Time course of the impairment of cerebral autoregulation during chronic cerebral vasospasm after subarachnoid hemorrhage in primates

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The time course of the impairment of cerebral autoregulation during chronic cerebral vasospasm after subarachnoid hemorrhage was studied in 18 monkeys. Changes in cerebral blood flow (CBF) at the regional level and central conduction times during either graded hypotension or hypertension were evaluated in these animals at three stages (3, 7, and 14 days) following the introduction of an autologous blood clot around the right middle cerebral artery (MCA). Angiograms revealed a reduction in vessel caliber (compared to the baseline level in the involved MCA) of 30% at 3 days, 50% at 7 days, and 10% at 14 days. At all stages, CBF remained constant at mean arterial blood pressures (MABP) of 60 to 160 mm Hg in the noninvolved hemisphere. In contrast, at the 3- and 7-day stages, there was an impairment of autoregulation in the involved hemisphere at MABP of 40 to 180 mm Hg. The right hemispheric CBF was significantly (p < 0.05) lower than that in the left throughout the period of investigation at MABP below 120 mm Hg, but rose to exceed the left CBF at MABP above 180 mm Hg at the 7-day stage and 160 mm Hg at the 14-day stage. The right-sided central conduction time showed significant (p < 0.05) prolongation at MABP below 60 mm Hg at the 3-day stage and 40 mm Hg at the 7-day stage. It is suggested that these results may help to develop guidelines for hemodynamic therapy for vasospasm in its various stages.

KEY WORDS: autoregulation · vasospasm · subarachnoid hemorrhage · cynomolgus monkey

While many therapeutic methods have been developed in an attempt to prevent the development of cerebral vasospasm following subarachnoid hemorrhage (SAH), few have succeeded in producing a prophylactic effect on the appearance of neurological deficits due to cerebral vasospasm. Augmentation of the cerebral blood flow (CBF) by increasing the cerebral perfusion pressure via induced hypertension or hypervolemia (hemodynamic therapy) is the method most widely used. This therapeutic method is based on the theory that when vasospasm or after SAH, autoregulation of CBF is impaired and an increase in the cerebral perfusion pressure may increase CBF sufficiently to maintain brain function over the ischemic threshold. In addition to the risk of systemic complications, it is suggested that this therapy has a hazardous aspect leading to a worsened neurological condition due to the development of brain edema. Therefore, in order to establish guidelines on the appropriate utilization of hemodynamic therapy, some problems must be solved, including when the hemodynamic therapy should be started and how long and to what degree it should be continued during the time course of cerebral vasospasm. No studies have dealt expressly with these problems, and it is difficult to investigate them systematically in clinical cases for ethical reasons.

Our previous experimental study in primates demonstrated that cerebral autoregulation is greatly impaired when the severity of vasospasm is at its maximum. In order to solve the above problems in hemodynamic therapy, it is important to study how the time course of the impairment of autoregulation correlates with the time course of vasospasm and how it affects the electrical function of the brain during the various stages of vasospasm. In the present study, we examined the sequential changes in CBF and the somatosensory evoked potentials (SEP's) during either induced hypotension or hypertension of arterial blood pressure in the early stage (3 days after SAH), the maximum stage (7 days after SAH), or the stage of remission (14 days after SAH) in the primate vasospasm model. By evalu-
Materials and Methods

Animals and Experimental Protocol

Eighteen female cynomolgus monkeys (Macaca fascicularis), each weighing 2.2 to 2.8 kg (mean 2.5 kg), were used in this study. The animals were cared for in accordance with the Guidelines for Animal Experimentation of the Fukui Medical School. The primates were randomly divided into three groups of six animals each: a “3-day group,” a “7-day group,” and a “14-day group.” All animals underwent angiography to determine the baseline vessel caliber of the cerebral arteries before SAH, which was induced by clot placement methods described in previous studies. Neurological assessment was performed twice daily after SAH induction. Three days after induction of SAH, angiography was repeated in the 3-day group animals to evaluate the degree of cerebral vasospasm, and CBF and SEP’s were measured during the graded changes in mean arterial blood pressure (MAP) to evaluate cerebral autoregulation and the effect of the graded changes on the electrophysiological function of the brain. Repeat angiography followed by CBF and SEP studies was performed 7 days after SAH in the 7-day group and 14 days after SAH in the 14-day group. After CBF and SEP studies were completed, the animals were killed by exsanguination under deep anesthesia.

Cerebral Angiography

Anesthesia was maintained by intraperitoneal administration of sodium pentobarbital (10 mg/kg/hr) following an intramuscular injection of ketamine hydrochloride (7.5 mg/kg). The animals were intubated and ventilated mechanically with room air. The rate of ventilation was fixed at 25 breaths/min and end-tidal volume was controlled to maintain PaCO₂ between 38 and 39 mm Hg. The animals were paralyzed with intravenous administration of pancuronium bromide (0.05 mg/kg/hr). Body temperature was monitored via a rectal thermometer and maintained at about 37°C, using a heating pad beneath the animal during angiography and other experimental procedures.

A No. 4 French radiopaque polyethylene catheter was placed under fluoroscopic control in the right axial artery and connected to a three-way stopcock. One outlet was connected to a pressure transducer* to measure arterial blood pressure, while another was connected to an angiographic injector. An arterial phase antero-posterior cerebral angiogram was obtained by injecting 8 ml ioxaglate at a rate of 250 lb/sq in., as contrast medium. After angiography, immobilization of the animals was reversed by intravenous administration of prostigmine methylsulfate (0.07 mg/kg) and atropine sulfate (0.02 mg/kg).

Subarachnoid Hemorrhage Induction

The animals were anesthetized with an intravenous injection of sodium pentobarbital (20 mg/kg/hr) and paralyzed with an intravenous injection of pancuronium bromide (0.05 mg/kg/hr). Artificial ventilation maintained PaCO₂ at 30 to 32 mm Hg during the operation, which was performed with sterile technique. A right frontotemporal craniectomy was made. The sylvian fissure was split by sharp dissection and the arachnoid membrane was opened over the proximal portion of the middle cerebral artery (MCA), the internal carotid artery (ICA), the proximal portion of the anterior cerebral artery (ACA), and the posterior communicating artery. After sufficient aspiration of cerebrospinal fluid, the temporal lobe was retracted posteriorly, the Liquest's membrane was opened, and the arachnoid membrane covering the summit of the basilar artery and the proximal portion of the posterior cerebral artery was sectioned. In all of the animals, a presurgically prepared autologous blood clot (mean 2.4 gm) was placed around the exposed cerebral arteries. The dura mater was closed in a watertight manner with 7-0 silk sutures, the temporal muscle and skin were sutured in layers, and an antibiotic (Amycasin sulfonate, 5 mg) was instilled into the subcutaneous layer. Paralysis was reversed as mentioned above, and the animals were extubated after recovery of the gag reflex.

Immediately after the second angiogram, physiological parameters (body weight, MAP, PaCO₂, and body temperature) and the regional CBF and SEP’s were determined for the three groups. Sequential changes in CBF and SEP’s were recorded during the graded drug-induced alterations in MAPB. During these measurements, anesthesia and immobilization were continued. Care was taken to maintain PaCO₂ near 38.5 mm Hg and body temperature near 37°C.

Measurement of Cerebral Blood Flow

Regional CBF was measured by the hydrogen clearance technique. The head of the animal was fixed in a stereotactic frame and two small burr holes were made on the parietal skull bilaterally. Platinum needle electrodes, 0.3 mm in diameter, were inserted stereotactically through the burr holes and placed 20 mm laterally to the midline, 10 mm posterior to the coronal suture, and 3 mm below the surface of the cortex, positioned in the gray matter of the parietal lobe bilaterally. Hydrogen gas was administered via the endotracheal tube at a concentration of 10% for 1 minute. The clearance curve for the hydrogen concentration in the brain tissue was recorded, and the regional CBF value was calculated by the initial-slope method.

Measurement of Somatosensory Evoked Potentials

Reciprocal electrical stimulation of the median nerve was performed at bilateral portions of the wrist. Re-

* Pressure transducer, Model P-50, manufactured by Gould Statham, Oxnard, California.
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![Graph showing recordings of somatosensory evoked potentials (SEP) in a normal monkey. The median nerve was stimulated electrically at the wrist; cortical SEP were recorded at the scalp overlying the primary sensory cortex (Po) and the neck SEP at the C2 (C2) spinous process. The central conduction time (CCT) was calculated as the difference in the latencies between the N6 peak in the neck SEP and the N10 peak in the cortical SEP. Fpz = reference electrode in the forebrain; ms = milliseconds.]

Recording subcutaneous needle electrodes were placed over the C-2 spinous processes and in the scalp overlying the bilateral primary sensory cortex. The SEP waves were obtained from an average of 500 responses and were recorded simultaneously with the measurement of CBF at least four times. To evaluate the electrophysiological changes in the brain due to the alteration of MABP, the difference between latencies for the N6 peak in the neck SEP's and the N10 peak in the cortical SEP's was evaluated as the central conduction time (Fig. 1). All SEP measurements and recordings were performed on a multi-evoked potential recorder.†

Induced Hypertension or Hypotension

Changes in MABP were induced by the administration of either a pressor or a depressor drug. Arterial blood pressure was raised by intravenous infusion of metaraminol bitartrate dissolved in physiological saline (0.1 mg/ml); hypotension was induced by intravenous administration of trimethaphan camphor sulfonate dissolved in a 5% dextrose solution (2.5 mg/ml). The administration of the solution was performed by means of an infusion pump at a rate that maintained MABP at the required level following initial rapid infusion of the drug. More than 5 minutes was allowed for stabilization of the cerebrovascular response to changes in MABP before CBF and SEPs were measured. The MABP was controlled to range from 40 to 180 mm Hg in steps of 20 mm Hg.

Radiological Assessment

The diameters of the intracranial cerebral arteries were measured at six points (bilateral suprachrroidal portions of the ICA, bilateral proximal portions of the MCA, and bilateral proximal portions of the ACA) on angiograms obtained before SAH induction (Day 0) and on Day 3, Day 7, or Day 14 after SAH induction, depending on the group. Measurements were taken five times by a blind observer using a calibrated micrometer and then averaged. The percent reduction in caliber of the ICA, MCA, ACA, and combined value of the vessels (ICA + MCA + ACA) on the second angiogram compared to the baseline value before SAH was calculated for each animal. The mean reduction for each vessel and the combined value for all vessels were determined for the three groups.

Statistical Analysis

Student's t-test was used for statistical evaluation. A p value of less than 0.05 was regarded as statistically significant in the analysis of all data. Analysis of variance of the mean CBF and mean central conduction time was carried out for bilateral intergroup comparison.

Histopathological Studies

After CBF and SEP measurements had been completed for each group, the animals were deeply anesthetized with an intravenous injection of pentobarbital. The brains were perfused transcardially with physiological saline (500 ml) followed by a 4% paraformaldehyde fixative solution, then removed. The main cerebral arteries were dissected from the base of the brain, immersed in a 10% formaldehyde solution for 1 week, then dehydrated and embedded in wax. Sections of the cerebral vessels were stained with hematoxylin and eosin. In the present study, we examined the MCA's bilaterally to compare the groups.

Results

Neurological Deficit and Physiological Parameters

In the 3-day group, one of the monkeys died the day after SAH induction; the other five animals showed no evidence of neurological deficit or deterioration of consciousness. In the 7-day group, no animal showed a neurological deficit; however, one animal exhibited slight deterioration of consciousness from Day 4 to Day 7. In the 14-day group, one animal died immediately after the second angiography; the other five showed no neurological deficit, although one showed a slight disturbance of consciousness and reduction in activity and appetite from Day 3 to Day 10 with recovery on Day 11. There were no significant differences in the physiological parameters recorded before and after SAH induction. In addition, the physiological values and the weight of the autologous blood clot for SAH induction showed no significant differences among the three groups (Table 1).

† Multi-evoked potential recorder, Model MEN-4104, manufactured by Nihon Kohden, Tokyo, Japan.

‡ Calibrated micrometer manufactured by Teraoka, Osaka, Japan.
TABLE 1
Values for physiological parameters in 18 monkeys before and after SAH induction*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>3-Day Group</th>
<th>7-Day Group</th>
<th>14-Day Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of monkeys</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>body weight (kg)</td>
<td>2.5 ± 0.2</td>
<td>2.6 ± 0.3</td>
<td>2.4 ± 0.3</td>
</tr>
<tr>
<td>MABP (mm Hg)</td>
<td>120 ± 15.0</td>
<td>115 ± 15.0</td>
<td>114 ± 13.1</td>
</tr>
<tr>
<td>PaCO2 (mm Hg)</td>
<td>38.5 ± 0.4</td>
<td>38.7 ± 0.3</td>
<td>38.4 ± 0.5</td>
</tr>
<tr>
<td>body temperature (°C)</td>
<td>37.0 ± 0.1</td>
<td>37.1 ± 0.2</td>
<td>36.9 ± 0.3</td>
</tr>
<tr>
<td>CBF (ml/100 gm/min)†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>left</td>
<td>46.5 ± 9.8</td>
<td>54.5 ± 10.1</td>
<td>56.8 ± 12.5</td>
</tr>
<tr>
<td>right</td>
<td>26.5 ± 5.8§</td>
<td>36.2 ± 12.5§</td>
<td>42.8 ± 15.4</td>
</tr>
<tr>
<td>CCT (msec)†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>left</td>
<td>4.45 ± 0.11</td>
<td>4.33 ± 0.28</td>
<td>4.28 ± 0.32</td>
</tr>
<tr>
<td>right</td>
<td>4.52 ± 0.15</td>
<td>4.34 ± 0.26</td>
<td>4.26 ± 0.25</td>
</tr>
<tr>
<td>weight of clot (gm)‡</td>
<td>2.4 ± 0.3</td>
<td>2.4 ± 0.3</td>
<td>2.5 ± 0.2</td>
</tr>
</tbody>
</table>

* Values are expressed as means ± standard deviation. SAH = subarachnoid hemorrhage; MABP = mean arterial blood pressure; CBF = cerebral blood flow; CCT = central conduction time.
† Measurements of CBF and CCT were obtained after angiography before induced alterations of arterial blood pressure.
§ Weight of clot = the amount of autologous blood clot placed around the cerebral artery to induce SAH.
‡ Significant difference from the contralateral side: p < 0.01.
† Significant difference from the other groups: p < 0.05.

FIG. 2. Angiograms obtained before induction of subarachnoid hemorrhage (SAH) (Baseline, upper left), 3 days after SAH (Day 3, upper right), 7 days after SAH (Day 7, lower left), and 14 days after SAH (Day 14, lower right). The cerebral arteries in the clot (right) side showed mild vasospasm on Day 3, severe vasospasm (arrow) on Day 7, and the severity of vasospasm abated on Day 14.

Time Course of the Angiographic Vasospasm

The mean percent reduction in the vessel caliber of each cerebral artery and the combined value for the three groups (ICA + MCA + ACA) are shown in Table 2. The degrees of vasospasm were defined as: no vasospasm (10% reduction), mild vasospasm (11% to 30% reduction), moderate vasospasm (31% to 50% reduction), and severe vasospasm (> 51% reduction). The mean reduction in the combined value for the left-sided (noninvolved) cerebral arteries showed no vasospasm; there were no significant differences among
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**TABLE 2**

Percent changes in vessel diameter after SAH induction in 16 monkeys*

<table>
<thead>
<tr>
<th>Vessel</th>
<th>3-Day Group</th>
<th>7-Day Group</th>
<th>14-Day Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right</td>
<td>Left</td>
<td>Right</td>
</tr>
<tr>
<td>no. of monkeys</td>
<td>5</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>ICA</td>
<td>-30.4 ± 6.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCA</td>
<td>-28.3 ± 8.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACA</td>
<td>-32.4 ± 8.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>combined value</td>
<td>-30.3 ± 7.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Percent changes in vessel diameter on the second angiogram compared to the baseline angiogram. Values are expressed as means ± standard deviations. SAH = subarachnoid hemorrhage; ICA = internal carotid artery; MCA = middle cerebral artery; ACA = anterior cerebral artery; combined value = value for the combined vessels (ICA + MCA + ACA).

† Significant difference from the contralateral side: p < 0.05.
‡ Significant difference from the contralateral side: p < 0.01.

**FIG. 3.** Graph showing the percent reduction in the combined values for the right-sided cerebral arteries on angiograms obtained 3, 7, and 14 days after the induction of subarachnoid hemorrhage (SAH) compared to the baseline value before SAH. * = p < 0.05, compared to the contralateral side; ** = p < 0.01, compared to the contralateral side; + = p < 0.05, compared to the value on Day 7.

The three groups. In the 3-day group, the percent reduction in the combined value for the right-sided (involved) cerebral arteries showed mild vasospasm in three animals and moderate vasospasm in two; the average reduction showed mild vasospasm. In the 7-day group, the percent reduction in the right-sided cerebral arteries showed moderate vasospasm in four animals and severe vasospasm in two; the average reduction revealed severe vasospasm. In the 14-day group, the percent reduction in the right-sided cerebral arteries showed no vasospasm in two animals and mild vasospasm in three; the average reduction amounted to no vasospasm. The results show that the degree of vasospasm is mild to moderate 3 days after SAH, becomes severe at the end of 1 week, and drops to less than mild at the end of 2 weeks (Table 2, Figs. 2 and 3).

Cerebral Blood Flow Changes

Before changes in MABP were induced, the mean regional CBF on the right (involved) side was significantly (p < 0.05) less than that on the left (noninvolved) side in the 3-day and 7-day groups, but not in the 14-day group. The right-sided mean regional CBF was significantly less in the 3-day group than in the other groups (Table 1).

The correlation between mean regional CBF and changes in MABP in the three groups are shown in Figs. 4 and 5. In all groups, the mean values for the left-sided regional CBF were not significantly different at MABP's of 60 to 160 mm Hg, but there was a significant (p < 0.05) decrease at an MABP of 40 mm Hg and a significant increase at an MABP of 180 mm Hg. These results were similar to those observed in the sham-treated control animals in the previous study, indicating that cerebral autoregulation is maintained in the nonspasm side at MABP's between 60 and 160 mm Hg.

In the 3-day group, the regional CBF in the right (involved) hemisphere was significantly (p < 0.05) lower than CBF in the left side at MABP's below 120 mm Hg. The increase in mean regional CBF paralleled an increase in MABP and presented a significant correlation coefficient (CBF = -0.733 + 0.327 MABP, r = 0.931) (p < 0.01). In the 7-day group, the right CBF was also significantly (p < 0.05) lower than in the left side at MABP's below 120 mm Hg. The right CBF's rose to exceed those on the left at MABP's above 180 mm Hg. The correlation between regional CBF and changes in MABP showed a significant coefficient (CBF = -7.00 + 0.47 MABP, r = 0.762) (p < 0.05). In the 14-day group, the values for the right regional CBF were smaller, but not significantly, than the values for the left regional CBF at MABP's between 40 and 140 mm Hg. The values for the right regional CBF did not differ significantly at MABP's of 60 to 140 mm Hg, indicating preservation of cerebral autoregulation in this MABP range. The right regional CBF became significantly greater than in the left at MABP's of 160 and 180 mm Hg, revealing the impairment of autoregulation at these MABP levels.

Central Conduction Time Changes

The correlation between central conduction time and changes in MABP in the three groups are shown in Fig. 6. In the 3-day group, the central conduction time on the left (noninvolved) side did not significantly differ at
In the 14-day group, there were no significant differences in bilateral central conduction times at any MABP level. The right-sided central conduction time at an MABP of 40 mm Hg was greater than those at MABP's above 60 mm Hg, but not significantly.

**Histopathological Findings**

The cerebral arteries derived from the left (nonclot) side showed no pathological changes (Fig. 7). The right MCA's from the 3-day group animals (presenting mild to moderate vasospasm on angiography) showed tortuous changes in the intimal and elastic lamina, and the adventitial layer showed thickening with an infiltration of inflammatory cells. In the 7-day group (demonstrating severe vasospasm on angiography), the spastic vessels had more marked corrugation of the intimal and elastic lamina than that observed in the 3-day group. The endothelial cells revealed swelling and vacuolization, and the medial and adventitial layer demonstrated the thick proliferative changes accompanied with cell infiltration. In the right MCA's obtained from the 14-day group, we observed reduced tortuosity of the elastic lamina and intimal layer but more marked degenerative changes in the endothelial layer and muscle cells in the medial layer.

**Discussion**

**Animal Model**

To investigate the effect of hemodynamic therapy at the various stages of vasospasm, it is important to use an animal model in which the time course of vasospasm and the characteristics of the cerebral circulation are fairly similar to those in humans. In previous studies, the time course of angiographic vasospasm as well as the histopathological findings of the spastic arteries in a primate model have been shown to be comparable to human cases. The finding of Nosko, et al., that
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Fig. 6. Graphs showing the correlation between central conduction time (CCT) and changes in the mean arterial blood pressure (MABP) during the induced hypotension 3 days (Day 3, upper), 7 days (Day 7, middle), and 14 days (Day 14, lower) after the induction of subarachnoid hemorrhage. ms = milliseconds. * = p < 0.05, compared to the contralateral side.

chronic vasospasm results in cerebral infarction in some monkeys suggests a critical reduction in CBF in the primate model. Accordingly, we were able to demonstrate the critical effects of either hyper- or hypotension on cerebral circulation and the electrophysiological changes in the brain during chronic vasospasm in this model.

Pathogenesis of the Impairment of Autoregulation

A number of experimental and clinical studies have demonstrated the impairment of cerebral autoregulation after SAH. This impairment may be attributable to several factors seen after SAH: vasospasm, tissue hypoxia, and acidosis. In the present study, we excluded both intracranial hypertension due to hydrocephalus and global infarction as the pathogenesis for the impairment of autoregulation because we did not observe them in the pathological examination. Abolition of both the lower and upper limits of cerebral autoregulation was seen at the maximum stage of vasospasm. It is recognized that, during vasospasm, compensatory vasodilatation takes place in the intracerebral parenchymal vessels.

In this state, intraparenchymal vessels may not be able to dilate further to maintain a constant CBF and prevent arterial hypotension; thus, the lower limit of autoregulation is lost. The abolition of the upper limit may be explained by the loss of activity in the adrenergic nerve endings on the wall of the spastic artery following SAH. In this state, adrenergic nerve endings presumably lose the ability to take up more of the adrenaline released at the endings or more of the circulating noradrenaline. The result is that these vessels are no longer able to contract in response to normal stimuli.

During the initial stage of cerebral vasospasm, the global impairment of cerebral autoregulation was observed in this study. It is recognized that the induction of SAH causes a decrease in the pH level of the cerebrospinal fluid in the early stage in experimental animals. It is presumed that a reduction in the pH level causes dilatation of the intracerebral vessels; thus, after a further reduction of perfusion pressure, these vessels cannot be dilated to maintain a constant CBF. The loss of activity of the perivascular sympathetic nerve fibers within a few days after SAH may explain why the cerebral arteries could not react to maintain CBF and prevent arterial hypertension in the acute stage of SAH, in spite of the mild angiographic vasospasm in the main cerebral arteries.

In the remitting stage of vasospasm, recovery of the lower limit of autoregulation was observed. This recovery is thought to be caused by an improvement of cerebral circulation above the critical level for ischemia and a decrease of the amount of chemical mediators from the blood clot in the subarachnoid space. The histopathological study in the present series revealed marked myonecrotic changes in the medial layer of the arterial wall, despite the abatement of vasospasm. This result suggests that the layers of muscle cells may not be able to constrict the vessels against arterial hypertension, thus presenting the impairment of the upper limit of autoregulation even when vasospasm abated.

Potential Risk of Hemodynamic Therapy for Brain Edema

Increasing the cerebral perfusion pressure is the only usable therapeutic method available at present to prevent and also to reverse neurological deficits due to vasospasm. On the other hand, it is well recognized that marked hypertension and altered hemody-
dynamic parameters above the upper limit of cerebral autoregulation lead to further impairment of an already damaged blood-brain barrier, resulting in the formation of vasogenic edema.\textsuperscript{14,20,22} Hence, one can readily appreciate that excessive elevation of the arterial blood pressure may result in vasogenic brain edema during the time course of vasospasm because of the impairment of cerebral autoregulation.

It is recognized that induced hypervolemia without the associated use of pressor drugs is an effective preventive method; the augmentation of intravascular volume may increase cardiac output and arterial blood pressure.\textsuperscript{4,15,21} Aside from treatment for vasospasm, hemodilution has been proposed as a potential therapy for cerebral ischemia.\textsuperscript{11} Experimental studies have demonstrated that hemodilution with a colloid solution is effective in reducing the infarct size in a focal ischemia model in dogs.\textsuperscript{27} However, it has been emphasized that hemodilution with a crystalloid is not beneficial and is presumed to contribute to brain edema in both dogs\textsuperscript{13} and monkeys\textsuperscript{24} following MCA occlusion. It is suggested that hypervolemic hemodilution therapy for cerebral vasospasm may be beneficial in decreasing the incidence of ischemic deficits but that, after infarction has occurred, this form of treatment may be detrimental.

**Appropriate Usage of Hemodynamic Therapy**

From the present study, it can be concluded that augmentation of cerebral perfusion pressure should be instituted early following an SAH and that hypovolemia and/or hypotension should be avoided. This increase in mean arterial perfusion pressure must be continued throughout the maximum stage of vasospasm. However, once the blood-brain barrier has been significantly damaged, hemodilution and elevation of arterial perfusion pressure can result in a significant increase in

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**Fig. 7.** Transverse sections of primate middle cerebral artery (MCA). H & E, × 220. A: The left (nonclot) MCA 7 days after subarachnoid hemorrhage (SAH) was induced. B: The right (clot) MCA 3 days after SAH. C: The right MCA 7 days after SAH. D: The right MCA 14 days after SAH.
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brain edema. Hopefully, the current study will be of some help in developing guidelines for hemodynamic therapy during the various stages of vasospasm.

References

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