose of intramuscular lidocaine is consistent with previously reported responses to comparable serum lidocaine levels.²⁶ Epidural blockade in this model produced prompt and profound hypotension. The rabbit meninges are very thin—indeed, transparent—and this may result in a much more rapid onset of blockade compared with man. The more prolonged MAP fall with increased concentrations of epidural lidocaine may be caused by the proportionately greater mass of drug administered and the longer presence of the drug as redistribution from the neural membranes and epidural depot takes place. The lack of excess NaHCO_3 requirement in the epidural animals compared with the control animals indicates that global tissue perfusion was not compromised.

The decrease in MAP after epidural anesthesia was as great as after global sympathetic block with hexamethonium. This indicates that the epidural injection blocked all the sympathetic fibers to the vascular beds that are important for maintaining MAP. The extent of

hypotension is comparable to the 46–52% MAP decrease reported in other studies of extensive thoracic epidural anesthesia in animals,^{27–29} and decreases of 25–54% in humans.^{30–32} In contrast, high thoracic segmental blocks restricted to T1–T5 produce a less than 10% change in MAP.^{33–36} This comparison indicates an important contribution to the production of hypotension by the blockade of the lower thoracic segments, including those that provide sympathetic innervation to the splanchnic circulation (T5–T11).

Vein Diameter

In this study, we have demonstrated that a significant degree of mesenteric venodilation accompanies the onset of thoracic epidural blockade. A 10.2% increase in VD corresponds to a 21.4% increase in vein capacity.³⁷ We studied only the mesenteric component of the splanchnic venous system, but capacitance of the global splanchnic venous bed is also highly responsive to sympathetic tone,^{38,39} and probably responds the same as the mesenteric veins to epidural blockade of sympathetic fibers. We did not prove that splanchnic venodilation contributed to hypotension, but the congruent time courses of VD and MAP changes for the various lidocaine doses indicate a causal connection. Capacitance changes are not the only cause of hypotension with sympathetic blockade; even after complete compensation with fluid administration for the increased capacitance that results from HX administration, MAP is still depressed.²²

Previous reports examining the changes in the splanchnic circulation from epidural anesthesia have focused on splanchnic blood flow, with variable findings.^{24,27,28,40,41} In a study monitoring blood distribution before and after epidural anesthesia in man,⁴² six subjects showed decreased abdominal blood volume and minimal hemodynamic changes. Two other subjects had an initial decrease in abdominal blood volume, but then showed an increasing abdominal blood volume accompanied by MAP decreases of 20 and 57%, with “incipient vasovagal syncope” in the latter subject. This supports our finding that splanchnic venodilation can contribute to decreased MAP.

Venodilation in this model could be caused by several factors. First, the vein may respond passively to an increase in venous pressure *via* increased inflow or decreased outflow from the segment.¹⁰ This is unlikely because of the extent of the arterial hypoten-

sion, but there are no reports of splanchnic venous pressures during neural blockade. Second, venous smooth muscle tone may decrease because of decreased circulating catecholamines. Epidural block is accompanied by decreased circulating norepinephrine levels,^{4,43,44} and *in vitro* study of identical veins showed significant responses to norepinephrine,⁴⁵ supporting this possibility. Finally, venodilation may be caused by diminished release of norepinephrine within the vein wall as sympathetic nerves are blocked by epidural anesthesia. The synchronous changes of SENA and VD in the various epidural lidocaine dosage groups make it likely that the decrease of sympathetic activity to the veins contributed significantly to the venodilation. This is further supported by a comparable venodilation with complete sympathetic blockade by HX, and with mechanical denervation of mesenteric veins in rats.¹⁴ Other studies have shown the strong dependence of VD on SENA.^{17,18,37–39} The relative contribution of decreased circulating catecholamines and decreased locally released norepinephrine to the production of splanchnic venodilation cannot be determined from the available data.

Lidocaine can produce vasomotor changes by direct action on the vessels. Serum lidocaine concentrations achieved in this study have no effect on the *in vitro* response of identical mesenteric vein segments to exogenous norepinephrine, but have a mild blocking effect on vein constriction induced by endogenous release of norepinephrine within the vein wall from adrenergic nerve terminals.⁴⁶ The tendency toward vasodilation after high-dose intramuscular lidocaine in this study may indicate a contribution by circulating lidocaine, but the significantly greater VD changes in the epidural groups, even with lower serum lidocaine concentrations, show this is not the dominant factor contributing to mesenteric venodilation during neural blockade.

Sympathetic Efferent Nerve Activity

The only other studies directly measuring changes in sympathetic activity during epidural block^{6,7} documented complete elimination of SENA in the human peroneal nerve by lumbar epidural anesthesia if sensory blockade was extended to at least T8. We found a variable, but intense, blockade of SENA in the splanchnic postganglionic nerves. Two opposing influences determine SENA during epidural anesthesia. Hypotension produces a baroreceptor-mediated stimulus for in-

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creased central sympathetic activity,¹⁷ but the peripheral blocking of preganglionic sympathetic fibers acts to decrease the SENA to the splanchnic veins. The balance of these factors explains the variable response of the splanchnic circulation. Once venodilatation has produced decreased cardiac filling, hypotension may be amplified by global sympathetic withdrawal and increased vagal tone triggered by mechanoreceptors in the left ventricle.^{47,48} This may have contributed to the cardiovascular collapse that developed in the rabbit that died, and in humans after extensive neuraxial anesthesia.^{42,49}

The significant differences in SENA between animals receiving lidocaine intramuscularly and epidurally indicates that the large decreases in the epidural groups are caused by neural blockade. The mild effect of high-dose intramuscular lidocaine agrees with other reports in which systemic lidocaine decreased SENA to the heart²⁶ and kidneys^{25,26} to an extent comparable to that observed here. Our data also concurs with direct peroneal SENA measurements in humans given intravenous lidocaine; serum levels of lidocaine similar to those in the current study modestly decreased efferent muscle sympathetic activity and obtunded the sympathetic response to stress.⁵⁰ Systemic lidocaine has been found to be effective in treating neuropathic pain^{51,52} with serum concentrations similar to those reported here. The effect on SENA indicates that decreased sympathetic activity may be a contributing analgesic mechanism.

No other study has examined the response of sympathetic activity to graded concentrations of epidural local anesthetic. That 0.5% lidocaine produces as complete a sympathetic block as more concentrated solutions supports the use of this solution for diagnostic differential block.

Conclusions

Because sympathetic vascular responses are not uniform throughout the body,^{38,53} our finding of splanchnic venodilatation cannot be extended to other vascular beds, and extrapolation to humans must be made with caution. However, this study supports early speculation⁵⁴ that sympathetic blockade during extensive regional anesthesia causes increased splanchnic capacitance, which, in turn, contributes to hypotension. It is probable that important homeostatic mechanisms involving the splanchnic circulation, such as responses to hypoxia¹⁸ and hypercarbia,⁵⁵ are disrupted by thoracic epidural anesthesia.

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