

Mechanism of Mesenteric Venodilatation after Epidural Lidocaine in Rabbits

Quinn H. Hogan, M.D.,* Anna Stadnicka, Ph.D.,† Thomas A. Stekiel, M.D.,* Zeljko J. Bosnjak, Ph.D.,‡
John P. Kampine, M.D., Ph.D.§

Background: Increased splanchnic venous capacitance has been observed during extensive thoracolumbar epidural anesthesia in rabbits, but the mechanism is not clear. The present study examines the contributions of intravascular pressure changes, catecholamine levels, neural input, and direct effects of lidocaine to mesenteric venodilatation.

Methods: Epidural catheters were inserted in rabbits anesthetized with α -chloralose. Vein diameter was measured by videomicrography from segments of ileum externalized *in situ*. Plasma epinephrine and norepinephrine levels were measured in animals receiving epidural blockade (0.4 ml/kg lidocaine 1.5%, $n = 5$) and in control animals given intramuscular lidocaine 15 mg/kg ($n = 5$). Intraluminal pressure was monitored during the onset of epidural anesthesia (0.4 ml/kg lidocaine 1.0%, $n = 9$) by a servo-null micropressure technique. The effect of inhibiting norepinephrine release from sympathetic nerves in the mesenteric veins was determined by using topical tetrodotoxin ($n = 8$) and by assessing the effect of topical lidocaine (10 and 100 μ g/ml, $n = 5$) administered in the solution bathing the mesentery.

Results: Epidural injectate extended from T2 to L5. Plasma epinephrine decreased $68.3 \pm 4.4\%$ (mean \pm SEM) with epidural

anesthesia, and norepinephrine was lower after epidural block than after intramuscular lidocaine ($1,868 \pm 290$ pg/ml *vs.* $3,049 \pm 712$ pg/ml). Mesenteric vein pressure decreased $35.3 \pm 3.5\%$ and vein diameter increased $10.2 \pm 3.3\%$ during epidural blockade. Tetrodotoxin caused mesenteric venodilatation ($7.6 \pm 2.0\%$) and prevented venodilatation by subsequent epidural lidocaine. Topical lidocaine 10 μ g/kg produced no change in vein diameter, but lidocaine 100 μ g/ml increased it $3.5 \pm 1.3\%$.

Conclusions: Splanchnic venodilatation during epidural anesthesia is an active process: a decrease in intravenous pressure concurrent with dilatation indicates that vein wall tension diminished. Significant dilatation with tetrodotoxin and lack of dilatation with subsequent epidural block point to a minor role for changes in circulating catecholamines. A direct effect of lidocaine does not contribute to splanchnic venodilatation except when circulating lidocaine concentrations reach very high levels. (Key words: Anesthetics, local: lidocaine. Anesthetic techniques: epidural. Intestine: mesenteric circulation; venous capacitance. Sodium channel blocker: tetrodotoxin.)

THE causes of hemodynamic changes during epidural anesthesia have not been fully clarified. In a previous study,¹ we observed splanchnic venous dilatation during extensive thoracolumbar epidural anesthesia in rabbits, accompanied by an almost total elimination of sympathetic activity to the mesenteric vessels. This suggests that sympathetic withdrawal *via* preganglionic neural blockade is a principle cause of increased mesenteric capacitance. A simultaneous decrease in sympathetic efferent nerve activity and mesenteric venodilatation does not establish causality or prove that decreased sympathetic activity is the only factor contributing to increased mesenteric capacitance, because other mechanisms might play a role. Local anesthetic has direct effects on vessels,^{2,||} which could lead to changes during epidural anesthesia from circulating drug. Also, isolated mesenteric veins have been demonstrated to be responsive to norepinephrine,[#] the levels of which change with the onset of epidural anesthesia.³⁻⁵ Finally, physiologic events leading to altered circulatory capacitance have often been shown to act through transmural venous pressures changes, produc-

* Assistant Professor, Department of Anesthesiology.

† Research Assistant Professor, Department of Anesthesiology.

‡ Professor, Departments of Anesthesiology and Physiology.

§ Professor and Chairman, Department of Anesthesiology; Professor, Department of Physiology.

Received from the Departments of Anesthesiology and Physiology, Medical College of Wisconsin, and the Zablocki Veterans Administration Medical Center, Milwaukee, Wisconsin, 53226. Accepted for publication May 26, 1994. Supported by Veterans Administration merit review 7793-02P and National Institutes of Health Anesthesiology Research Training Grant GM08377.

Address reprint requests to Dr. Hogan: Medical College of Wisconsin, Department of Anesthesiology, 8700 West Wisconsin Avenue, Milwaukee, Wisconsin 53226.

|| Stadnicka A, Hogan QH, Stekiel TA, Bosnjak ZJ, Kampine JP: Inhibitory effects of lidocaine and bupivacaine on endogenous norepinephrine (NE) responses in isolated mesenteric capacitance veins of rabbit. *FASEB J* 8:A886, 1994.

Stadnicka A, Hogan QH, Stekiel TA, Bosnjak ZJ, Kampine JP: Dose-dependent effects of lidocaine in isolated small mesenteric veins of the rabbit. *Reg Anesth* 18:S89, 1993.

ing passive venodilatation or venoconstriction rather than an active change in vessel smooth muscle tension.⁶ The venous system is highly distensible, so that small shifts in venous transmural pressure can result in large changes in volume contained in the veins. The importance of passive responses of venous capacitance is demonstrated by the example of decreased hind-limb venous volume during sympathetic stimulation. This change is attributable entirely to sympathetic effects on precapillary resistance vessels which produce decreased inflow to the veins without any active venoconstriction.⁶ In the absence of contrary evidence, mesenteric venodilatation during epidural anesthesia could possibly represent passive distention of the mesenteric veins by increased venous pressure.

To clarify the mechanism of mesenteric venodilatation during epidural anesthesia, this study reports additional findings which examine changes in mesenteric intravenous micropressure and circulating catecholamine levels after epidural lidocaine. We also describe the effects of topical lidocaine on the mesenteric vessels and the responses after interruption of the neural control of the vein segment with topical tetrodotoxin.

Materials and Methods

Preparation

The basic preparation is the same as in a previous report,¹ where it is described in greater detail. 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). An epidural catheter (0.965 mm OD) was placed through a small incision at the T12–L1 interspace. The trachea, femoral artery and femoral vein were cannulated. The study was performed during the infusion of vecuronium (0.3 mg·kg⁻¹·h⁻¹), and ventilation was controlled. Heart rate and mean arterial pressure were determined from the pressure trace from the femoral artery catheter. Normal CO₂ tension (35–40 mmHg) and pH (7.35–7.45) were maintained by ventilator adjustments and NaHCO₃ administration guided by arterial blood gas determination. Rectal temperature was maintained between 36.5 and 37.5°C by a warming pad.

A loop of ileum was externalized through a midline laparotomy and mounted in a temperature-regulated plastic chamber. The diameter of mesenteric vein (500–800 μ m) was measured continuously with an

on-line videomicrometer system. The ileum and associated mesentery were superfused continuously with warmed physiologic salt solution formulated to simulate peritoneal fluid. This solution was maintained at 37°C and at pH 7.35–7.45 and was continuously bubbled with a gas mixture of 5% O₂, 5% CO₂, and 90% N₂. The preparation was considered acceptable if the vein was confirmed to be responsive by contracting during hypoxic stress (inspired O₂ fraction 0% for 40 s); in approximately 70% of the animals, the first vein examined proved to be satisfactory. The vertebral columns of the animals were dissected at the completion of the protocol to confirm epidural catheter placement and fluid distribution, indicated by staining of the dura and spinal canal by ink included in the injectate.

Intravenous Pressure

Intraluminal mesenteric vein pressure was determined by means of a servo-null system.⁷ Glass micropipettes, beveled to a 5–10- μ m tip diameter, were filled with 2 M NaCl, inserted into the vein using a micromanipulator, and used as sensing electrodes with a WPI Servo-null Pressure Measuring System (model 900, World Precision Instruments, New Haven, CT). Mesenteric vein diameter (VD) was measured simultaneously in the same vessel segment. Observations were made after epidural injection of lidocaine 1.0% 0.4 ml/kg (n = 9), a concentration and volume that produces splanchnic venodilatation lasting 30 min with a subsequent full return of hemodynamics and VD to baseline.¹ Pressure changes were also examined after the intramuscular injection of lidocaine 1.5% 1.0 ml/kg (15 mg/kg) (n = 4). Warmed normal saline 25 ml/kg was administered intravenously 15 min before the injection of lidocaine. Normal saline 0.4 ml/kg was injected epidurally in the animals receiving intramuscular lidocaine, and normal saline 1.0 ml/kg was injected intramuscularly in the animals receiving epidural lidocaine.

Catecholamines

Epinephrine and norepinephrine concentrations were measured in five animals receiving epidural anesthesia and five control animals. Epidural anesthesia was induced using 1.5% lidocaine 0.4 ml/kg, and normal saline 1.0 ml/kg was injected intramuscularly. This epidural lidocaine concentration, the maximum used in our previous study, was chosen to assure maximal changes in circulating catecholamines. In control rabbits, after intravenous fluid loading as described above,

MESENTERIC DILATATION WITH EPIDURAL BLOCK

lidocaine 1.5% 1.0 ml/kg (15 mg/kg) was injected intramuscularly to achieve comparable plasma lidocaine levels ($2.7\text{--}3.6\text{ }\mu\text{g/ml}^{-1}$),¹ and normal saline 0.4 ml/kg was injected epidurally. Arterial blood samples (3 ml) were drawn just before lidocaine injection, 15 min afterward, and again 1 h afterward, and the sampled blood was replaced with twice as much warmed normal saline. Each sample was placed in a chilled tube containing 5.4 mg sodium ethyleneglycol-bis-(β -aminoethyl ether) tetraacetic acid and 3.6 mg glutathione, and the plasma stored at -80°C . The plasma was extracted with acid-washed alumina in Tris buffer and concentrated with 0.1 M perchloric acid, after which norepinephrine and epinephrine concentrations were determined by high-performance liquid chromatography using a reverse-phase column ($25\text{ cm} \times 2.1\text{ cm}$) (Supelco LC18, Bellefonte, PA). Every sample was determined with an internal synthetic standard (dihydroxybenzylamine) which has a similar recovery to actual norepinephrine ($88 \pm 8\%$) and epinephrine ($76 \pm 9\%$). The coefficient of variation for the determinations is 4.9%.

Topical Tetrodotoxin

In eight animals, tetrodotoxin 10^{-6} M was applied topically to the mesenteric vessels by administration in the superfusate to test the effect of blocking norepinephrine release at the sympathetic nerve terminals. Responses were observed during 15 min of exposure, after which epidural anesthesia (1.0% lidocaine 0.4 ml/kg) was induced during the continued exposure of the vessel to tetrodotoxin. In four of the animals, sympathetic efferent activity of the postganglionic splanchnic nerve was monitored concurrently by a method described previously.¹ In brief, the nerve was isolated from the adjacent tissue maintaining continuity proximally and distally, and a bipolar recording electrode, composed of two single-strand coated stainless steel wires (0.25 mm OD) in silicone elastomere tubing, was fixed to the nerve with Silgel (Wacker-Chemie, Munich, Germany). The directly measured nerve activity was amplified, filtered, and averaged to produce an analog output proportional to sympathetic efferent nerve activity.

Topical Lidocaine

To examine the direct effects of lidocaine, VD was measured in five animals as lidocaine was applied topically to the mesenteric vessels by administration in the superfusate. The vessels were exposed to lidocaine $10\text{ }\mu\text{g/ml}$

for 15 min, to superfusate without lidocaine (washout) for 15 min, and then to lidocaine $100\text{ }\mu\text{g/ml}$ for 15 min. To calculate VD changes, the maximal VD during lidocaine $10\text{ }\mu\text{g/ml}$ was compared with the original baseline, and the VD during lidocaine $100\text{ }\mu\text{g/ml}$ was compared with the VD during the washout interval.

Statistics

Micropressure data were evaluated by analysis of variance for repeated measures with individual contrasts (Super ANOVA; Abacus Corporation; Berkeley, CA), comparing measurements with baseline. Catecholamine levels, analyzed by analysis of variance, were compared with baseline and between epidural and control groups. Changes in VD during tetrodotoxin and lidocaine application were evaluated by a two-tailed paired *t* test. Results are reported as mean \pm standard error. Findings are considered significant if $P < 0.05$.

Results

Animals weighed $1.43 \pm 0.06\text{ kg}$. NaHCO_3 $0.91 \pm 0.17\text{ mEq} \cdot \text{kg}^{-1}$ was administered, with no differences between groups. The spread of injectate in the epidural space was from a median cephalad limit of T2 (range T1–T3) to a median caudal limit of L5 (range L3–L6).

Intravenous Pressure

Epidural injection of lidocaine was followed by a maximum mean arterial pressure decrease of $50.4 \pm 1.9\%$ (initial mean arterial pressure $77.4 \pm 3.2\text{ mmHg}$) (fig. 1). There was no change in heart rate (initial $282 \pm 6\text{ s}^{-1}$). VD increased $10.2 \pm 3.3\%$, and mesenteric vein pressure (initial $8.58 \pm 0.39\text{ mmHg}$) simultaneously decreased $35.3 \pm 3.5\%$. After intramuscular lidocaine, there were no significant changes in mean arterial pressure (initial $83.0 \pm 3.1\text{ mmHg}$) or mesenteric vein pressure (initial $9.25 \pm 0.92\text{ mmHg}$); the largest change in any vein after intramuscular lidocaine was $-5.1 \pm 2.6\%$ at 10 and 15 min.

Catecholamines

There were no differences in epinephrine concentrations between the epidural and control groups at baseline, after injection or at recovery (fig. 2). There was, however, a significant decrease compared with baseline after epidural lidocaine injection. Although norepinephrine concentration was significantly less in the epidural group than in the intramuscular group after

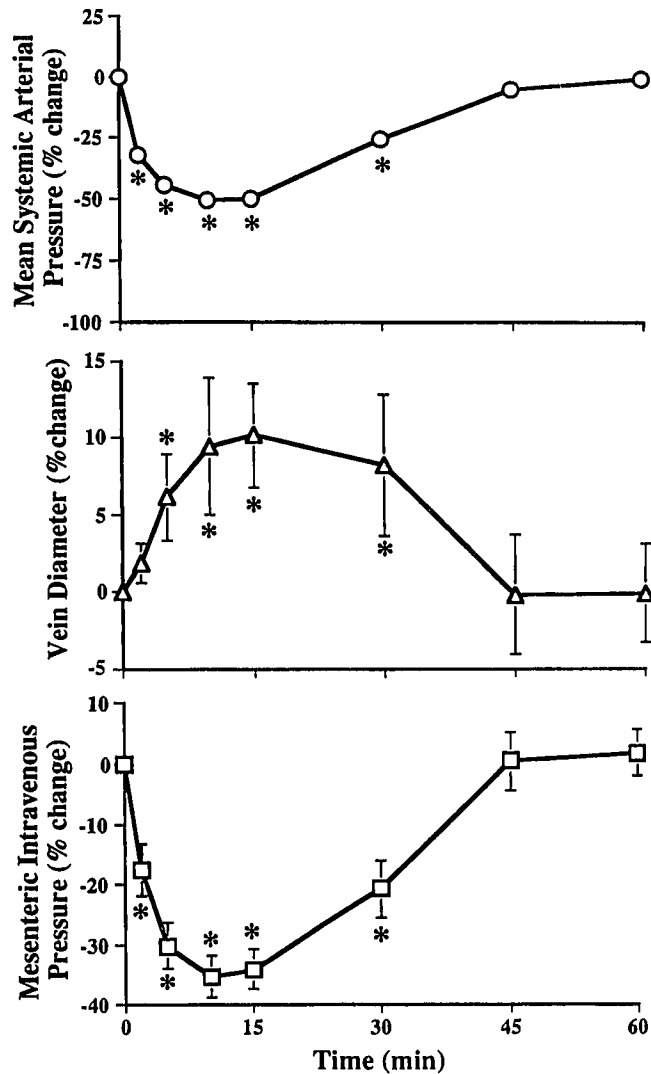


Fig. 1. Mesenteric intravenous pressure, mesenteric vein diameter, and mean systemic arterial pressure changes after epidural block with lidocaine 1.0%. Values are means \pm SEM. * $P < 0.05$ compared with baseline (time = 0). (For mean arterial pressure, error bars are smaller than the symbol for the data point.)

lidocaine injection, norepinephrine in the epidural group was not significantly different from baseline.

Topical Tetrodotoxin

After topical application of tetrodotoxin to the mesenteric vessels, there were no changes in heart rate (initial $284 \pm 7.7 \text{ s}^{-1}$), systemic arterial pressure (initial $76.7 \pm 3.6 \text{ mmHg}$), or sympathetic efferent nerve activity, but VD increased $7.6 \pm 2.0\%$ (fig. 3). Subse-

quent epidural lidocaine decreased heart rate $13.7 \pm 4.4\%$, decreased systemic blood pressure $58.0 \pm 3.2\%$, and entirely eliminated sympathetic efferent nerve activity, but did not change VD ($-1.4 \pm 0.9\%$, difference not significant).

Topical Lidocaine

There were no changes in heart rate or systemic arterial pressure after topical application of either con-

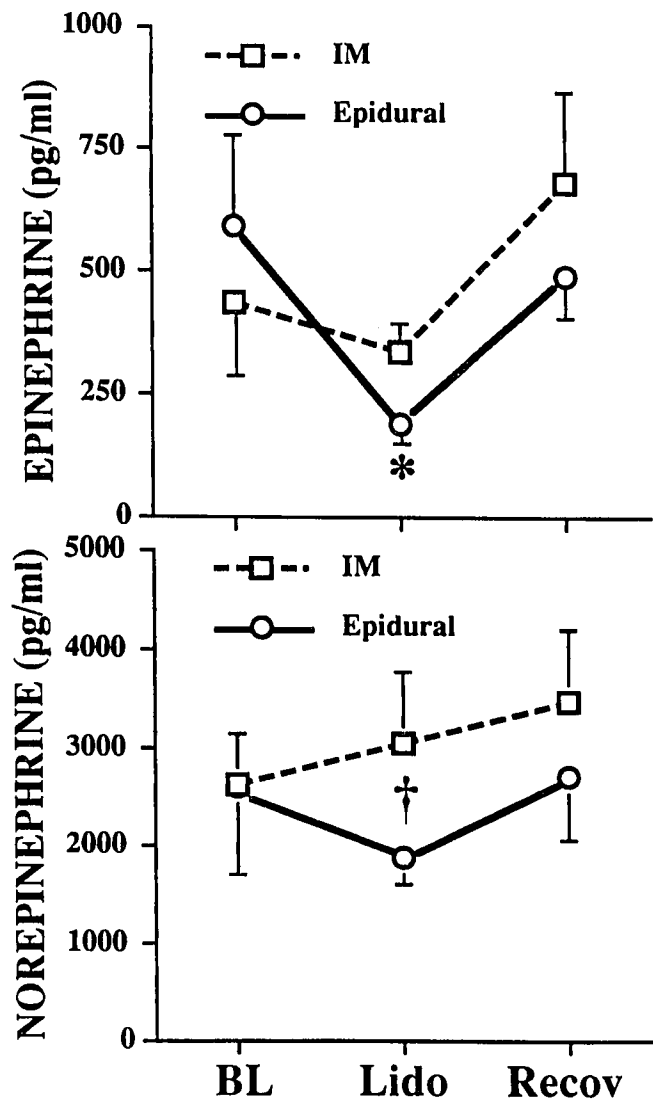


Fig. 2. Epinephrine and norepinephrine levels at baseline (BL); after lidocaine (Lido), either epidurally (1% 0.4 ml/kg, $n = 5$) or intramuscularly (15 mg/kg, $n = 5$); and after recovery (Recov). Values are means \pm SEM. * $P < 0.05$ compared with baseline; † $P < 0.05$ epidural compared with intramuscular at that time point.

MESENTERIC DILATATION WITH EPIDURAL BLOCK

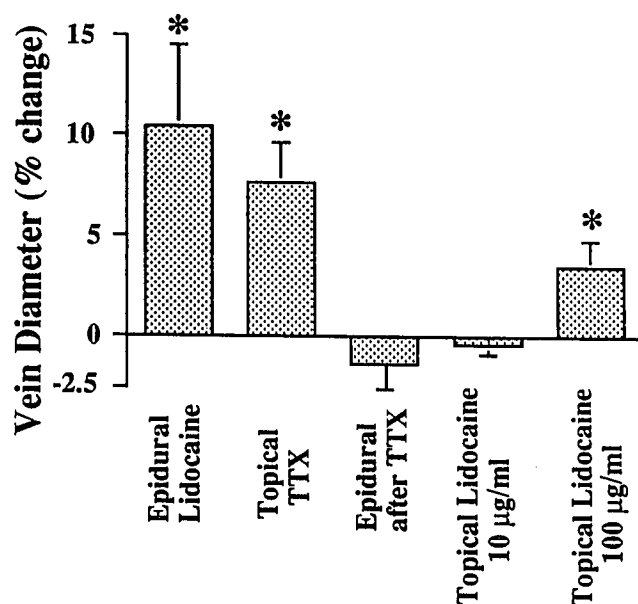


Fig. 3. Change in mesenteric vein diameter from epidural lidocaine (1% 0.4 ml/kg, $n = 9$), topical tetrodotoxin 10^{-6} M ($n = 8$), epidural lidocaine after tetrodotoxin ($n = 8$), and topical lidocaine at 10 and 100 μ g/ml ($n = 5$). Values are means \pm SEM. * $P < 0.05$ compared with baseline.

centration of lidocaine to the mesenteric vessels. There was no significant change in VD during topical exposure to lidocaine 10 μ g/ml ($-0.4 \pm 0.5\%$), but significant dilatation ($3.5 \pm 1.3\%$) was observed during exposure to lidocaine 100 μ g/ml (fig. 3).

Discussion

Hemodynamic changes are a major limiting factor in the use of epidural anesthesia. Arteriolar dilatation from sympathetic blockade predictably decreases systemic vascular resistance and blood pressure⁸ but alone can not decrease cardiac output. Blockade of sympathetic fibers to the heart produces minimal changes in cardiac performance.⁹⁻¹¹ However, interruption of sympathetic innervation to the veins, especially those of the splanchnic circulation that play the major role in capacitance control, has the potential to disrupt the homeostatic mechanisms that maintain venous return and therefore cardiac output.⁶ We confirmed splanchnic venodilatation during epidural anesthesia in a previous study.¹ Although concurrent sympathetic blockade to the gut was observed by direct measurement of sympathetic efferent nerve activity, this was not confirmed as the sole pathogenic factor. Identification of the cause

of splanchnic vein dilatation may aid in the prevention and treatment of sudden, unexpected cardiovascular collapse which occasionally occurs during clinical use of neuraxial anesthesia.¹² Because epidural lidocaine 0.5-1.5% in this rabbit model produced comparable changes in mean arterial pressure, VD, and sympathetic efferent nerve activity,¹ only single doses were examined in this study.

Mechanisms besides sympathetic neural blockade which might contribute to mesenteric VD changes with epidural anesthesia include a passive response to increased transmural pressure, altered circulating catecholamines, or a direct effect of local anesthetics upon the vessel. In the present study, increased VD with the onset of blockade was accompanied by a 35% decrease in vein pressure, eliminating the possibility of passive distention contributing to venodilatation. The decreased transmural pressures with epidural anesthesia indicate that VD changes underestimate the actual decrease of vein wall tension. We previously observed no VD changes with comparable plasma lidocaine levels in the absence of neural blockade,¹ making vein pressure changes in the control group unlikely. This was confirmed in the current study, because there were no changes in vein pressure with intramuscular lidocaine.

Epidural anesthesia has been shown to decrease circulating catecholamine levels,³⁻⁵ and *in vitro* study of mesenteric veins has documented their responsiveness to exogenous catecholamines.¹³ This raises the possibility that altered catecholamine levels could be a contributing factor to VD changes during blockade. Plasma norepinephrine and epinephrine levels in our rabbit model were very high,¹⁴ probably because of the extensive surgical preparation and the use of α -chloralose as the anesthetic. There were no differences in epinephrine levels between the epidural and intramuscular lidocaine groups, and the decrease in norepinephrine was only 28% (not significant) with onset of blockade in the epidural group. Because levels remained very high, a slight withdrawal of endogenous vasoconstrictor is of uncertain importance in splanchnic venodilatation during epidural anesthesia. Sustained catecholamine production despite extensive thoracolumbar block and documented ablation of sympathetic efferent nerve activity¹ is unexplained.

The direct effects of local anesthetic on mesenteric veins has been studied *in vitro*, examining the contraction of vein rings in response to exogenously applied norepinephrine and to norepinephrine released by the sympathetic nerve terminals during field stim-

ulation.¶ Lidocaine slightly amplifies contraction from exogenous norepinephrine at lidocaine concentrations of 20–100 µg/ml but otherwise has no effect. Response to field stimulation is decreased 25% by lidocaine 5 µg/ml and progressively more at higher concentrations. Although this implies a possible contribution by circulating lidocaine to venodilatation, the absence of increased VD in control animals with plasma lidocaine concentrations similar to the epidural animals¹ indicates at most a minor role.

The direct action of lidocaine upon the mesenteric veins was further examined in the current study by topical application to the veins *in situ*. A review of the literature reveals that vessel responses to local anesthetics depends strongly on the animal of origin, whether artery or vein, the organ or origin, the concentration of local anesthetic and the details of the model. There is no consistent effect reported for lidocaine when delivered to vessels in superfusate. Lidocaine 1,000 µg/ml dilated *in situ* rat femoral arteries.¹⁵ Blood flow is diminished in rat sciatic nerves after exposure to lidocaine 1,000 µg/ml or more.¹⁶ Concentrations of lidocaine as great as 30 µg/ml potentiate vasoconstriction in isolated rabbit ear arteries, with higher concentrations producing vasodilatation.¹⁷ The opposite occurs in rat cremaster muscle arterioles studied *in situ*, with exposure to topical lidocaine 1,000 µg/ml or less resulting in constriction, whereas concentrations above this produce dilatation.¹⁸ In our study of mesenteric veins, no change in diameter was observed while the veins were exposed to lidocaine 10 µg/ml, and 3.5% dilatation followed topical exposure to lidocaine 100 µg/ml. In a previous study in which an identical preparation was used, intramuscular lidocaine (1.5% 1.0 ml/kg) produced a plasma lidocaine concentration of 3.6 ± 0.4 µg/ml and epidural lidocaine (1.0% 0.4 ml/kg) a concentration of 2.1 ± 0.1 µg/ml.¹ Although it is uncertain that vessel tissue concentrations after equilibration with lidocaine delivered in the superfusate are comparable to levels achieved by delivery in the circulating blood, other studies have indicated similar vasomotor effects of lidocaine independent of whether it is intraluminal or in the superfusate.¹⁷ The lack of response to topical lidocaine at 10 µg/ml is additional evidence against an important contribution of systemic lidocaine in in-

creased VD after epidural blockade. Venodilatation after mesenteric exposure to topical lidocaine at 100 µg/ml supports a role of splanchnic venodilatation in cardiovascular collapse after massive intravascular injection of lidocaine.

We hypothesized that the principal factor causing mesenteric venodilatation during epidural anesthesia is decreased sympathetic activity to the veins from neural blockade. This predicts an absence of epidural venodilatation in veins topically exposed to tetrodotoxin, which blocks norepinephrine release from sympathetic neural terminals but does not affect vascular smooth muscle responses to exogenous norepinephrine.^{2,18,19} In fact, there was a trend toward venoconstriction (1.41% decrease in VD, not statistically reliable), which may have resulted from decreasing transmural pressures with unchanged wall tension. An absence of venodilatation from epidural anesthesia during exposure of the mesentery to tetrodotoxin supports our supposition that neural blockade of sympathetic tone is the major mechanism in epidural venodilatation: if circulating norepinephrine had contributed to vessel tone before blockade and norepinephrine withdrawal was important in producing VD changes with blockade, this would be evident by dilatation from epidural lidocaine even after tetrodotoxin, which leaves responses to circulating norepinephrine intact (unreported data).

Tetrodotoxin alone produced an increase in VD comparable to the dilatation from epidural anesthesia without tetrodotoxin. This is supportive evidence for near-complete sympathetic denervation produced by epidural lidocaine.

Our model uses general anesthesia, paralysis and mechanical ventilation. α -Chloralose, the anesthetic used in this preparation, has minimal sympatholytic potency,^{20,21} so homeostatic mechanisms will be minimally impeded. Mechanical ventilation, however, may amplify the depressant effect of epidural blockade upon venous return by increasing mean intrathoracic pressure. The extent of hemodynamic disruption induced by blockade in our study and in others using mechanical ventilation^{22–24} is greater than when epidural anesthesia is induced in spontaneously breathing animals.^{25–27} Because of this, our findings are most relevant to patients receiving neural blockade combined with general anesthesia and mechanical ventilation.

We conclude that splanchnic venodilatation during epidural anesthesia is attributable primarily to an active decrease in vein wall tension, caused by neural block-

¶ Nelson SH, Steinsland OS: Variable effects of lidocaine, mepivacaine, and bupivacaine on neurovascular transmission (abstract). ANESTHESIOLOGY 69:A140, 1988.

MESENTERIC DILATATION WITH EPIDURAL BLOCK

ade of sympathetic efferent fibers which innervate the splanchnic veins. Minimizing lidocaine absorption or catecholamine changes are of secondary importance for limiting the hemodynamic consequences of splanchnic venodilatation. Efforts to diminish hemodynamic change should focus on restricting neural blockade to the operative site and avoiding blockade of splanchnic innervation when possible.

References

- Hogan QH, Stadnicka A, Stekiel TA, Bosnjak ZJ, Kampine JP: Effects of epidural and systemic lidocaine on sympathetic activity and mesenteric circulation in rabbits. *ANESTHESIOLOGY* 79:1250-1260, 1993
- Lofstrom JB: The effect of local anesthetics on the peripheral vasculature. *Reg Anesth* 17:1-11, 1992
- Stanek B, Schwarz M, Zimper M, Raberger G: Plasma concentrations of noradrenaline and adrenaline and plasma renin activity during extradural blockade in dogs. *Br J Anaesth* 52:305-310, 1980
- Ecoffey C, Eduard A, Pruszczyński W, Taly E, Samii K: Effects of epidural anesthesia on catecholamines, renin activity, and vasopressin changes induced by tilt in elderly men. *ANESTHESIOLOGY* 62:294-297, 1985
- Stevens R, Artuso J, Kao T, Bray J, Spitzer L, Louwsma D: Changes in human plasma catecholamines concentrations during epidural anesthesia depend on the level of the block. *ANESTHESIOLOGY* 74:1029-1034, 1991
- Hainsworth R: Vascular capacitance: Its control and importance. *Rev Physiol Biochem Pharmacol* 105:101-173, 1986
- Ozono K, Bosnjak ZJ, Kampine JP: Reflex control of mesenteric vein diameter and pressure *in situ* in rabbits. *Am J Physiol* 256:H1066-H1072, 1989
- Bonica JJ, Berges PU, Morikawa K: Circulatory effects of peridural block: Effects of level of analgesia and dose of lidocaine. *ANESTHESIOLOGY* 33:619-626, 1970
- Ottesen S: The influence of thoracic epidural analgesia on the circulation at rest and during physical exercise in man. *Acta Anaesthesiol Scand* 22:537-547, 1978
- Wattwil M, Sundberg A, Arvill A, Lennquist C: Circulatory changes during high thoracic epidural anaesthesia: Influence of sympathetic block and of systemic effect of the local anaesthetic. *Acta Anaesthesiol Scand* 29:849-855, 1985
- Hasenbos M, Liem TH, Kerkkamp H, Gielen M: The influence of high thoracic epidural analgesia on the cardiovascular system. *Acta Anaesthesiol Belg* 39:49-54, 1988
- Caplan R, Ward R, Posner K, Cheney F: Unexpected cardiac arrest during spinal anesthesia: A closed-claims analysis of predisposing factors. *ANESTHESIOLOGY* 68:5-11, 1988
- Stadnicka A, Flynn N, Bosnjak ZJ, Kampine JP: Enflurane, halothane, and isoflurane attenuate contractile responses to exogenous and endogenous norepinephrine in isolated small mesenteric veins of the rabbit. *ANESTHESIOLOGY* 78:326-334, 1993
- Hart BB, Stanford GG, Ziegler MG, Lake CR, Chernow B: Catecholamines: Study of interspecies variation. *Crit Care Med* 17:1203-1222, 1989
- Blair WF, Greene ER, Eldridge M, Cipoletti R: Hemodynamic response of small arteries to lignocaine. *J Surg Res* 31:77-81, 1981
- Partridge BL: The effects of local anesthetics and epinephrine on rat sciatic nerve blood flow. *ANESTHESIOLOGY* 75:243-251, 1991
- Johns RA, DiFazio CA, Longnecker DE: Lidocaine constricts or dilates rat arterioles in a dose-dependent manner. *ANESTHESIOLOGY* 62:141-144, 1985
- Holman ME, McLean A: The innervation of sheep mesenteric veins. *J Physiol (Lond)* 190:55-69, 1967
- Van Helden DF: Electrophysiology of neuromuscular transmission in Guinea-pig mesenteric veins. *J Physiol (Lond)* 401:469-488, 1988
- Zimpfer M, Sit SP, Vatner SF: Effects of anesthesia on the canine carotid chemoreceptor reflex. *Circ Res* 48:400-406, 1981
- Holzgreffe HH, Everett JM, Wright EM: Alpha-chloralose as a canine anesthetic. *Lab Anim Sci* 37:587-595, 1987
- Sivarajan M, Amory D, Lindbloom L: Systemic and regional blood flow during epidural anesthesia without epinephrine in the rhesus monkey. *ANESTHESIOLOGY* 45:300-310, 1976
- Greitz T, Andreen M, Irestedt L: Haemodynamics and oxygen consumption in the dog during high epidural block with special reference to the splanchnic region. *Acta Anaesthesiol Scand* 27:211-217, 1983
- Lundberg J, Biber B, Delbro D, Martner J, Werner O: Effects of dopamine on intestinal hemodynamics and motility during epidural analgesia in the cat. *Acta Anaesthesiol Scand* 33:487-493, 1989
- Blomberg S, Ricksten S: Thoracic epidural anaesthesia in conscious and anaesthetized rats: Effects on central haemodynamics compared to cardiac beta adrenoreceptor and ganglionic blockade. *Acta Anaesthesiol Scand* 32:166-172, 1988
- Peters J, Kutkuhn B, Medert HA, Schlaghecke R, Schuttler J, Arndt JO: Sympathetic blockade by epidural anesthesia attenuates the cardiovascular response to severe hypoxemia. *ANESTHESIOLOGY* 72:134-144, 1990
- Stevens RA, Lineberry PJ, Arcario TJ, Bacon GS, Cress LW: Epidural anaesthesia attenuates the catecholamine response to hypoventilation. *Can J Anaesth* 37:867-872, 1990