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Cerebral Blood Flow and Somatosensory Evoked Potentials in Dogs with Experimental Vasospasm Caused by Double Injection

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Introduction

An extensive research has been carried out on cerebral blood flow (CBF), electroencephalography (EEG), or somatosensory evoked potentials (SEPs) in patients with subarachnoid hemorrhage[12,14,20,23]. Many kinds of experimental models of cerebral vasospasm have also been reported[6,8,15,16,19]. However, the models suitable for studying physiological aspects of cerebral circulation and metabolism are scarce. As a cisternal injection of autologous blood seems to be a simple maneuver similar to a spontaneous subarachnoid hemorrhage (SAH) in humans, we studied in this experiments whether or not the double injection model in dogs is suitable for further physiologic and pharmacologic studies of cerebral blood flow and metabolism.

Materials and Methods

Experiments were conducted with strict adherence to the *Standards of Animal Experiment and Animal Care* of our institution.

Thirty mongrel dogs of either sex weighing 10 to 16 kg were used. They were divided into 4 groups. Ten dogs of Group A served as control animals. In Group B, 10 dogs were anesthetized with an intramuscular administration of 20 mg/kg of ketamine hydrochloride (Ketalar®, Sankyo, Tokyo). Seven ml of cerebrospinal fluid was removed by a cisternal puncture and thereafter 7 ml of fresh autologous arterial blood was injected into the cisterna magna under fluoroscopic control (day 0). On day 2, the dogs were similarly anesthetized, and 3 ml of autologous blood was injected into the cisterna magna without removal of cerebrospinal fluid. In Group C, 5 dogs were anesthetized in the same manner, and bilateral common carotid arteries were exposed via a longitudinal ventral cervical incision and ligated. In 5 dogs comprising Group D, bilateral common carotid arteries were ligated as in Group C, and a cisternal injection of 7 ml of autologous blood was carried out 7 days later (day 0), followed by a second intracisternal injection of 3 ml of blood after another 2 days, as in Group B.

Measurement of rCBF and SEPs

Measurements were performed 7 days after the second intracisternal injection of blood in

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索引語：体性感覚誘発電位，局所脳血流量，低血圧，高炭酸ガス，脳血流量，脳血管攣縮.
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Table 1 Stimulation and recording parameters for SEPs.

Stimulation	
Site	: right median nerve
Duration	0.2 msec
Intensity	25 volts
Rate	5 Hz
Electrode	steel needle
Recording	
Montage	: Fz-C2, Fz-Cs (left sensory cortex)
Electrode	: silver ball
Sweep time	50 msec
Repetition	: 256 (×2～4)
Band pass	32 Hz～1.6 kHz

Groups B and D, and 14 days after carotid ligation in Group C.

Anesthesia was induced with an intramuscular administration of 20 mg/kg of ketamine, and the sites of surgical manipulation were infiltrated with 1% lidocaine (Xylocaine®, Fujisawa, Osaka). Animals were immobilized with an intravenous injection of 0.08 mg/kg/hour of pancuronium bromide (Mioblock®, Sankyo, Tokyo) after an endotracheal intubation via a tracheostomy, and ventilation was maintained on a respirator (Harvard respirator model 613, Harvard, South Natick, Ma.) to keep PaO_2 at ca. 100 mmHg and $PaCO_2$ at ca. 35 mmHg.

Left femoral artery and vein were cannulated for continuous monitoring of arterial blood pressure and fluid administration, respectively. Mean arterial pressure (MAP) was calculated as diastolic pressure+1/3 pulse pressure. Measurements of regional CBF (rCBF) with a hydrogen clearance method[3,5,13] were performed in; (1) right sensory cortex, (2) right thalamus, (3) brainstem, and (4) cerebellar vermis.

SEPs were recorded with silver ball electrodes placed epidurally on the right sensory cortex and

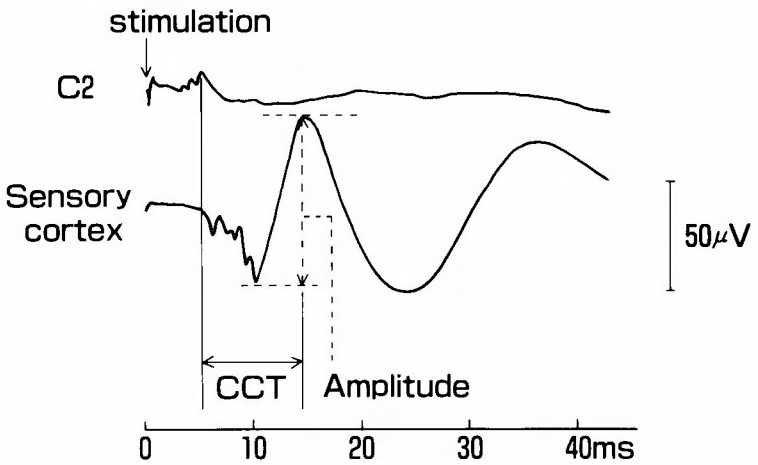

Fig. 1 Measurements of SEPs. Central conduction time (CCT) was defined as an interpeak latency between maximal negative cervical peak and first negative cortical potential. Amplitude was measured from maximal positive deflection to maximal negative deflection of initial cortical response.

over the second cervical spinous process. Left median nerve was stimulated at elbow (Table 1), and the central conduction time (CCT) and amplitude were measured as shown in Figure 1.

In each group, rCBF, SEPs, and several physiologic parameters were determined in the following five experimental conditions in sequence; (1) Control I, (2) Hypercapnia induced by 5% CO_2 inhalation, (3) Control II, (4) Hypotension I, and (5) Hypotension II. Hypotension was induced by a continuous intravenous infusion of trimetaphan camsilate (Arfonad®, Japan Roche, Tokyo) at a rate of 6.4 to 36.8 mg/kg/hour. When a sufficient decrease in blood pressure could not be attained, exsanguination was added. Measurements of rCBF and SEPs were carried out when the MAP was stabilized at the desired levels for 5 minutes. Body temperature was monitored by a oropharyngeal thermistor probe and maintained at about 37°C by use of a heating blanket.

Results

rCBF

There was no significant differences in $PaCO_2$ values between Groups A and B, and between Groups C and D, at each sequential experimental condition as summarized in Table 2.

At the experimental stages of *Control I* and *Control II*, rCBF values and SEP parameters did not differ significantly between Groups A and B or between Groups C and D.

During CO_2 inhalation (*Hypercapnia*), $PaCO_2$ increased from control values of 33.7～34.4 mmHg to 43.2～46.8 mmHg, in all groups A through D (Table 2). The rCBF increased significantly at all sites in Groups A and B, but only in the thalamus and cerebellum in Group C and in the cerebellum in Group D (Tables 4, 5, 6, & 7).

In the stage of *Hypotension I*, MABP was maintained at 70～71 mmHg (Table 3). The rCBF values showed a tendency to fall at all sites in every group. Statistically significant decrease in rCBF was noted in the sensory cortex and brainstem in Group A, in the sensory cortex, brainstem and cerebellum in Group B, and in the thalamus and cerebellum in Group D (Tables 4, 5, 6, & 7).

Table 2 Mean $PaCO_2$ values (Mean±SE, mmHg)

	n	Experimental conditions				
		Control I	Hypercapnia	Control II	Hypotension I	Hypotension II
Group A	10	34.4± 0.8	46.6± 1.2	33.8± 0.7	34.0± 1.6	32.9± 2.1
Group B	10	34.3± 0.5	46.8± 1.2	34.5± 0.7	36.4± 1.2	33.2± 1.6
Group C	5	34.0± 0.8	43.2± 2.0	31.9± 0.7	35.0± 2.5	29.4± 2.6
Group D	5	33.7± 1.2	45.9± 0.4	35.1± 1.6	32.2± 3.2	28.8± 1.8

Table 3 Mean arterial pressure changes (Mean± SE, mmHg)

	n	Experimental conditions				
		Control I	Hypercapnia	Control II	Hypotension I	Hypotension II
Group A	10	137.3± 3.4	139.3± 3.9	135.3± 3.5	70.0± 0.7	40.0± 1.0
Group B	10	128.1± 5.3	128.1± 4.5	125.7± 3.7	70.5± 0.5	39.5± 1.6
Group C	5	137.0± 8.0	146.0± 8.1	132.0± 9.0	71.0± 1.0	40.0± 0.0
Group D	5	147.0± 6.6	146.0± 6.2	140.0± 6.9	71.0± 1.0	41.0± 1.0

Table 4 rCBF and SEPs in Group A (Mean± SE)

	n	Experimental conditions				
		Control I	Hypercapnia	Control II	Hypotension I	Hypotension II
rCBF (ml/100 g brain/min)						
Cortex	10	52.5± 4.8	64.7± 6.1**	51.7± 4.6	46.6± 4.9*	39.1± 4.1***
Thalamus	10	50.4± 4.9	69.1± 8.0**	51.9± 4.6	49.6± 4.8	36.9± 4.2**
Brainstem	10	41.9± 5.8	53.4± 7.5**	43.6± 5.9	38.7± 4.9*	35.2± 4.2*
Cerebellum	9	45.9± 5.4	54.9± 6.5**	45.7± 5.4	37.8± 2.8	30.6± 2.2*
SEPs						
CCT (msec)	10	8.5± 0.2	8.6± 0.2	8.6± 0.2	8.9± 0.2*	10.1± 0.5*
Amplitude (μV)	10	56.7± 8.9	57.2± 8.9	62.5±10.1	63.4±10.0	44.1± 9.9*

*: $p<0.05$, **: $p<0.01$, ***: $p<0.001$ (Compared with the value of Control I in Hypercapnia, or Control II in Hypotension I or II, unpaired t-test)

Table 5 rCBF and SEPs in Group B (Mean± SE)

	n	Experimental conditions				
		Control I	Hypercapnia	Control II	Hypotension I	Hypotension II
rCBF (ml/100 g brain/min)						
Cortex	10	53.3± 4.5	64.5± 6.5***	55.0± 4.7	48.4± 5.3*	42.2± 4.8***
Thalamus	10	47.7± 5.5	65.0± 7.3*	47.9± 5.4	43.9± 5.4	32.8± 3.9**
Brainstem	9	40.6± 5.3	55.1± 5.5***	40.5± 5.0	37.8± 4.5*	30.6± 4.4*
Cerebellum	10	44.6± 4.6	51.3± 5.5**	46.3± 5.0	40.7± 4.0*	36.5± 4.2**
SEPs						
CCT (msec)	10	8.7± 0.3	8.7± 0.3	8.7± 0.2	9.3± 0.2**	10.6± 0.7**
Amplitude (μV)	10	53.7± 7.7	51.1± 7.3	49.3± 6.7	44.5± 8.6	38.8± 8.2*

*: $p<0.05$, **: $p<0.01$, ***: $p<0.001$ (Compared with the value of Control I in Hypercapnia, or Control II in Hypotension I or II, unpaired t-test).

Table 6 rCBF and SEPs in Group C (Mean± SE)

	n	Experimental conditions				
		Control I	Hypercapnia	Control II	Hypotension I	Hypotension II
rCBF (ml/100 g brain/min)						
Cortex	5	52.9± 8.3	65.2± 7.0	52.3± 7.9	34.8±10.3	27.2± 9.8*
Thalamus	5	40.4± 4.8	61.7± 5.7**	38.3± 3.6	34.3± 2.5	32.3± 2.5
Brainstem	5	50.1± 5.2	63.8± 6.9	49.4± 4.6	47.0± 4.7	39.7± 9.1
Cerebellum	5	47.6± 8.3	56.7±10.1*	45.1± 8.5	40.3±10.3	36.4± 8.2*
SEPs						
CCT (msec)	5	8.7± 0.7	8.7± 0.7	8.8± 0.7	10.1± 1.2	11.5± 1.2
Amplitude (μV)	5	55.7± 1.4	58.2± 1.1	58.1± 3.4	49.7± 5.2	29.4±14.0

*: $p<0.05$, **: $p<0.01$, ***: $p<0.001$ (Compared with the value of Control I in Hypercapnia, or Control II in Hypotension I or II, unpaired t-test).

Table 7 rCBF and SEPs in Group D (Mean± SE)

	n	Experimental conditions				
		Control I	Hypercapnia	Control II	Hypotension I	Hypotension II
rCBF (ml/100 g brain/min)						
Cortex	5	57.5± 4.7	57.7± 5.1	57.3± 5.2	37.6± 9.6	20.8± 7.6**
Thalamus	5	33.5± 3.9	36.6± 5.4	32.1± 5.1	24.7± 6.7*	23.2± 7.6
Brainstem	5	37.4± 4.8	52.6±16.5	40.2± 5.4	30.4± 7.8	31.7±10.3
Cerebellum	5	38.5± 3.4	40.4± 3.5*	38.0± 4.0	28.2± 3.5**	21.3± 0.7*
SEPs						
CCT (msec)	5	9.2± 0.4	9.2± 0.5	9.4± 0.3	10.0± 0.3*	12.1± 1.5
Amplitude (μV)	5	49.8± 8.4	49.1± 8.3	48.9±10.8	34.1± 9.3	21.6± 9.4

*: $p<0.05$, **: $p<0.01$, ***: $p<0.001$ (Compared with the value of Control I in Hypercapnia, or Control II in Hypotension I or II, unpaired t-test).

Table 8 Difference in rCBF or SEPs between Groups A and B.

	Experimental conditions				
	Control I	Hypercapnia	Control II	Hypotension I	Hypotension II
rCBF					
Cortex	N.S.	N.S.	N.S.	N.S.	N.S.
Thalamus	N.S.	N.S.	N.S.	N.S.	N.S.
Brainstem	N.S.	N.S.	N.S.	N.S.	N.S.
Cerebellum	N.S.	N.S.	N.S.	N.S.	N.S.
SEPs					
CCT	N.S.	N.S.	N.S.	N.S.	N.S.
Amplitude	N.S.	N.S.	N.S.	N.S.	N.S.

N.S.: No statistically significant difference between Groups A and B (Dunnett examination).

Table 9 Difference in rCBF or SEPs between Groups C and D

	Experimental conditions				
	Control I	Hypercapnia	Control II	Hypotension I	Hypotension II
rCBF					
Cortex	N.S.	N.S.	N.S.	N.S.	N.S.
Thalamus	N.S.	*	N.S.	N.S.	N.S.
Brainstem	N.S.	N.S.	N.S.	N.S.	N.S.
Cerebellum	N.S.	N.S.	N.S.	N.S.	N.S.
SEPs					
CCT	N.S.	N.S.	N.S.	N.S.	N.S.
Amplitude	N.S.	N.S.	N.S.	N.S.	N.S.

N.S.: No statistically significant difference between Groups C and D. *: $p<0.05$ (Dunnett examination).

When severe hypotension reaching 40 to 41 mmHg was induced (*Hypotension II*), rCBF significantly decreased at all sites in Groups A and B, in the sensory cortex and cerebellum in Group C, and in the sensory cortex, thalamus and cerebellum in Group D (Tables 3, 4, 5, 6, & 7).

SEPs

In the condition of *Control I*, CCT ranged from 8.5 to 9.2 msec in all Groups A through D (Tables 4, 5, 6, & 7). CCT was more or less elongated in Group D (9.2±0.4 msec) than in Groups A, B, & C. CCT remained unchanged after CO_2 inhalation (*Hypercapnia*) in either group. At the stage of *Hypotension I*, CCT was significantly prolonged in Groups A, B, and D. It also showed a tendency to prolong in Group C, but the difference did not reach the level of statistical significance.

At the stage of *Hypotension II*, CCT was significantly prolonged in Groups A and B. It showed a tendency to prolong, but the difference failed to reach the statistical significance in Groups C and D.

Amplitudes of SEPs ranged from 49.8 to 56.7 μV in the condition of *Control I*. Amplitudes were somewhat smaller in Group D, but the difference was statistically not significant. During CO_2 inhalation (*Hypercapnia*) and at the stage of *Hypotension I*, no significant change in amplitudes was observed in any of Groups A through D. Amplitudes decreased significantly, however, at the stage of *Hypotension II* in Groups A and B.

Further statistical analysis between Groups A and B, and between Groups C and D, were carried out. Dispersion of Groups A and B was uniform (Bartlett examination) and there was no statistically significant differences between Groups A and B in any values of rCBF and SEPs (Dunnet examination). One value of SEPs did not show uniform dispersion between Groups C and D. No statistically signifincant difference between Groups C and D was found either, except for rCBF during hypercapnia. The rCBF in the thalamus was significantly higher in Group C than in Group D during hypercapnia (Tables 8 & 9).

Discussion

"Double injection method" has been established as an experimental model of subarachnoid hemorrhage leading to cerebral vasospasm[2,6,15,16,21], and many pharmacological, pathological and pathophysiological studies have been reported using this animal model[7,15,16]. Using double injection technique in dogs, SAITO and NAKAZAWA[15] reported that the caliber of the basilar artery decreased by 46.4±3.0% one week after the second injection and thereafter the caliber gradually restored to normal in 2 to 3 weeks. Such a time course of vasoconstriction is in good accordance with that seen in clinical vasospasm in patients with subarachnoid hemorrhage. A report on the sequential morphological changes of the artery rendered spastic by double subarachnoid injection of autologous blood is currently being prepared (NAKAZAWA, in preparation). The purpose of the present experiment is to clarify whether such a double injection model in dogs developing spasm of the basilar artery shows any derrangements of cerebral blood flow and flow reactivity, or of electrophysiological parameters such as SEPs.

In the present study, systemic blood pressure and $PaCO_2$ did not differ significantly among 4 experimental groups. The rCBF measured in 4 regions was not affected at all by either double injection (Group B), bilateral carotid ligation (Group C), or bilateral carotid ligation plus double injection (Group D). Normal CO_2 reactivity of CBF was well maintained in Group B animals (double injection without carotid ligation), suggesting that double injection of blood and resultant vasoconstriction of the basilar artery did not affect CO_2 reactivity, either. When bilateral carotid arteries were ligated with or without following double injection of the blood, poor CO_2 response was seen in some regions (Groups C and D).

Using middle cerebral artery occlusion model in cats, NAKAGAWA[10] showed that a stasis of blood

stores CO_2 in the tissue around arterioles and makes vessels continuously dilated, and therefore that the hypercapnia cannot cause further dilatation of the vessels. SHIMA[18] speculated that under normocapnia an increased basilar flow following bilateral common carotid artery occlusion might compensate a decrease in the total CBF due to carotid occlusion, however, a compensatory rise in the basilar flow under hypercapnia might not be enough to supply the dilated vascular beds in the carotid and basilar territories.

MELDRUM et al[11] induced a severe hypotension reaching the MAP of 25 mmHg by trimetaphan in monkeys. Following 30 minutes' hypotensive period, absence or a marked reduction of amplitude in SEPs was observed[11]. WIEDERHOLT et al[24] observed that, EEG activity flattened or disappeared when the MAP of 30 to 40 mmHg was obtained by trimetaphan in dogs. ARTRU[1] reported that, when hypotension was induced by trimetaphan in dogs, cerebral blood flow started to decrease at the MAP of 70 mmHg, and metabolic rate of oxygen was disturbed at the MAP of 40 mmHg. A lower limit of autoregulation is in general thought to be 50 to 70 mmHg in animals without subarachnoid hemorrhage[4].

Under a mild hypotension around 70 mmHg of MAP in the study, rCBF showed a decrease in all groups, but a decrease of rCBF in Group C was statistically not significant at any sites. Under a severe hypotension (MAP=40 mmHg), a significant decrease of rCBF was observed in all regions in Groups A and B, and in the cerebral cortex and cerebellum in Groups C and D. A decrease in CBF failed to reach a level of statistical significance in other regions, probably because of a small number of animals studied. In our study, rCBF in the brainstem was least affected by hypotension.

CO_2 inhalation caused generalized increase in rCBF, but it did not affect SEPs. A decrease in rCBF during induced hypotension showed a tendency to elongate the CCT and to decrease the amplitude of SEPs. Amplitudes of SEPs differed significantly among animals so that the significance of absolute values is difficult to evaluate. The CCTs, in contrast, were rather constant and uniform among animals, and their changes correlated well with a change of rCBF, particularly that in the sensory cortex.

KAPLAN et al[7] demonstrated that in the canine double injection model an induced hypotension at the MAP of 40 mmHg caused no changes in SEPs, auditory evoked potentials, and focal neurologic abnormalities. ROSENSTEIN[14] described a relationship between hemispheric CBF and CCT in patients with aneurysmal subarachnoid hemorrhage. He reported that CCT tended to become increasingly prolonged in association with a gradual deterioration of clinical conditions of the patients. From these and other results, it seems that the important factors which affect EEG or SEPs are: degree of a decrease in CBF, severity and duration of hypotension, method of induction and maintenance of hypotension, state of autoregulation, presence or absence of metabolic acidosis, and others[1,11,17,24].

In our study, there was no difference in rCBF and SEPs between Groups A and B at any conditions (*Control I, Hypercapnia, Control II, Hypotension I, and Hypotension II*). It is apparent therefore that, although a double injection of autologous blood causes a marked constriction of the basilar artery 7 days later, it does not result in a significant reduction of rCBF, prolongation of CCT, or changes in reactivity of CBF against hypercapnia or hypotension. It seems therefore that a double injection method in dogs is not a satisfactory experimental model of vasospasm, as far as further studies on cerebral blood flow and metabolism, or electrophysiological ones are considered.

Similarly, SWIFT[22] measured rCBF by [^{14}C]butanol indicator fractionation technique in single injection SAH model of rats. He found that cerebral blood flow was significantly decreased 3 hours

after an injection. However, CBF returned to control levels by 24 hours after an injection, and it failed to show any delayed decrease up to 14 days after SAH. He stressed that rats had extensive collateral pathways and that the vascular networks of rats were more primitive and therefore might be more resilient to mild insults such as SAH. SUGIYAMA[21] reported that a maximal decrease of rCBF was about 20 to 30% in double injection model in dogs. The rCBF was maintained above 33 to 40 ml/100 g brain/min and CCT failed to change despite an apparent reduction in angiographic arterial caliber. Well developed cerebral collateral pathways in dogs probably explain this[9]. Furthermore, CSF circulation is relatively well maintained in those experimental animals because of anatomically simple cisternal structures[16], and it is stressed by SUGIYAMA[21] that in sharp contrast to the case of aneurysmal rupture in humans, a relatively mild increase in the intracranial pressure or a mild brain damage due to autologous blood injection into the cisterns hardly causes an impairment of function of hypothalamus or brainstem in experimental animals.

In order to restrict the collateral circulation to the brain, we added bilateral common carotid occlusion in the neck (Groups C and D). ENDO et al[2] similarly reported a study of symptomatic vasospasm model in rabbits with bilateral carotid artery ligation followed by an experimental induction of SAH (double injection method). Unfortunately in the present study, no difference between Groups C and D was observed in rCBF or SEPs at either a control condition or a stage of hypotension. Even after an interruption of bilateral carotid artery flow in the neck, vasoconstriction by a double injection method in dogs failed to cause changes in rCBF or SEPs. Dogs in Group D, namely those underwent bilateral carotid ligation followed by double injection of autologous blood, did not serve as an animal model of vasospasm to be used for physiological studies. SASAKI[16] also stated that there was no vasospasm model acceptable for everybody, and that it was important to recognize the character of each experimental model and select the model adequate for the purpose of each experiment.

In conclusion, a double injection model in dog develops a marked constriction of the basilar artery that is most prominent 7 days after the second injection[15]. Although such a time course of vasoconstriction is comparable to that of angiographic vasospasm in patients with SAH, significant reduction in rCBF, derrangements of flow reactivity against changes in $PaCO_2$ or blood pressure, or changes in SEPs were not observed in this model. An additional ligation of bilateral carotid arteries in the neck also failed to provide the animal model suitable for further physiological studies.

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和文抄録

大槽内二回注入法によるイヌ脳血管攣縮モデルにおける脳血流量および体性感覚誘発電位

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大槽内二回注入法における実験的脳血管攣縮モデルを雑種成犬を用いて作製し，二酸化炭素負荷あるいは低血圧負荷時の局所脳血流量 (rCBF) 及び体性感覚誘発電位 (SEPs) について検討した．二酸化炭素負荷時には rCBF は有意に増加したが，SEPs は変化しなかった．平均血圧を 70 mmHg とした低血圧下では，脳血管攣縮モデルで，同側頭頂葉皮質，脳幹，小脳で rCBF は減少し，SEPs 変化も見られた．平均血圧を 40 mmHg とした低血圧下では，すべての部位で rCBF 減少及び SEPs 変化が見られたが，control 群と血管攣縮モデル群との間に有意差はなかった．側副血行路を介しての血流供給が，両群に有意差が得られなかった主な原因と考え，これを減少させるために両側総頸動脈の結紮をクモ膜下出血作製 7 日前に加えた．しかしながら，大槽内二回注入法に両側総頸動脈閉塞を加えた群と，両側総頸動脈閉塞群 (control) との間にも有意差はなかった．本モデルでは血管撮影上，脳底動脈の直径減少や，電子顕微鏡上微細構造変化が認められているが，側副血行路，髄液動態がヒトとは異なり，また臨床例のような出血による直接損傷がないことが症候性の血管攣縮とならなかった原因と考えられた．