Anesthesiology
1999; 91:479-85

Direct Effects of α_1- and α_2-Adrenergic Agonists on Spinal and Cerebral Pial Vessels in Dogs

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Background: **The effects of adrenergic agonists, often used as local anesthetic additives or spinal analgesics, on spinal vessels have not been firmly established. The authors investigated the effects of α_2- and α_1-adrenergic agonists on spinal and cerebral pial vessels *in vivo*.**

Methods: **Pentobarbital-anesthetized dogs (n = 28) were prepared for measurement of spinal pial-vessel diameter in a spinal-window preparation. The authors applied dexmedetomidine, clonidine, phenylephrine, or epinephrine in three different concentrations (0.5, 5.0, and 50 μg/ml; [2.1, 1.9, 2.5, and 2.3] x [10^{-6}, 10^{-5}, and 10^{-4}] M, respectively) under the window (one drug in each dog) and measured spinal pial arteriolar and venular diameters in a sequential manner. To enable the comparison of their effects on cerebral vessels, the authors also administered these drugs under a cranial window.**

Results: **On topical administration, each drug constricted spinal pial arterioles in a concentration-dependent manner. Phenylephrine and epinephrine induced a significantly larger arteriolar constriction than dexmedetomidine or clonidine at 5 μg/ml (8%, 11%, 0%, and 1%, respectively). Spinal pial venules tended to be less constricted than arterioles. In cerebral arterioles, greater constrictions were induced by dexmedetomidine and clonidine than those induced by phenylephrine and epinephrine (14%, 8%, 0%, and 1%, respectively). Cerebral pial venules tended to exhibit larger constrictions than cerebral arterioles (unlike in spinal vessels).**

Conclusion: **Dexmedetomidine and clonidine constricted spinal vessels in a concentration-dependent manner, but such vasoconstrictions were smaller than those induced by phenylephrine and epinephrine. (Key words: Adrenergic agents; spinal microcirculation; vasoconstrictor.)**

FOR many years vasoconstrictors have been used to prolong the duration of action of various local anesthetics following subarachnoid administration. However, the effects of adrenergic agonists on spinal cord blood flow (SCBF) and spinal vessels have not yet been clearly defined. Kozody *et al.*[1] reported that subarachnoid epinephrine (0.2 mg) or phenylephrine (5 mg) did not decrease SCBF in dogs, whereas Dohi *et al.* also in the dogs, demonstrated that subarachnoid phenylephrine (2, 3, and 5 mg) decreased SCBF,[2] although subarachnoid epinephrine (0.1, 0.3, and 0.5 mg) did not significantly change SCBF.[3] Crosby *et al.*[4] reported that subarachnoid clonidine reduced both SCBF and glucose utilization in conscious rats; Gordh *et al.*[5] found that epidural clonidine (3 μg/kg) did not affect regional SCBF in pigs. As far as dexmedetomidine is concerned, there have been several reports about cerebral blood flow[6-8] and vessels,[9] but little attention has been paid to its effects on SCBF and spinal vessels. However, our previous study indicated that vasoconstrictors affect both spinal and cerebral pial vessels.[10]

A better assessment of the direct spinal microvascular actions of adrenergic agonists might enable a better evaluation of their contribution to the prolongation of spinal anesthesia and their safety (in terms of their effects on the spinal microcirculation). There has been little attempt to evaluate the comparative effects of adrenergic agonists on the spinal and cerebral vascular beds in *in vivo* experiments. For this reason, we decided to investigate the concentration-related effects of dexmedetomidine, clonidine, phenylephrine, and epinephrine on spinal and cerebral pial vascular diameter using spinal and cranial window techniques.

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Received from the Department of Anesthesiology and Critical Care Medicine, Gifu University School of Medicine, Gifu City, Japan. Submitted for publication September 4, 1998. Accepted for publication March 31, 1999. Supported by grant-in aid for scientific research no. 09671555 and no. 08457405 (Ministry of Education, Science and Culture, Japan). Presented in part at the annual meeting of the American Society of Anesthesiologists, New Orleans, Louisiana, October 19-23, 1996, and at the XVIIIth International Symposium on Cerebral Blood Flow and Metabolism, Baltimore, Maryland, June 15-19, 1997.

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Materials and Methods

The experimental protocols were approved by our Institutional Committee for Animal Care, and the experiments were performed in 52 anesthetized dogs weighing between 6 and 10 kg. Anesthesia was induced with pentobarbital sodium (20 mg/kg intravenously) and maintained with a continuous infusion of pentobarbital sodium (2 mg · kg^{-1} · min^{-1}). After tracheal intubation, each dog was mechanically ventilated with oxygen-enriched room air. The tidal volume and respiratory rate were adjusted to maintain an end-tidal carbon dioxide pressure of 35–40 mmHg. Polyvinyl chloride catheters were placed in the femoral vein for administration of drugs and fluids, and in the femoral artery for blood pressure monitoring and blood sampling. Rectal temperature was maintained between 36.5°C and 37.5°C with a warming blanket.

In the first set of experiments (n = 28), a closed spinal window was used for observation of the spinal pial microcirculation. The animal was placed in the sphinx position with the head immobilized in a stereotactic frame. After the skin was retracted following a longitudinal midline incision, the thoracolumbar paraspinal muscles were exposed from the lower thoracic level to the third lumbar vertebra. The periosteum and muscle attachments from the 12th thoracic to the 2nd lumbar vertebrae were separated from the laminae and spinous and articular processes with the aid of electrocautery. The block of paraspinal muscles in that region was removed. After the spinous process had been removed with a rongeur, a laminectomy was performed (5 × 10 mm) with an electric drill in the first lumbar vertebra. The surfaces of the laminae were ground flat using an electric grinder, and the dura and arachnoid membrane were cut carefully. A ring fitted with a cover glass was placed over the hole and secured with dental acrylic. The ends of four polyvinyl chloride catheters were inserted through the ring. The space under the window was filled with artificial cerebrospinal fluid (aCSF), the composition of which has been described elsewhere.[11,12] All solutions were bubbled with 5% CO_2 in air at 37.0°C. One catheter was attached to a reservoir bottle containing aCSF so as to maintain a constant intrawindow pressure of 5 mmHg. Two other catheters were used for infusion and drainage of aCSF and experimental drug solutions, and the final catheter was for continuous monitoring of intrawindow pressure. The volume below the window was between 0.5 and 1.0 ml.

In the second set of experiments (n = 24), a closed cranial window was used to observe the pial microcirculation. The scalp was retracted, the temporal muscle removed, and a hole 2 cm in diameter was made in the parietal bone. After coagulation of dural vessels with the aid of a bipolar electrocoagulator, the dura and arachnoid membrane were cut and retracted over the bone. A ring fitted with a cover glass was placed over the hole and secured with dental acrylic. The cranial window system used was similar to the spinal one described for the first set of experiments.

All *in vivo* experiments were carried out in the following manner. Dexmedetomidine, clonidine, phenylephrine, and epinephrine were freshly dissolved in aCSF, three different concentrations (0.5 μg/ml, 5 μg/ml, and 50 μg/ml; 2.1 x [10^{-6}, 10^{-5}, and 10^{-4}] M for dexmedetomidine, 1.9 x [10^{-6}, 10^{-5}, and 10^{-4}] M for clonidine, 2.5 x [10^{-6}, 10^{-5}, and 10^{-4}] M for phenylephrine, and 2.3 x [10^{-6}, 10^{-5}, and 10^{-4}] M for epinephrine) being prepared for the spinal experiments, and two (0.5 μg/ml and 5 μg/ml) for the cranial. In practice, the highest concentration (50 μg/ml) of phenylephrine and epinephrine was not used in the spinal experiments (see Results). The animals were allowed to recover from the surgical procedures for at least 30 min. Pial arteriolar and venular diameters, mean arterial pressure, heart rate, arterial blood-gas tensions, *p*H, blood sugar, and serum electrolytes were measured before and after topical application of each concentration of the drugs into the spinal window (n = 7 for each concentration of each agent) or cranial window (n = 6 for each concentration of each agent). To establish the baseline size of the various vessels, the window was continuously flushed with aCSF at the rate of 0.5 to 1.0 ml/min for 20 min after each measurement. Twenty minutes after the last administration of the study solutions, the spinal pial vascular diameter had returned to control values (except after the higher concentration [5 μg/ml] of phenylephrine and epinephrine [see Results]).

The diameters of two pial arterioles and venules were measured sequentially after the administration of each solution of the drugs, the measurements being made using a videomicrometer (Olympus Flovel model, VM-20, Tokyo, Japan) attached to a microscope (Olympus model SZH-10). The data from each view were stored on videotape for later playback and analysis.

Statistical Analysis

All variables used to assess the concentration-dependent effects of experimental drugs were tested by a one-way analysis of variance for repeated measurements,

Table 1. Hemodynamic Changes during Spinal Topical Administration of Adrenergic Agonists

Concentration (μg/ml)		Dexmedetomidine		Clonidine		Phenylephrine		Epinephrine	
		MAP (mmHg)	HR (bpm)	MAP (mmHg)	HR (bpm)	MAP (mmHg)	HR (bpm)	MAP (mmHg)	HR (bpm)
0.5	Before	112 ± 10	154 ± 17	103 ± 21	151 ± 37	115 ± 21	169 ± 37	107 ± 23	155 ± 24
	After	112 ± 10	158 ± 15	103 ± 22	152 ± 38	115 ± 21	171 ± 37	106 ± 23	156 ± 25
5	Before	114 ± 10	160 ± 15	102 ± 22	151 ± 37	116 ± 22	168 ± 38	107 ± 24	156 ± 26
	After	112 ± 7	159 ± 15	101 ± 21	153 ± 42	116 ± 22	170 ± 38	107 ± 25	156 ± 26
50	Before	110 ± 7	162 ± 15	100 ± 22	153 ± 46	—	—	—	—
	After	110 ± 10	160 ± 15	98 ± 23	151 ± 47	—	—	—	—

Values are mean ± SD.

MAP = mean arterial pressure; HR = heart rate.

with Scheffé's test being used for *post hoc* comparisons. Differences among drugs at the same concentration were tested by a one-way analysis of variance followed by Scheffé's test. The difference between spinal and cerebral values was tested by a two-way analysis of variance, followed by an unpaired *t* test for comparing within the same drug and concentration. Significance was set at $P < 0.05$. All results are expressed as mean ± SD.

Results

Neither mean arterial pressure nor heart rate changed significantly following the topical administration of dexmedetomidine, clonidine, phenylephrine, or epinephrine at the two or three different concentrations used in experiments involving spinal or cranial preparations (tables 1 and 2). Moreover, arterial blood- gas tensions and *p*H, serum electrolytes, and blood sugar were all unchanged by any concentration of these drugs in either set of experiments (tables 3 and 4). The baseline diameters were 86 ± 30 μm for spinal arterioles and 122 ± 66 μm for spinal venules, and the corresponding values for cerebral vessels were 93 ± 40 μm and 107 ± 39 μm, respectively.

A concentration-dependent decrease in the diameter of spinal pial arterioles was observed after the topical administration of each of these drugs (fig. 1A). At 5 μg/ml, phenylephrine and epinephrine induced significantly greater arteriolar constriction (8.1 ± 5.4% and 10.6 ± 7.8%) than dexmedetomidine and clonidine (0.0 ± 0.0% and 0.8 ± 2.2%). Dexmedetomidine and clonidine at 50 μg/ml caused arteriolar constrictions (6.1 ± 3.1% and 9.2 ± 4.4%) that were similar in size to those induced by 5 μg/ml of phenylephrine and epinephrine. Because the vessels had not recovered from the vasoconstrictions induced by 5 μg/ml phenylephrine and epinephrine 2 h after drug administration, the 50-μg/ml doses of these two agents were not tested. In spinal pial venules, the pattern of change was similar to that seen in spinal arterioles (fig. 1B).

A concentration-dependent decrease in diameter was also observed in cerebral arterioles after topical administration of the same drugs (fig. 2). In cerebral arterioles, the vasoconstrictions induced by 5 μg/ml dexmedetomidine and clonidine (14.0 ± 9.5% and 8.0 ± 11.0%) were much larger than those induced by the same dose of phenylephrine and epinephrine (0.3 ± 3.2% and 1.5 ± 4.1%) (in contrast to the situation in spinal arterioles at 5 μg/ml). Cerebral pial venules exhibited qualitatively sim-

Table 2. Hemodynamic Changes during Cranial Topical Administration of Adrenergic Agonists

Concentration (μg/ml)		Dexmedetomidine		Clonidine		Phenylephrine		Epinephrine	
		MAP (mmHg)	HR (bpm)	MAP (mmHg)	HR (bpm)	MAP (mmHg)	HR (bpm)	MAP (mmHg)	HR (bpm)
0.5	Before	116 ± 18	132 ± 31	114 ± 14	129 ± 29	115 ± 26	142 ± 21	112 ± 18	140 ± 20
	After	116 ± 18	131 ± 30	115 ± 15	129 ± 30	116 ± 25	150 ± 28	113 ± 19	142 ± 23
5	Before	115 ± 20	132 ± 30	116 ± 15	127 ± 31	112 ± 21	152 ± 35	111 ± 17	139 ± 18
	After	116 ± 21	130 ± 31	116 ± 15	131 ± 32	115 ± 24	154 ± 36	109 ± 19	138 ± 16

Values are mean ± SD.

MAP = mean arterial pressure; HR = heart rate.

Table 3. Physiologic Measurements during Spinal Topical Application of Adrenergic Agonists

	Concentration (μg/ml)	*p*H	Pa_{CO_2} (mmHg)	Pa_{O_2} (mmHg)	Na (mEq/L)	K (mEq/L)	BS (mg/dl)
	0.5	7.41 ± 0.02	34.1 ± 2.7	203.8 ± 29.9	147.7 ± 4.2	4.41 ± 0.64	124 ± 22
Dexmedetomidine	5	7.41 ± 0.05	34.4 ± 3.2	205.4 ± 33.3	147.9 ± 4.4	4.41 ± 0.71	129 ± 22
	50	7.41 ± 0.05	35.0 ± 3.4	203.9 ± 30.9	148.0 ± 4.9	4.37 ± 0.64	125 ± 27
	0.5	7.36 ± 0.04	37.7 ± 3.8	168.5 ± 29.6	149.6 ± 5.7	4.11 ± 0.83	137 ± 23
Clonidine	5	7.37 ± 0.04	37.0 ± 3.7	174.9 ± 32.3	150.0 ± 5.6	4.07 ± 0.70	134 ± 23
	50	7.36 ± 0.04	37.6 ± 4.0	169.8 ± 28.9	149.4 ± 5.8	4.10 ± 0.75	134 ± 23
	0.5	7.42 ± 0.05	34.4 ± 4.4	159.0 ± 29.4	149.7 ± 6.8	4.01 ± 0.43	126 ± 15
Phenylephrine	5	7.41 ± 0.04	35.4 ± 3.9	159.5 ± 28.4	150.0 ± 5.9	4.00 ± 0.46	124 ± 17
	50	—	—	—	—	—	—
	0.5	7.39 ± 0.03	37.2 ± 2.5	201.9 ± 32.2	148.1 ± 5.7	4.04 ± 0.22	123 ± 13
Epinephrine	5	7.37 ± 0.03	37.9 ± 2.5	198.0 ± 39.8	146.9 ± 5.6	4.13 ± 0.63	126 ± 12
	50	—	—	—	—	—	—

Values are mean ± SD. All values are arterial.

BS = blood sugar.

ilar but mostly larger changes than cerebral arterioles (in contrast to the situation in spinal venules).

Discussion

The major findings in the present study were that, on topical application, dexmedetomidine, clonidine, phenylephrine, and epinephrine all constricted spinal pial arterioles and venules in a concentration-dependent manner, and that at the same dose phenylephrine and epinephrine induced significantly larger constrictions of spinal arterioles and venules than dexmedetomidine and clonidine. In contrast to the situation in spinal arterioles, dexmedetomidine and clonidine constricted cerebral arterioles to a more significant degree than phenylephrine and epinephrine. Cerebral venules were also constricted by these adrenergic agonists, and they were more sensitive than their spinal counterpart. Thus, as far as their effects on the spinal microcirculation are concerned, α_2-adrenergic agonists, such as dexmedetomidine and clonidine, may have a wider margin of safety than phenylephrine and epinephrine (see subsequent sections).

In general, the prolongation of local anesthesia effect induced by adrenergic agonists might be expected to result from their vasoconstrictor action or an effect on nociception resulting from α_2-adrenoceptor stimulation. Thus, a proper understanding of the comparative effect of adrenergic agonists on spinal vessels would be expected to help clarify the interaction between local anesthetics and adrenergic agonists. However, the direct effects of adrenergic agonists on SCBF and spinal cord blood vessels have not yet been clearly defined. Previous studies found that subarachnoid epinephrine did not affect SCBF,[1,3], or that it attenuated the increase in SCBF induced by concomitantly administered subarachnoid tetracaine or lidocaine in dogs,[13,14] whereas subarachnoid phenylephrine in dogs either reduced SCBF dose-dependently[3] or did not affect SCBF at all.[1] Moreover, although Crosby *et al.*[4] reported that sub-

Table 4. Physiologic Measurements during Cranial Topical Application of Adrenergic Agonists

	Concentration (μg/ml)	*p*H	Pa_{CO_2} (mmHg)	Pa_{O_2} (mmHg)	Na (mEq/L)	K (mEq/L)	BS (mg/dl)
	0.5	7.42 ± 0.01	34.3 ± 2.2	185.9 ± 22.7	142.1 ± 3.1	4.03 ± 0.50	124 ± 7
Dexmedetomidine	5	7.41 ± 0.01	33.4 ± 2.4	188.0 ± 22.3	141.3 ± 3.4	3.88 ± 0.59	121 ± 11
	0.5	7.42 ± 0.03	35.4 ± 3.0	183.3 ± 22.7	142.3 ± 2.4	3.88 ± 0.52	122 ± 13
Clonidine	5	7.42 ± 0.02	34.5 ± 2.7	185.8 ± 30.3	141.8 ± 2.5	3.87 ± 0.48	124 ± 12
	0.5	7.38 ± 0.07	37.8 ± 5.0	182.9 ± 31.6	143.5 ± 2.1	3.75 ± 0.61	132 ± 11
Phenylephrine	5	7.37 ± 0.05	36.1 ± 3.5	182.3 ± 31.9	143.7 ± 1.9	3.70 ± 0.67	134 ± 13
	0.5	7.35 ± 0.05	38.5 ± 3.2	180.6 ± 21.6	144.8 ± 3.9	3.85 ± 0.62	127 ± 19
Epinephrine	5	7.38 ± 0.03	38.1 ± 2.7	182.2 ± 22.1	144.8 ± 4.0	3.78 ± 0.69	127 ± 18

Values are mean ± SD. All values are arterial.

BS = blood sugar.

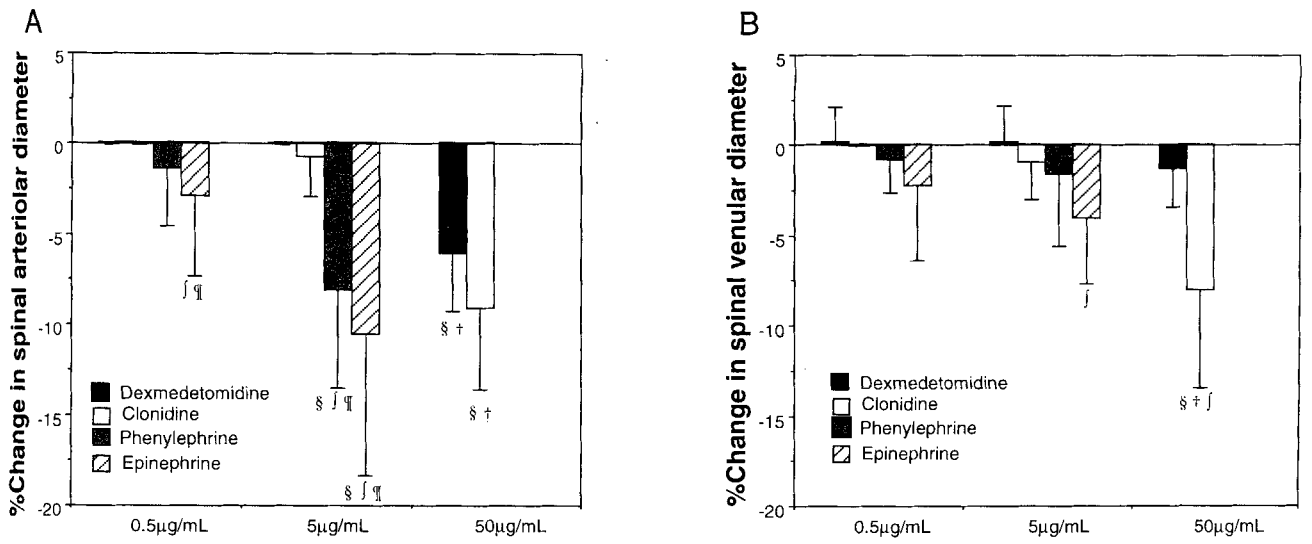

Fig. 1. Concentration-related effects of adrenergic agonists on the diameter of spinal pial arterioles (*A*) and venules (*B*) in 28 dogs. Data are expressed as percentage change in diameter. A concentration-dependent decrease in the diameter of spinal pial arterioles was observed after topical administration of each agonist. At 5 μg/ml, phenylephrine and epinephrine induced significantly larger arteriolar constrictions than clonidine and dexmedetomidine. Spinal pial venules showed a similar pattern of change, but the changes tended to be smaller than in arterioles. Values are mean ± SD (n = 7 for each column). §P < 0.05 compared with corresponding value at 0.5 μg/ml. †P < 0.05 compared with corresponding value at 5 μg/ml. ∫P < 0.05 compared with corresponding value for dexmedetomidine. ¶P < 0.05 compared with corresponding value for clonidine. For molar concentration of these agents, see text.

arachnoid clonidine reduced SCBF in conscious rats, Mensink *et al.*[5] found that it increased regional SCBF in the dog. In the current study, although dexmedetomidine, clonidine, phenylephrine, and epinephrine all constricted spinal pial arterioles, the latter two agents induced significantly larger vasoconstrictions of spinal arterioles than dexmedetomidine and clonidine. However, previous reports have demonstrated that changes in superficial pial arterioles may not reflect changes in total SCBF.[15,16] The large contribution made by intraparenchymal arterioles to overall vascular resistance in the cerebral circulation suggests that spinal intraparenchymal arterioles may also play a greater role than their pial counterparts in the regulation of SCBF. Porter *et al.*[17] demonstrated that subarachnoid epinephrine did not induce demonstrable changes in SCBF during spinal anesthesia with lidocaine, mepivacaine, or tetracaine, although the absorption of such local anesthetics was reduced by added epinephrine. They suggested that such reduced vascular absorption of local anesthetic may result from vasoconstriction of the most superficial vessels in the spinal cord. On the basis of the published data discussed previously and the current results, it seems possible that the changes in pial-vessel diameter seen in the current study might not themselves lead to a critical decrease in total SCBF, even though regional SCBF may in fact be affected by such topically administered adrenergic agonists.

Previous studies have demonstrated that different combinations of local anesthetics and adrenergic agonists have different effect. The addition of phenylephrine or epinephrine seems to prolong hyperbaric tetracaine spinal anesthesia[18,19] but has a less obvious effect on the spinal anesthesia produced by lidocaine or bupivacaine.[20,21] It was postulated that such differences might result from differences in the vasodilator actions of the various local anesthetic drugs. Other studies have demonstrated that clonidine could be useful for prolonging the duration of action of local anesthetics whether given by the subarachnoid[22,23] or oral[24-26] route in similar doses. In the current study, α_2-agonists constricted spinal pial arterioles less than epinephrine and phenylephrine. On this basis, the contribution of vasoconstriction to the prolongation of spinal anesthesia could be less with α_2-agonists than with phenylephrine and epinephrine. Therefore, it is possible that α_2-agonists may prolong the duration of local anesthetic effects during spinal anesthesia by a mechanism that is independent of their vasoactive action on spinal vessels.

As far as we know, there is little information as to differences between the responses of spinal and cerebral

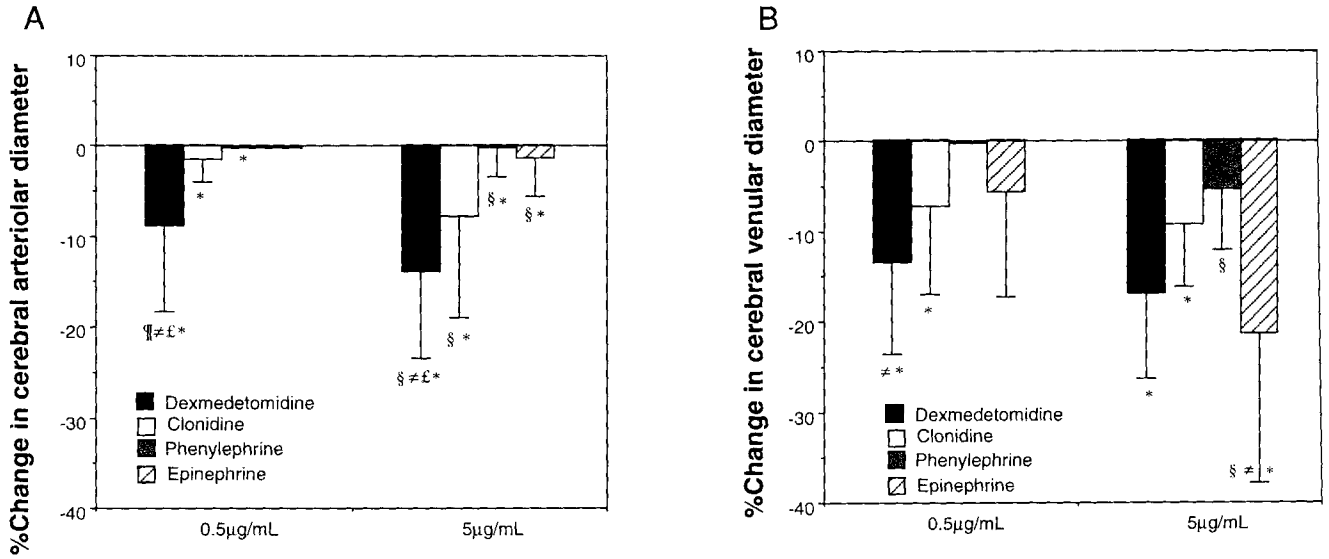

Fig. 2. Concentration-related effects of adrenergic agonists on the diameter of cerebral pial arterioles (*A*) and venules (*B*) in 24 dogs. Data are expressed as percentage change in diameter. A concentration-dependent decrease in diameter in cerebral arterioles was observed after topical administration of each agonist. The vasoconstriction induced in cerebral arterioles by dexmedetomidine and clonidine was much larger than that induced by phenylephrine and epinephrine (in contrast to the situation with spinal arterioles). Cerebral pial venules tended to show larger changes than arterioles (in contrast to the situation in spinal vessels). Values are mean ± SD (n = 6 for each column). §P < 0.05 compared with corresponding value at 0.5 μg/ml. ¶P < 0.05 compared with corresponding value for clonidine. ‡P < 0.05 compared with corresponding value for phenylephrine. £P < 0.05 compared with corresponding value for epinephrine. *P < 0.05 compared with corresponding value for spinal vessels. For molar concentration of these agents, see text.

vessels to adrenergic agonists. To judge from the results of the current study, spinal arterioles seem to be more sensitive to α_1-adrenergic stimulation than to α_2-adrenergic stimulation, whereas cerebral arterioles are more sensitive to α_2-adrenergic stimulation than to α_1-adrenergic stimulation. In contrast to the situation in arterioles, spinal venules seemed to be less sensitive to α-adrenergic stimulation than their cerebral counterparts. Such differences between spinal and cerebral vessels in their responses to adrenergic stimulation might conceivably contribute to spinal ischemic damage during adrenergic agonist administration after cerebrospinal reperfusion.

It is well known that vessels of different sizes often respond quite differently to both vasodilators and vasoconstrictors. However, in the spinal-window preparation used in the present study, spinal vessels, especially arterioles, were few. We could not always find vessels of wide range in size. Thus, we chose sizes of vessels 86 ± 30 μm for spinal arterioles and 122 ± 66 μm for spinal venules, which were observed in every spinal window preparation. Moreover, in our pilot study, we could not find any size-dependent vasoreactivity within the range of size observed in the current study. Because we want to compare the spinal vessels with cerebral ones, we fit the size of cerebral vessels to that of spinal vessels. If we could choose larger arterioles or artery, different vasoreactivity may be induced by these agent, as previous reports indicated.[27,28]

Previous studies have indicated that the clinically effective doses of so-called vasopressors as local anesthetic additives are approximately 1–5 mg for phenylephrine,[19,21] 0.1–0.3 mg for epinephrine,[18,20] and 0.075–0.15mg for clonidine.[22,23]. There is no information about the effective dose of dexmedetomidine as a local anesthetic additive in the clinical setting. To judge from the results of animal studies,[29,30] the required clinical dose of dexmedetomidine, if it were used as a local anesthetic additive, would be similar or smaller than the required dose of clonidine. When used as local anesthetic additives or analgesic agents by subarachnoid administration, α_2-agonists such as dexmedetomidine and clonidine could be safer, in terms of their effects on spinal vessels than epinephrine or phenylephrine.

In conclusion, dexmedetomidine and clonidine constrict spinal pial vessels in a concentration-dependent manner. In this respect, their actions are essentially similar but less powerful than those of epinephrine and

phenylephrine. The differences between these drugs' actions may contribute to the clinical variabilities seen when local anesthetics and vasoconstrictors are given together. In addition, α_2-agonists could be safer than α_1-agonists when used as local anesthetic additives or analgesic agents, at least in terms of their effects on the spinal microcirculation.

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