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The Effects of Subarachnoid Lidocaine and Phenylephrine on Spinal Cord and Cerebral Blood Flow in Dogs

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To investigate the central nervous system circulation during spinal anesthesia, local spinal cord blood flow (SCBF) and cerebral blood flow (CBF) were measured simultaneously by the hydrogen clearance technique following subarachnoid lidocaine, phenylephrine, or a combination of both. The mean control values of SCBF and CBF were 22.4 ± 7.9 ml·100 g^{-1}·min^{-1} and 53.1 ± 12.0 ml·100 g^{-1}·min^{-1}, respectively, in dogs lightly anesthetized with halothane.

The subarachnoid administration of lidocaine solutions (1, 2, 3, and 5%), 1 ml, failed to produce statistically significant changes in SCBF ($P > 0.05$). Whereas, when phenylephrine (0.1, 0.2, 0.3, and 0.5%), 1 ml, was injected into the spinal subarachnoid space, SCBF decreased significantly with concentrations greater than 0.2% ($P < 0.05$). When a mixture of lidocaine (24 mg) and phenylephrine (1 mg) was administered into the subarachnoid space, SCBF decreased significantly and returned to control within 60–90 min. CBF did not change significantly with any of the injections, remaining within less than ±12% of control. Dextrose solutions in water (5 and 7.5%), which were used for dilution of the drugs, did not affect either SCBF or CBF. These results indicate that local spinal cord blood flow can be affected significantly during spinal anesthesia when phenylephrine is added to the local anesthetic solution. However, the circulatory effects of drugs injected into the spinal subarachnoid space appear to be restricted to the local spinal cord *per se* and do not involve other parts of the CNS. (Key words: Anesthetics, local: lidocaine. Anesthetic technique: spinal. Brain: blood flow. Spinal cord: blood flow. Sympathetic nervous system: sympathectomy; phenylephrine.)

ALTHOUGH OUR KNOWLEDGE of spinal cord blood flow (SCBF) is still insufficient, its control mechanisms are thought to parallel those affecting the cerebral circulation, with minor differences mainly in threshold and sensitivity.[1–8] Thus, systemically administered drugs known to affect cerebral blood flow (CBF) similarly should affect SCBF. However, when a drug is administered directly into the spinal subarachnoid space, it may be a different matter. Recently, we reported that spinal subarachnoid morphine did not significantly alter SCBF, although its intravenous administration produced a parallel decrease in both SCBF and CBF.[9]

Lidocaine is one of the most frequently used local anesthetics for spinal anesthesia. Its systemic administration can produce some alterations in the circulation including the central nervous system.[10–13] When it is given intravenously to rats, a convulsive dose produces a 44% decrease in CBF at a plasma concentration of 6.4 μg/ml.[13] When given locally, vasoconstriction is observed more frequently at low concentrations and vasodilatation at high concentrations.[14] Since it is known that locally administered lidocaine acts on vascular smooth muscle either directly or by blockade of innervating autonomic nerves,[11,14–16] it is reasonable to suppose that subarachnoid administration of the drug might influence SCBF. Similarly, potent vasoconstrictors such as phenylephrine, when added to a local anesthetic for prolongation of spinal anesthesia, also could have a direct action on the vessels of the spinal cord[16,17] and thus decrease SCBF. There is, however, little direct evidence for these suppositions. Therefore, we measured SCBF and CBF simultaneously following the subarachnoid administration of lidocaine, phenylephrine, or a combination of both in dogs lightly anesthetized with halothane.

Methods

Experiments were performed in 47 unpremedicated mongrel dogs (8–14 kg). All animals initially were anesthetized with thiamylal 500 mg ip. Succinylcholine chloride, 20 mg, im, was given to facilitate endotracheal intubation, and thereafter 50 mg/h was administered iv to maintain muscle paralysis. The dogs were ventilated mechanically with an animal respirator (AIKA, 60) to maintain an end-tidal CO_2 concentration of 4.6 ± 0.1% as measured by a CO_2 analyzer (Datex Normocap CO_2 and O_2 monitor). Anesthesia was maintained with halothane 1.0–1.5% inspired with oxygen and air. A femoral arterial catheter was inserted for blood–gas determinations and continuous blood pressure measurement. A femoral vein catheter was inserted for drug administration and continuous intravenous fluid administration of lactated Ringer's solution at a rate of 5 ml·kg^{-1}·h^{-1}.

The parietal cortex and sagittal sinus were exposed by a midline frontal-occipital incision and extensive craniectomy. A standard dorsal laminectomy also was performed

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at L_{3-5} to expose the dura mater. A polyethylene catheter, 18 G, was inserted into the lumbar subarachnoid space for subarachnoid injection of drugs.

Following surgical preparation, the dogs were placed in a prone position with the head slightly elevated in order to minimize gravitational spread of the drugs toward the brain. One platinum electrode, 100 μm diameter, (Standard wire type, UHE-201) was placed in the brain, while another was placed in the lumbar spinal cord through a small hole in the dura mater. These electrodes were advanced to a depth of approximately 3–5 mm from the surface of the brain and the spinal cord. The electrode in the spinal cord was placed within 1 cm caudad from the tip of the subarachnoid catheter. A silver/silver chloride electrode (Disk type, UHE-001), placed subcutaneously in the animal's back, was used as a reference electrode. The two platinum electrodes were connected to a hydrogen detecting system (Head; Unique Medical, UH meter, PHG-201) and a recorder (Unicorder™, U-626 DS). Then, the inspired halothane concentration was decreased and maintained at 0.5% with oxygen and air through a modified Ayre's T-tube throughout the study; the end-tidal halothane concentration, measured by a calibrated mass spectrometer, was 0.26 ± 0.07% (mean ± 1 SD). Body temperature was monitored by a nasopharyngeal probe and was kept constant at 36.8 ± 0.4°C with a heating pad. Serum electrolytes were maintained within normal limits, and sodium bicarbonate was given as needed to maintain a normal buffer base.

Cerebral and spinal cord blood flows were measured by the hydrogen clearance method[18] in the following manner: Hydrogen gas, approximately 10%, was added to the inspired gas for 4 min. After cessation of hydrogen inhalation, the "wash out" curve of hydrogen was recorded through the appropriate amplifier circuit. Cerebral and spinal cord blood flows were calculated by dividing 69.3 by the half time for desaturation in minutes.[9,18]

The control measurements of CBF, SCBF, HR, MAP, and arterial blood gases were taken 2 h after the decrease in the inspired halothane concentration. In 42 dogs, 1 ml of lidocaine (1, 2, 3, or 5%) or 1 ml of phenylephrine (0.1, 0.2, 0.3, or 0.5%) then was injected into the subarachnoid space, and the measurements were repeated 30 min later. The 1 and 2% solutions of lidocaine were obtained by dilution of 3% lidocaine hydrochloride (in 7.5% dextrose solution, Fujisawa Co., Tokyo), and the 5% solution was made by dissolving crystalloid lidocaine HCl in 7.5 dextrose solution. The lower concentrations of phenylephrine were obtained by diluting the 0.5% phenylephrine with 5% dextrose in water. Ten animals that were given lidocaine more than 2 h previously also were used for the phenylephrine study. In 18 of the 42 dogs, the subarachnoid administration of 5 or 7.5% dextrose in water preceded or followed the injection of either drug. In five animals, a mixture of lidocaine, 24 mg (0.8 ml of 3% solution), and phenylephrine, 1 mg (0.2 ml of 0.5% solution), was injected into the subarachnoid space. The *p*H values for each solution are listed in table 1.

TABLE 1. The Concentration and *p*H Value of Each Solution Tested

Solution	Concentration	*p*H
Dextrose in water	5%	5.64–6.56
	7.5%	5.39–5.73
Lidocaine		
1%	10 mg/ml	6.24–6.28
2%	20 mg/ml	6.25–6.29
3%	30 mg/ml	6.28–6.29
5%	50 mg/ml	5.80–6.31
Phenylephrine		
0.1%	1 mg/ml	5.84–6.00
0.2%	2 mg/ml	5.76–5.95
0.3%	3 mg/ml	5.71–5.81
0.5%	5 mg/ml	5.55–5.65
Lidocaine plus phenylephrine	24 mg + 1 mg/ml	6.25–6.28

STATISTICS

Data were reported as mean ± 1 SD. Significant differences among control values were determined by analysis of variance for multiple comparisons followed by Student's *t* test for paired data within each group, assuming $P < 0.05$ to be statistically significant.

Results

The mean control values for SCBF and CBF were 22.4 ± 79 ml·100 g^{-1}·min^{-1} and 53.1 ± 12.0 ml·100 g^{-1}·min^{-1}, respectively. There were no significant differences in control values for MAP, HR, and blood gases

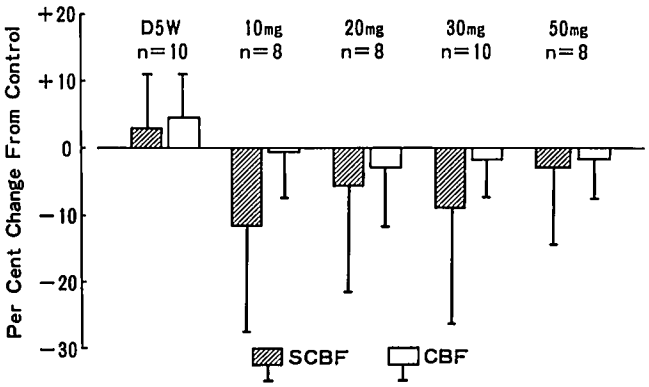

FIG. 1. Percentage changes of SCBF and CBF from control following the subarachnoid administration of lidocaine solutions (1 ml; 1, 2, 3 and 5%) and 5% dextrose solution in water. Vertical bars indicate 1 SD.

TABLE 2. Effects of Subarachnoid Lidocaine on Spinal Cord Blood Flow (SCBF, ml · 100 g^{-1} · min^{-1}) Cerebral Blood Flow (CBF, ml · 100 g^{-1} · min^{-1}) Mean Arterial Pressure (MAP, mmHg), Heart Rate (HR, bpm), and Mean Values of Blood Gas Analyses (BGA) during Measurements

Lidocaine	Control				After Subarachnoid Adm.				BGA			
	SCBF	CBF	MAP	HR	SCBF	CBF	MAP	HR	$P_{a_{O_2}}$ (mmHg)	$P_{a_{CO_2}}$ (mmHg)	pH_a	BE (mEq/l)
1% n = 8	21.8 ± 11.8	52.7 ± 15.8	127 ± 16	110 ± 16	19.3 ± 10.3	50.3 ± 12.7	107 ± 21*	98 ± 22	220 ± 37	36.4 ± 1.7	7.374 ± 0.001	−2.9 ± 1.8
2% n = 8	20.1 ± 8.2	47.9 ± 19.8	113 ± 21	98 ± 27	18.5 ± 7.7	47.0 ± 20.8	93 ± 21*	86 ± 23*	252 ± 50	36.7 ± 2.4	7.389 ± 0.023	−2.4 ± 1.3
3% n = 10	24.4 ± 9.9	54.1 ± 21.6	108 ± 17	108 ± 28	22.0 ± 6.5	53.5 ± 21.0	92 ± 15*	95 ± 18	222 ± 45	37.3 ± 2.7	7.375 ± 0.030	−3.2 ± 1.9
5% n = 8	23.0 ± 5.4	50.1 ± 12.1	122 ± 16	121 ± 25	22.5 ± 6.7	48.4 ± 11.3	97 ± 21†	106 ± 28*	234 ± 57	36.4 ± 2.1	7.410 ± 0.033	−2.4 ± 0.8

Values are mean ± SD.
* $P < 0.05$ *vs.* control.
† $P < 0.01$ *vs.* control.

among the three groups. The subarachnoid administration of 5% dextrose in water did not cause noticeable changes in either SCBF or CBF (the mean values of these were 23.7 ± 9.3 ml · 100 g^{-1} · min^{-1} and 49.8 ± 16.4 ml · 100 g^{-1} · min^{-1} during control, and 24.1 ± 8.6 and 51.6 ± 16.1 ml · 100 g^{-1} · min^{-1} following the 5% dextrose in water, respectively). Similarly, SCBF and CBF remained unchanged following the subarachnoid administration of 7.5% dextrose in water in eight dogs; 23.7 ± 5.7 and 45.1 ± 6.4 ml · 100 g^{-1} · min^{-1} during control and 23.4 ± 6.1 and 48.3 ± 8.3 ml · 100 g^{-1} · min after the administration, respectively. In addition, neither MAP nor HR changed following subarachnoid 5 and 7.5% dextrose in water. The administration of lidocaine or phenylephrine caused some changes in MAP and HR, especially in MAP within a few minutes following lidocaine. After MAP and HR became stable, measurements were taken (20–30 min following the administration of the drugs).

Effects of Subarachnoid Lidocaine on SCBF and CBF

The subarachnoid administration of lidocaine, 1 ml, at various concentrations, produced no significant changes in SCBF (fig. 1, table 2). The variation in CBF following subarachnoid lidocaine was insignificant and remained within ±12% of control in all animals (−3.3 ± 5.4%, n = 34).

The values for MAP following lidocaine were lower than those during control at all lidocaine concentrations (table 2, $P < 0.05$), but MAP remained above 80 mmHg in all dogs. No correlation between the changes in SCBF and changes in MAP was found.

Effects of Subarachnoid Phenylephrine on SCBF and CBF

The subarachnoid administration of phenylephrine caused insignificant changes in SCBF at 0.1% but produced significant decreases in SCBF at the greater concentrations (fig. 2, table 3). CBF remained constant following the subarachnoid phenylephrine at all concentrations. Although a dose relationship is suggested by figure 2, there was no statistically significant difference in per cent decreases in SCBF among the three phenylephrine solutions (0.2, 0.3, and 0.5%).

Minimal changes in MAP and HR were observed 10–20 min following subarachnoid phenylephrine in some dogs, especially when high concentrations were used, but these changes were not statistically significant.

Effects of Subarachnoid Lidocaine and Phenylephrine in a Combination on SCBF and CBF

Subarachnoid administration of lidocaine (24 mg) and phenylephrine (1 mg) in combination caused decreases

in SCBF without significant changes in CBF in all five dogs studied. These decreases in SCBF returned to control values 60–90 min later (fig. 3). MAP decreased transiently but was controlled at the same level as preadministration values by fluid administration before the measurements were made.

Discussion

The striking observation in the present study is that subarachnoid lidocaine did not produce significant alterations in the spinal cord blood flow. Intravenous lidocaine has been shown to decrease intracranial pressure in humans[19,20] as well as CBF in animals.[12,13] Thus lidocaine, even at clinical doses, should produce some decrease in CBF and possibly a decrease in SCBF as well. Furthermore, lidocaine has been shown by Usubiaga *et al.*[21] to appear in CSF rapidly following intravenous administration, the CSF/plasma ratio reaching 0.9 within 20 min. Therefore, we expected to observe that subarachnoid lidocaine would produce a significant decrease in SCBF. However, we did not realize this expectation. Possibly the biologic barrier formed by the lipid endothelial lining of the neuraxial capillaries[22] could account for the discrepancy between intravenous and subarachnoid administration of lidocaine.

In theory, the subarachnoid administration of lidocaine could affect SCBF in at least five different ways: 1) a direct action on the vascular smooth muscle of the spinal cord; 2) a direct action on the innervating autonomic nerves of the spinal cord *per se;* 3) a systemic action by a pharmacologically active plasma concentration achieved by local absorption; 4) a direct supraspinal action by ascent of the drug through the CSF circulation; and 5) passive effects due to altered systemic hemodynamics and decreased metabolic demands secondary to spinal anesthesia. Subarachnoid administration of lidocaine is not free of pharmacologic systemic effects.[23] We reasoned that, if a pharmacologically effective plasma concentration of the drug were achieved or if direct supraspinal action by ascent of the drug occurred, the CBF, which presumably is more sensitive than SCBF, should be affected. Since there were no noticeable changes in CBF, the effects of those two factors on SCBF might be negligible. In addition, despite a significant decrease in MAP during spinal anesthesia, CBF remained unchanged in the present study as was reported previously.[24] Therefore, the subarachnoid administration of lidocaine only could affect SCBF either by a direct action on vascular smooth muscle or on the innervating autonomic nerves of the spinal cord, or both.

No study concerning direct actions of lidocaine on vascular smooth muscle of spinal cord has been reported. Recently, Altura and Lassoff[25] examined the effect of local application of lidocaine on pial terminal arterioles of rat brain by means of a direct *in situ* microcirculatory

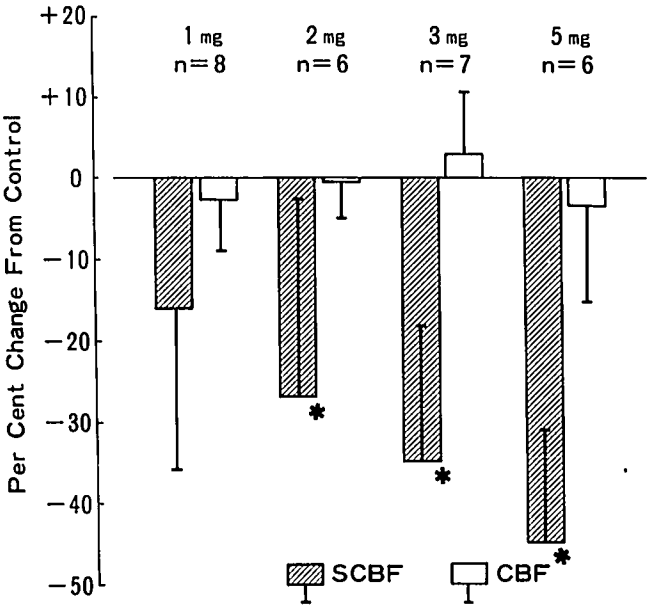

FIG. 2. Percentage changes of SCBF and CBF from control following the subarachnoid administration of phenylephrine (1 ml; 0.1, 0.2, 0.3, and 0.5% solution). Vertical bars indicate 1 SD. *Difference from control statistically significant $P < 0.05$.

study and observed significant dose-dependent dilation (15.7–45.3%). They attributed this to lidocaine's direct action on the cerebral arteriolar vascular smooth muscle cell. The pial vessels of brain, however, have dense adrenergic and cholinergic innervation, which may play an important role in autoregulation mechanisms of CBF.[26–28] Therefore, although the resting sympathetic tone of cerebral vessels must be minimal,[28–30] one cannot exclude the possibility that blockade of the innervating autonomic nerves of cerebral vessels might have affected the results of their study. Indeed, blockade of the preganglionic sympathetics with lidocaine has been reported to increase local cerebral blood flow[31] and cerebral blood volume.[32,33]

Similar to cerebral vessels, spinal cord vessels also have extensive sympathetic innervation.[7] There have been a few studies concerning the effects on SCBF of sympathetic nervous system blockade at various sites: adrenergic receptor sites,[6] peripheral sympathetic ganglia,[34] or the effects of separation of the spinal cord from central hypothalamic control of the sympathetic nervous system.[5] Kobrine *et al.*[6] reported that in monkeys with phenoxybenzamine blocked α-adrenergic receptors, SCBF varied linearly with changes in MAP, suggesting a dominant role of the sympathetic nervous system in control of SCBF. Their previous study showed that spinal cord autoregulation remained intact after high cervical cord section.[5] In cats with paravertebral sympathectomy, Young *et al.*[34] found that SCBF autoregulation was impaired and sympathectomy *per se* seemed to decrease SCBF. However,

TABLE 3. Mean Values (±SD) of Spinal Cord Blood Flow (SCBF, ml·100 g^{-1}·min^{-1}), Cerebral Blood Flow (CBF, ml·100 g^{-1}·min^{-1}), Mean Arterial Pressure (mmHg) and Heart Rate (HR, bpm) during Control and after Subarachnoid Phenylephrine, and Blood Gas Analyses (BAG) during Measurements.

Phenylephrine	Control				After Phenylephrine Adm.				BGA			
	SCBF	CBF	MAP	HR	SCBF	CBF	MAP	HR	Pa_{O_2} (mmHg)	Pa_{CO_2} (mmHg)	pH_a	BE (mEq/l)
0.1% n = 8	21.8 ± 13.2	57.7 ± 13.8	110 ± 15	113 ± 21	18.4 ± 9.0	60.2 ± 14.2	124 ± 17	107 ± 16	223 ± 41	37.7 ± 2.5	7.400 ± 0.019	−2.1 ± 1.2
0.2% n = 6	20.9 ± 13.8	51.0 ± 19.7	116 ± 11	114 ± 17	13.8 ± 11.7*	50.3 ± 19.7	127 ± 15	103 ± 17	214 ± 19	36.2 ± 2.4	7.399 ± 0.043	−1.9 ± 1.9
0.3% n = 7	19.8 ± 10.1	47.7 ± 18.0	98 ± 17	103 ± 20	14.0 ± 4.2*	49.0 ± 18.5	108 ± 21	90 ± 29	240 ± 42	37.2 ± 2.1	7.369 ± 0.029	−2.8 ± 3.2
0.5% n = 6	22.3 ± 8.5	55.6 ± 29	116 ± 18	100 ± 24	11.7 ± 6.0*	50.3 ± 21	125 ± 18	105 ± 17	225 ± 69	37.0 ± 3.4	7.374 ± 0.022	−3.0 ± 2.0

Values are mean ± SD.
* $P < 0.05$ *vs.* control.

none of these results can be compared directly with the results of the present study for the following reasons: First, the transection of spinal cord could alter the direction of blood flow in spinal cord arteries[35] and may not block peripheral sympathetic fibers to the spinal cord by way of paravertebral sympathetic ganglia.[36] Secondly, blockade of paravertebral sympathetic ganglia cannot provide blockade of all sympathetic fibers to spinal cord vessels; the central sympathetic fibers alongside the anterior and posterior spinal arteries branching from the vertebral arteries remain intact, as well as possible other neural control systems to the spinal cord.

In our study, using spinal anesthesia, all of the above sites mentioned were blocked by subarachnoid lidocaine at the regional cord level. In addition, we used halothane for background anesthesia; although this agent should provide stable central nervous system circulation,[37] it may influence the vascular reactivity of spinal cord by the reduction of central sympathetic and vagal outflow.[38] Furthermore, though the role of the sympathetic nervous system in the regulation of CBF during hypotension appears to be minimal,[28,39] the significant decrease in MAP following the subarachnoid lidocaine might have affected SCBF in the present study. Nevertheless, our results suggest that the resting sympathetic tone of spinal cord vessels may be minimal and that lidocaine, *per se,* or acute preganglionic sympathectomy induced by spinal anesthesia has little or no effect on SCBF.

Phenylephrine has been shown to not decrease internal carotid flow, despite dose-dependent decreases in common carotid arterial flow.[40,41] When phenylephrine is applied to isolated pial arteries of brain, it causes constriction in a dose-dependent manner.[42,43] Although the arteries supplying blood to spinal cord, like intracranial arteries,[43] may be less reactive to vasopressor agents,[44] SCBF and spinal cord vessels have been reported to be affected by intraarterial[45] and perivascular (spinal pial arterial) administration[46] of norepinephrine, respectively. Accordingly, the dose-related decreases in SCBF following subarachnoid phenylephrine apparently result from direct vasoconstriction of the spinal cord vessels. The practice of adding a vasopressor to local anesthetic solutions has been proposed as a possible cause of spinal cord ischemia.[47,48] The effects we have shown with lidocaine (24 mg) and phenylephrine (1 mg) in combination on SCBF may provide some experimental support for this proposal. A plausible explanation for this interaction may be due to the fact that lidocaine potentiates the responses of vascular smooth muscle to catecholamine.[49]

All the solutions employed in the present study were acidic, and the cerebrospinal fluid is poorly buffered.[27] The low pH of the solution might influence directly vessels of the spinal cord.[46] Metabolic changes in blood *p*H over physiologic range have, however, very little, if any, effect

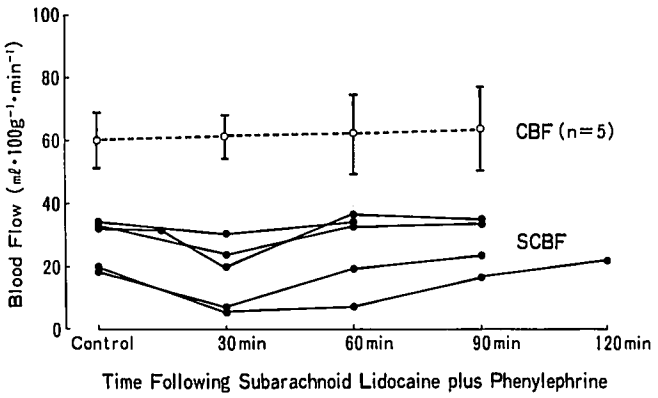

FIG. 3. Time course of changes in SCBF and CBF following the subarachnoid administration of lidocaine (24 mg) and phenylephrine (1 mg) in combination. Vertical bars indicate 1 SD.

on CBF because of slow transmission of hydrogen ions across the blood–brain barrier, indicating that brain tissue *p*H is sheltered from the effect of acute change in blood *p*H.[50] On the other hand, the *p*H of the extracellular fluid of the brain has a major influence on controlling the vascular tone of the smooth muscle of small arteries and arterioles in the brain.[27,50] Changes in the spinal cord vessels associated with *p*H of the extracellular fluid are presumably similar to those of brain, namely decreasing CSF *p*H by the acidic solution should increase SCBF. However, since we observed a decrease in SCBF, we can preclude the possibility of an important effect induced by the *p*H of the solutions on the results of the present study. Therefore, the decrease of SCBF produced by phenylephrine alone or by its combination with lidocaine can be accounted for by the local pharmacologic action of phenylephrine on spinal cord vessels.

We thus conclude that in spinal anesthesia with lidocaine the local spinal cord blood flow is not affected significantly. In contrast, phenylephrine does have a significant effect when added to the local anesthetic solution or alone.

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