Anesthesiology
1997; 87:75-81

Direct Effects of Ropivacaine and Bupivacaine on Spinal Pial Vessels in Canine

Assessment with Closed Spinal Window Technique

Hiroki Iida, M.D.,* Yukinaga Watanabe, M.D.,† Shuji Dohi, M.D.,‡ Tadahiko Ishiyama, M.D.,§

Background: **Ropivacaine produces a vasoconstriction of cutaneous vessels in contrast to vasodilation produced by bupivacaine. To evaluate direct spinal microvascular actions of these local anesthetics, the authors investigated the concentration-related effects of ropivacaine and bupivacaine on spinal pial vascular diameters using the spinal window technique.**

Methods: **Anesthetized dogs (n = 14) divided into two groups (ropivacaine, n = 7; bupivacaine, n = 7) were prepared for measurement of spinal pial vessel diameters by intravital microscopy in a spinal window preparation. The authors administered six concentrations of each drug (10^{-8}–10^{-3} M) under the window and directly measured the spinal pial arteriolar and venular diameters at sequential times. Physiologic data including mean arterial blood pressure (MAP) and heart rate (HR) were determined before and after topical application of each concentration of the drugs. In additional experiments (n = 18), the action of topical ropivacaine and bupivacaine solution on spinal vessels was evaluated in the presence of yohimbine, prazosin, and propranolol.**

Results: **Ropivacaine significantly constricted whereas bupivacaine dilated pial arterioles and venules, both in a concentration-dependent manner. Microvascular alteration was not blocked with any of the adrenoceptor antagonists tested (yohimbine, prazosin, propranolol), each of which *per se* did not affect pial vessel diameters. Topical application of ropivacaine or bupivacaine did not induce any change in MAP or HR.**

Conclusions: **The present results indicate that ropivacaine constricts and bupivacaine dilates the pial vessels of the spinal cord in a concentration-dependent fashion, and the mechanisms involved in such actions do not seem to be mediated *via* α- or β-adrenoceptor of spinal vasculature. (Key words: Anesthetics, local: bupivacaine; ropivacaine. Blood vessels: vasoconstriction; vasodilation. Spinal cord, microcirculation.)**

Ropivacaine is a new amino-amide local anesthetic agent structurally related to bupivacaine and has pharmacologic properties resembling bupivacaine in studies on animals and humans. However, ropivacaine has been suggested to produce a vasoconstriction of cutaneous and epidural vessels, which contrasts with the vasodilation seen after bupivacaine use.[1,2] The peripheral vascular effects of local anesthetics in previous reports are controversial, resulting in vasodilation and vasoconstriction.[1-4] Amino-amide local anesthetics are reported to have a biphasic action on the smooth muscles in peripheral blood vessels.[4,6] Further, vascular beds are known to vary in their response to drugs and stimuli; thus their results cannot be extrapolated to other tissues.

Spinal cord vessels may have different responses to drugs administered into the subarachnoid space. Spinal cord blood flow has been measured experimentally to understand the physiologic effects of spinal anesthesia. To our knowledge, no work has been conducted to observe a spinal vessel directly during topical administration of local anesthetics. Characterization of the direct spinal microvascular actions of each local anesthetic using a range of concentrations would be of value for evaluating its absorption from cerebrospinal fluid and for assessing its toxicologic aspects during intrathecal administration. Therefore, we investigated concentration-related effects of ropivacaine and bupivacaine on spinal pial vascular diameters using the spinal window technique. In addition, we evaluated the effects of adrenergic antagonists on the vasoactive effects of ropivacaine and bupivacaine.

Materials and Methods

After the experimental protocols were approved by our Institutional Committee for Animal Care, experi-

* Assistant Professor, Department of Anesthesiology and Critical Care Medicine.

† Instructor, Department of Anesthesiology and Critical Care Medicine.

‡ Professor and Chair, Department of Anesthesiology and Critical Care Medicine.

§ Presently Chief, Department of Anesthesia, Tono General Hospital.

Received from the Department of Anesthesiology and Critical Care Medicine, Gifu University School of Medicine, Gifu City, Japan. Submitted for publication August 28, 1996. Accepted for publication February 10, 1997. This study was supported by Grant-in-Aid for Scientific Research No.08457405.

Address reprint requests to Dr. Iida: Department of Anesthesiology and Critical Care Medicine, Gifu University School of Medicine, Gifu City, Gifu 500, Japan. Address electronic mail to: iida@cc.gifu-u.ac.jp

ments were performed in 32 anesthetized dogs weighing 6–10 kg. Anesthesia was induced with pentobarbital sodium (20 mg/kg, intravenous) and maintained with a continuous infusion of pentobarbital sodium (2 $mg \cdot kg^{-1} \cdot min^{-1}$). After tracheal intubation, each dog was mechanically ventilated with oxygen-enriched room air and received pancuronium bromide for muscle paralysis. The tidal volume and respiratory rate were adjusted to maintain an end-tidal CO_2 of 35–40 mmHg. Polyvinyl chloride catheters were placed in the femoral vein and artery for administration of drugs and fluids and for blood pressure monitoring and blood sampling. Rectal temperature was maintained between 36.5 and 37.5°C by a warming blanket.

A closed spinal window was used to observe the spinal pial microcirculation. The animal was placed in a sphinx posture with the head immobilized in a stereotaxic frame. After the skin was retracted, thoracolumbar paraspinal muscles were exposed by a longitudinal midline skin incision from the lower thoracic level to L3. Periosteum and muscle attachments from T12 to L2 were separated from laminae and spinous processes by electrocautery. The block of paraspinal muscles in that region was removed. After the spinous process was removed with a rongeur, laminectomy was performed (5 x 10 mm) with an electric drill at L1. The surface of each lamina was planed flatly with an electric grinder, and the dura and arachnoid membrane were opened carefully. A ring with a cover glass was placed over the hole and secured with dental acrylic. Four polyvinyl chloride catheters were inserted into the ring. The space under the window was filled with artificial cerebrospinal fluid (aCSF), the composition of which was previously described.[7] The solution was bubbled with 5% CO_2 and air at 37.0°C. One catheter was attached to a reservoir bottle containing aCSF to maintain a constant intrawindow pressure of 5 mmHg. Two catheters were used for infusion and drainage of aCSF and experimental drug solutions, and the final one was used for continuous monitoring of intrawindow pressure. The volume below the window was between 0.5 and 1 ml.

Ropivacaine (Astra, Södertälje, Sweden) and bupivacaine (Sigma, St. Louis, MO) were freshly dissolved in aCSF; six different concentrations (10^{-8}, 10^{-7}, 10^{-6}, 10^{-5}, 10^{-4}, and 10^{-3} M were prepared and used for the present study. Diameters of two or three spinal pial arterioles and venules were measured sequentially for the different concentrations of each drug by a videomicrometer (Olympus Flovel Videomicrometer, Model VM-20, Flovel, Tokyo, Japan) attached to a microscope (Model SZH-10, Olympus, Tokyo, Japan). The data of pial view was stored on videotape for later playback and analysis.

All *in vivo* experiments were carried out in the following manner. The animals were allowed to stabilize from the surgical preparation for at least 30 min. Spinal pial arteriolar and venular diameters, mean arterial blood pressure (MAP), heart rate (HR), rectal temperature, arterial blood gas tensions, pH, blood glucose, and serum electrolytes were measured before and after topical application of six different concentrations of each drug into the spinal window in sequential manner in 14 dogs (ropivacaine, n = 7; bupivacaine, n = 7). To establish the baseline diameter of vessels for any concentration of drug, the window was continuously flushed with aCSF at the rate of 0.5–1.0 ml/min for 20 min after each measurement. After 20 min from the last administration of study solutions, the spinal pial vascular diameter returned to baseline level (Protocol 1).

The ability of adrenoceptor antagonists yohimbine (10^{-3} M), prazosin (10^{-5} M), and propranolol (10^{-3} M) to block the vasoactive effects of topical ropivacaine solution, 10^{-3} M, or bupivacaine solution, 10^{-3} M, was evaluated in each of six dogs according to the experimental design (n = 18). Yohimbine and propranolol were dissolved in aCSF. Prazosin was dissolved in 100% dimethyl sulfoxide (DMSO) and then diluted with aCSF. The final concentration of DMSO in the 10^{-5} M prazosin solution was 0.1%. At first, ropivacaine or bupivacaine solution alone was tested. The window was continuously flushed with aCSF similar to Protocol 1. After the completion of baseline measurements of vessel diameter after topical application of yohimbine and prazosin, ropivacaine solution was applied, and measurements were repeated. A similar experiment was repeated with propranolol solution, followed by bupivacaine solution (Protocol 2).

Spinal pial arterioles were divided into two groups on the basis of initial diameter—greater than 100 μm or less than 100 μm in Protocol 1, but not Protocol 2. All data for concentration-dependent effects of experimental drugs were tested by one-way analysis of variance (ANOVA). For the ANOVA, if the F test indicated significance ($P < 0.05$), differences between individual means were subjected to Scheffe's F test for *post hoc* comparison. A paired t test was used to identify differences between blood vessel diameters before and after drug administration and with or without adrenergic blockers. Significance was considered to be $P < 0.05$.

Table 1. Hemodynamic and Physiologic Measurements during Topical Administration

		MAP (mmHg)	HR (bpm)	*p*H	Pa_{CO_2} (mmHg)	Pa_{O_2} (mmHg)	Na (mEq/L)	K (mEq/L)	BT (°C)
Ropivacaine (10^{-8} M)	Before	110 ± 15	172 ± 31	7.39 ± 0.03	36.6 ± 1.9	175.1 ± 19.5	148.1 ± 3.3	4.3 ± 0.9	36.4 ± 1.0
	After	110 ± 14	175 ± 32						
Ropivacaine (10^{-7} M)	Before	109 ± 14	175 ± 32	7.39 ± 0.02	37.3 ± 2.1	173.4 ± 20.8	148.0 ± 4.6	4.2 ± 0.8	36.4 ± 0.9
	After	109 ± 14	175 ± 33						
Ropivacaine (10^{-6} M)	Before	109 ± 14	174 ± 32	7.38 ± 0.03	37.2 ± 1.9	171.5 ± 17.7	147.7 ± 4.6	4.2 ± 0.9	36.4 ± 1.0
	After	110 ± 14	175 ± 33						
Ropivacaine (10^{-5} M)	Before	110 ± 15	173 ± 32	7.39 ± 0.01	37.4 ± 2.2	171.8 ± 16.7	147.4 ± 4.7	4.2 ± 0.9	36.5 ± 1.0
	After	109 ± 13	172 ± 30						
Ropivacaine (10^{-4} M)	Before	111 ± 14	172 ± 31	7.38 ± 0.02	37.5 ± 2.3	171.6 ± 15.0	149.3 ± 4.7	4.2 ± 0.9	36.4 ± 0.9
	After	110 ± 13	172 ± 34						
Ropivacaine (10^{-3} M)	Before	113 ± 18	172 ± 31	7.39 ± 0.02	36.3 ± 1.3	172.6 ± 16.5	148.1 ± 4.5	4.3 ± 0.9	36.5 ± 0.9
	After	107 ± 16	172 ± 29						
Bupivacaine (10^{-8} M)	Before	120 ± 26	134 ± 45	7.40 ± 0.02	37.9 ± 3.5	183.2 ± 18.1	148.4 ± 4.5	3.7 ± 0.5	36.2 ± 0.6
	After	121 ± 24	133 ± 45						
Bupivacaine (10^{-7} M)	Before	120 ± 26	133 ± 45	7.40 ± 0.02	37.8 ± 3.8	189.4 ± 16.8	147.4 ± 4.4	3.9 ± 0.4	36.2 ± 0.5
	After	121 ± 25	133 ± 44						
Bupivacaine (10^{-6} M)	Before	122 ± 25	134 ± 47	7.40 ± 0.02	38.1 ± 3.8	178.3 ± 23.2	147.4 ± 4.0	3.9 ± 0.4	36.3 ± 0.5
	After	123 ± 25	134 ± 45						
Bupivacaine (10^{-5} M)	Before	120 ± 25	134 ± 46	7.40 ± 0.02	39.3 ± 6.3	174.8 ± 29.9	147.1 ± 4.1	3.9 ± 0.5	36.4 ± 0.5
	After	122 ± 24	137 ± 49						
Bupivacaine (10^{-4} M)	Before	123 ± 24	135 ± 47	7.40 ± 0.02	38.3 ± 5.5	172.0 ± 28.3	148.1 ± 4.3	3.9 ± 0.5	36.3 ± 0.5
	After	123 ± 24	135 ± 45						
Bupivacaine (10^{-3} M)	Before	122 ± 24	135 ± 43	7.40 ± 0.01	36.5 ± 4.0	168.4 ± 28.6	147.7 ± 4.0	3.9 ± 0.5	36.4 ± 0.7
	After	122 ± 23	136 ± 43						

Values are mean ± SD.

BT = body temperature.

All results were expressed as mean ± SD, except for graphic variables, which were expressed as SEM.

Results

Mean arterial blood pressure and HR did not change significantly before or after topical administration of ropivacaine or bupivacaine in the experiments at any of the six different concentrations tested. In addition, arterial blood gas tensions and pH, serum electrolytes, and body temperature were not changed at any stage of the experiments (table 1).

Ropivacaine produced significant constrictions for large and small spinal pial arterioles and venules (10^{-5} M, 10^{-6} M, and 10^{-4} M, respectively; table 2), whereas bupivacaine significantly dilated large and small spinal pial arterioles and venules (10^{-6} M, 10^{-5} M, and 10^{-6} M, respectively; table 3). A concentration-dependent decrease for ropivacaine and increase for bupivacaine in diameter of large and small spinal pial arterioles and venules was observed after topical administration (figure 1). There was no difference in responsiveness to each drug between large and small arterioles.

Topical application of prazosin and yohimbine did not inhibit spinal pial arteriolar constriction caused by 10^{-3} M ropivacaine. In addition, propranolol did not affect the bupivacaine-induced vascular dilation (figure 2). MAP, HR, pH, arterial gas tensions, serum electrolytes, and body temperature were not changed after administration of these adrenoceptor blockers.

Discussion

The major findings of the present study are that the topical application of ropivacaine produces a vasoconstriction of spinal pial arterioles and venules in a concentration-dependent manner, whereas the topical application of bupivacaine causes vasodilation. These alterations of the spinal vessels are not accompanied by any change in systemic hemodynamics or physiologic variables. Thus, these responses we detected are likely to be a result of direct effects of both drugs on the pial

Table 2. Effects of Ropivacaine on Spinal Pial Arterioles and Venules

	Concentration					
	10^{-8} M	10^{-7} M	10^{-6} M	10^{-5} M	10^{-4} M	10^{-3} M
Large arterioles (μm)						
Before	168.0 ± 96.4	168.1 ± 96.4	168.1 ± 96.4	168.1 ± 96.4	168.1 ± 96.4	168.1 ± 96.9
After	168.0 ± 96.4	167.1 ± 95.7	166.7 ± 97.7	165.3 ± 98.9*	162.5 ± 97.7†	161.6 ± 95.2†
Small arterioles (μm)						
Before	68.6 ± 15.9	68.6 ± 15.9	68.6 ± 15.9	68.9 ± 15.5	68.4 ± 15.4	69.1 ± 14.9
After	69.1 ± 15.3	68.4 ± 15.4	67.4 ± 16.5*	66.4 ± 14.4†	64.2 ± 14.0†	64.0 ± 13.7†
Venules (μm)						
Before	85.2 ± 53.8	85.2 ± 53.8	85.2 ± 53.8	85.7 ± 54.0	85.9 ± 54.0	85.9 ± 53.9
After	84.9 ± 53.9	83.9 ± 51.7	83.9 ± 51.7	85.4 ± 53.3	83.3 ± 53.7†	82.3 ± 52.9†

Values are mean ± SD.

*$P < 0.05$ *versus* corresponding control.

†$P < 0.001$ *versus* corresponding control.

vasculature. Because the responses of the spinal pial vessels to local anesthetics are not inhibited by yohimbine, prazosin, or propranolol, such actions of ropivacaine and bupivacaine could not be mediated by mechanisms that depend on adrenergic receptors within the spinal vasculatures.

Results of the peripheral vascular effects of local anesthetics in previous studies are not definitive because they provide evidence for vasodilatory and vasoconstrictive actions.[3,4] Similarly, with regard to spinal blood flow (SBF), previous findings about direct effects of bupivacaine on SBF have not been confirmed. Kozody *et al.*[8] reported that 0.4% subarachnoid bupivacaine induces a significant decrease in spinal blood flow to all regions in canine, and a decrease of cardiac output concurrently occurred. Crosby[9] showed that subarachnoid bupivacaine reduced local spinal cord blood flow associated with reduced glucose utilization and mean blood pressure in conscious rats. Their data were not consistent with our present results, which measured pial vessel diameters in the spinal cord of dogs. In both previous studies,[8,9] the authors suggested that drug-induced alterations in spinal cord blood flow could be a result of changes in spinal cord metabolic activity, blocks of sympathetic activity, or effects of systemic circulation. When the physiologic variables of arterial blood pH, P_{CO2}, P_{O2}, mean blood pressure, and body temperature are kept constant, spinal cord blood flow

Table 3. Effects of Bupivacaine on Spinal Pial Arterioles and Venules

	Concentration					
	10^{-8} M	10^{-7} M	10^{-6} M	10^{-5} M	10^{-4} M	10^{-3} M
Large arterioles (μm)						
Before	133.8 ± 30.0	133.8 ± 30.0	133.8 ± 27.7	134.7 ± 29.3	135.7 ± 29.5	136.1 ± 29.2
After	134.3 ± 29.5	134.7 ± 29.7	140.7 ± 33.5*	144.9 ± 34.3†	148.6 ± 33.4‡	150.9 ± 36.9‡
Small arterioles (μm)						
Before	62.7 ± 14.7	62.7 ± 14.7	62.5 ± 15.4	62.7 ± 15.2	63.3 ± 15.2	64.0 ± 15.0
After	62.7 ± 14.7	62.9 ± 15.0	64.0 ± 15.9	66.9 ± 15.9†	68.4 ± 15.4†	70.1 ± 14.3†
Venules (μm)						
Before	102.4 ± 75.8	102.6 ± 75.7	102.4 ± 75.0	102.4 ± 74.8	102.0 ± 75.1	102.2 ± 75.2
After	102.9 ± 75.7	104.4 ± 75.6	105.9 ± 76.2*	105.9 ± 74.7†	108.6 ± 76.4†	108.8 ± 76.2†

Values are mean ± SD.

*$P < 0.05$ *versus* corresponding control.

†$P < 0.001$ *versus* corresponding control.

‡$P < 0.01$ *versus* corresponding control.

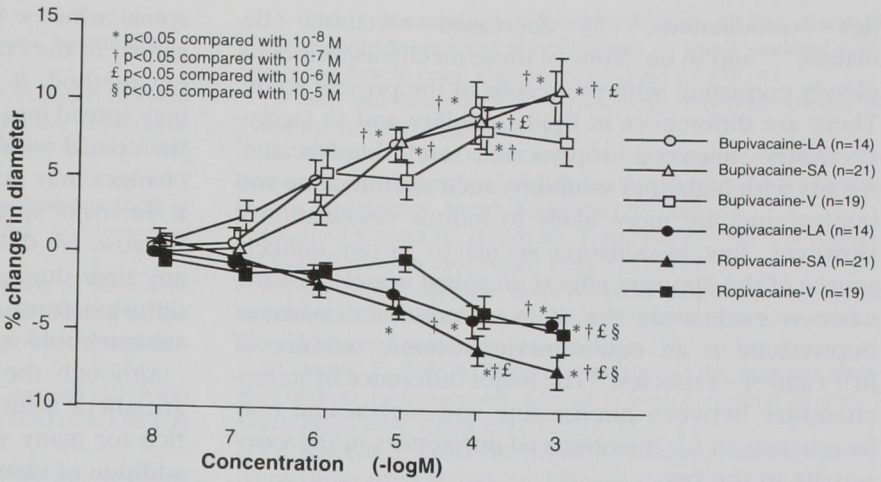

Figure 1. Concentration-related effects of ropivacaine and bupivacaine on spinal pial arteriolar (LA = large arteriole; > 100 μm, n = 14 each; SA = small arteriole; < 100 μm, n = 21 each) and venular diameter (V = venule; n = 19 each) in 14 dogs. Data are expressed as percent change in diameter. Ropivacaine produced a concentration-related constriction in spinal pial arterioles and venules; bupivacaine caused vasodilation. Values are mean ± SEM. * $P < 0.05$ compared with corresponding ropivacaine or bupivacaine 10^{-8} M. † $P < 0.05$ compared with corresponding ropivacaine or bupivacaine 10^{-7} M. ‡ $P < 0.05$ compared with corresponding ropivacaine or bupivacaine 10^{-6} M. § $P < 0.05$ compared with corresponding ropivacaine or bupivacaine 10^{-5} M.

will be maintained if spinal metabolic activity is unchanged. The administration of ropivacaine and bupivacaine did not induce any change in these physiologic variables. Therefore, the changes of spinal vessel diameter in the present study were probably not related to the physiologic changes caused by systemic effects of these drugs.

As far as we know, no previous studies have observed spinal vessels after administration of ropivacaine. Ropivacaine is a new amino-amide local anesthetic agent structurally related to bupivacaine.[10] The chemical properties of ropivacaine are similar to those of bupivacaine (pKa = 8.1 and protein bindings > 90% for both), but the lipid solubility is lower for ropivacaine. Kopacs *et al.*[1] showed that ropivacaine produces cutaneous vasoconstriction, in contrast to bupivacaine, which induces cutaneous vasodilation in pigs. They suggested that their results for ropivacaine and bupivacaine pertain only to their effects on cutaneous capillary vessels. Dahl *et al.*,[2] measured ^{133}Xe washout curve in reference to spinal and epidural blood flow in awake humans. They showed epidural blood flow increased after epidural bupivacaine administration, but ropivacaine caused epidural blood flow to decrease. Although there may be considerably different responses between spinal and epidural vessels, their findings in humans seem to agree with our present *in vivo* study of dogs. Dahl *et al.* speculated from other experimental studies[11] that spinal blood flow would show similar changes after administration of both drugs.

The mechanisms by which ropivacaine and bupivacaine alter spinal pial vessels is not clear. It seems unlikely that the local anesthetic action of spinal anesthesia *per se* induces the changes in diameter of spinal vessels because bupivacaine and ropivacaine caused the exact opposite effects in the present study. Several investigators have speculated that local anesthetics cause changes in vessels *via* the following mechanisms: 1) direct smooth muscle activation of precapillary or postcapillary vessels;[1] 2) indirect release of vasoactive substance or blockade of vasoactive substance release;[12] 3) blockade of the sympathetic nerves innervating the spinal cord vessels;[13] 4) increased cytoplasmic calcium (vasoconstriction) or calcium channel blocking proper-

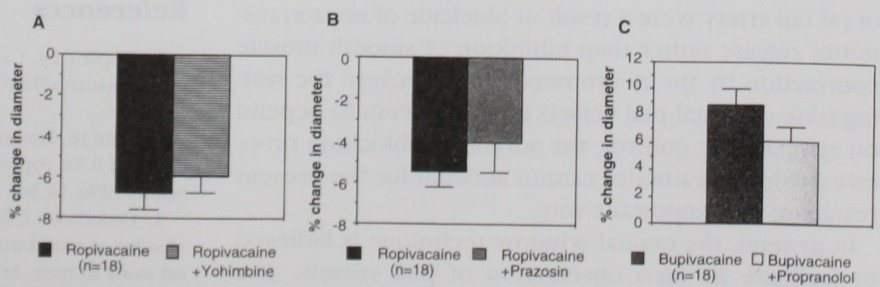

Figure 2. Effects of prazosin, yohimbine, or propranolol on 10^{-3} M ropivacaine-induced vasoconstriction or bupivacaine-induced vasodilation for spinal pial arterioles (n = 18 each) in 18 dogs. With pretreatment of these blockers, alteration of spinal pial arterioles after subsequent 10^{-3} M ropivacaine or bupivacaine were not inhibited. Values are expressed as mean ± SEM.

ties (vasodilation);[4] 5) decreased metabolic demands;[9,13] and so on. None of these mechanisms is completely consistent with the results of the present study. There are differences in lipid solubility and in stereochemistry between ropivacaine and bupivacaine. Agents with high-lipid solubility, such as etidocaine and bupivacaine, are more likely to induce vasodilation.[14] However, this vasodilation seems to be an unlikely source of the opposite effects on spinal vessels. Ropivacaine is exclusively the S(−) stereoisomer, whereas bupivacaine is an equiisomeric, recemic mixture of R(+) and S(−) species.[10] The major difference in stereochemistry between bupivacaine and ropivacaine may be one reason for the observed differences in the vasoactivity of the two.

In the present study, α_1-, α_2-, and β-adrenoceptor antagonists did not cause any change in the diameter of spinal pial vessels during their topical administration. These results seem to indicate that the resting tone of spinal pial vessels did not depend on α- and β-adrenergic control. These results agree with our previous observations in cerebral arterioles and venules,[15,16] although considerable differences seem to exist in the responses between cerebral and spinal vessels. With regard to the spinal cord blood flow (SCBF) after subarachnoid administration of adrenoceptor inhibitors in dogs, phenylephrine (an α_1 agonist) decreased SCBF in a dose-related manner,[13] whereas epinephrine (an α, β agonist) did not affect local SCBF.[17] As far as cerebral pial vessels are concerned, β_1 agonists, such as isoproterenol and dobutamine, caused pial arteriolar dilation *via* activation of β adrenoceptors in bovine.[18] Norepinephrine also produced β_1-adrenoceptor-mediated dilation of rat basilar arterioles[19] and dexmedetomidine (an α_2 agonist) caused α_2-adrenoceptor-mediated vasoconstriction of canine pial vessels.[15] All of these studies were done using the cranial window technique. The effects of norepinephrine and dexmedetomidine seem to involve, at least partly, the activation of ATP-sensitive K^+ channels and thus cAMP.[15,20,21] Szocic *et al.*[12] have suggested that the effects of local anesthetics on the smooth muscle of rat tail artery were a result of blockade of neurotransmitter release rather than inhibition of smooth muscle contraction by the neurotransmitter. Because the resting tone of spinal pial vessels does not seem to depend on sympathetic control, the adrenergic blocking property of local anesthetics cannot account for the present results in any important way.

In general, the cranial window technique is believed to facilitate *in vivo* observation of pial vessels. The spinal window technique used in the present study is similar to the cranial window technique. With the present method, it is possible that experimental solution may spread into general volume of CSF much more than the cranial window technique. Systemic hemodynamic changes may occur during epidural or spinal blockade if the major spreading of experimental solution occurs. Because we did not observe hemodynamic changes at any time during this study, it is unlikely that a major diffusion from the window into adjacent epidural or subarachnoid space occurred.

Although the inclusion of vasoconstrictors in local anesthetic solutions has been a clinically accepted practice for many years, it is not conclusive whether the addition of vasoconstrictors to bupivacaine is generally beneficial in epidural and spinal anesthesia.[22] The present findings for bupivacaine imply that addition of vasoconstrictors to bupivacaine solution can provide a certain clinical benefit. Feldman *et al.*[23] showed that epinephrine added to ropivacaine and bupivacaine solution could not prolong the duration of epidural block. Kopacz *et al.*[1] reported that the addition of epinephrine to ropivacaine solution did not alter the maximum decrease in cutaneous blood flow, but epinephrine did significantly decrease cutaneous blood flow when added to bupivacaine solution. The present results in spinal vessels suggest that in spinal anesthesia using ropivacaine the addition of epinephrine cannot prolong the duration of anesthesia, or it may cause neuronal damage when used with a higher concentration of ropivacaine.

In conclusion, although the mechanisms involved are unknown, our findings suggest that the microvascular alteration shown by ropivacaine and bupivacaine may influence the duration during spinal and epidural anesthesia. Additionally, the constrictive effect of ropivacaine on spinal pial vessels could eliminate a need for adding a vasopressor such as epinephrine into the ropivacaine solution.

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