SUMMARY A model for producing chronic cerebral vasospasm in monkeys by injecting autologous blood into the basal cistern is described. Spasm/narrowing was observed by angiography one hour after SAH in 8 out of 10 monkeys and in 5 of these 8, spasm was observed both one and two weeks later. No narrowing of the vessels was observed in the control cases. In monkeys that showed spasm one week after SAH, narrowing of the extracranial vertebral arteries was also observed. Repeated injections of blood at intervals of one and two weeks caused intensification of spasm in the intracranial portion of vertebral arteries and the basilar arteries. It is suggested that cerebral vasospasm following SAH may in part be mediated by a central control mechanism acting through the sympathetic nervous system in that extracranial vessels remote from direct contact with blood showed reactive narrowing.

CEREBRAL ARTERIAL SPASM following subarachnoid hemorrhage (SAH) is a most important unresolved problem in neurosurgery. Clinically, it is reported that cerebral arterial spasm occurs about the 4th to 10th days after SAH; therefore surgery during this period is usually avoided by most people. Many unsuccessful attempts have been made to relieve the symptoms or relax the vasospasm but there is still incomplete understanding of the pathogenesis of the condition. For this reason, we initiated this study of SAH in monkeys and observed the changes in the intracranial pressure (ICP), systemic blood pressure (BP) and cerebral angiography with a view to a better understanding of the mechanisms of vasospasm.

Methods

Fifteen Macaque fascicularis monkeys, weighing between 2.3 kg and 3.2 kg, were used in this study. Three of them were excluded from the data due to technical errors with the radiological and surgical procedures. SAH was created in ten of the remaining animals by injecting fresh autologous arterial blood into the subarachnoid space by means of cisternal puncture. The other two were injected with Elliot’s B-solution to serve as controls. The monkeys were given atropine sulphate (0.05 mg/kg), followed by 5–10 mg/kg of ketamine hydrochloride (IP). After intubation, angiography was carried out. The animals were placed in a supine position with the head fixed such that the orbito-meat line was horizontal. Bilateral retrograde brachial arteriography was carried out using Conray 60 administered via a mechanical pressure injector at the rate of 2 cc/sec through a Y-connector. Double magnification angiogram films were taken in the basal projection at the rate of 2 films per second for 5 seconds, then 1 film per second for the next 5 seconds. PCO2 was measured at the time of angiography.

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Autopsy examination revealed accumulation of blood in the prepontine and chiasmal cistern and basal surface of the brains. Moreover, in brains examined one week after the last injection of blood, clot was still seen in the prepontine and chiasmal cisterns. There was also fibrous arachnoiditis accompanied by hemosiderosis around the basilar artery and the circle of Willis.

During the injection of blood, ICP and BP were continuously monitored and when ICP reached 100 mm/Hg, the injection was stopped. BP rose proportionately with ICP after a lag period. The ICP decreased gradually but still remained at 20–40 mm/Hg.
FIGURE 1. Points where arterial diameters were measured on angiograms. A. 5 mm below basilar tip. B. 10 mm below V.B. junctions. C. 10 mm below 1st loop of vertebral artery.

for more than 30 minutes. On the other hand, the BP soon returned to normal pre-SAH level.

While injecting the blood into the cistern, some monkeys developed apnea or weak irregular respiration and had to be artificially ventilated. Usually spontaneous normal respiration recovered within a few minutes. The EKG showed elevation in the ST region with variation of the T wave and bradycardia but these changes were usually only transient.

The common clinical symptoms were a retardation of motor activity, loss of appetite and signs of meningismus. This usually persisted for two to three days, then resolved. Two animals with most pronounced signs of meningeal irritation and hemiplegia were found to have considerable vasospasm one week following SAH.

Three patterns emerged on examination of the changes in the basilar artery diameters (measured at point A) taken from the angiograms up to two weeks following SAH (fig. 2). Pattern I (fig. 3) — acute spasm/narrowing. Three of 10 SAH monkeys showed spasm/narrowing in the vertebral and basilar arteries at one hour and 24 hours after SAH. One week later, however, the vessels had returned to normal size. Pattern II (fig. 4) — biphasic or prolonged spasm. In five monkeys, there was evidence of spasm/narrowing in the angiography at 1 hour, 1 week and 2 weeks following SAH. Three of these animals showed biphasic spasm. Pattern III (fig. 5) — vasodilatation. In two monkeys, vasodilatation rather than spasm/narrowing was seen one hour after SAH. One day later, the angiogram showed slight shrinkage of the vessels, but one week later the vessels were again seen to have expanded beyond their original pre-SAH size. In the control cases into which Elliot’s B-solution was injected, there was no change of the vessel diameters (fig. 11). Angiography of these animals was carried out under the same anesthesia and under the same conditions and there was no change in the PCO₂ compared with the test animals.

![Figure 2. Basilar artery diameter (measurement A) following SAH. Arrows indicate time of SAH.](http://stroke.ahajournals.org/doi/abs/10.1161/01.STR.13.4.474?journalCode=strok)
Figure 3. Pattern I: (Acute Spasm Only). Top left — baseline. Top right — 1 hr after SAH. Bottom left — 1 day after SAH. Bottom right — 1 week after SAH. Angiograms show narrowing of vertebral and basilar arteries one hour post-SAH and a normal appearance 1 week later.

The measurements at point B of the intracranial/vertebral artery were consistent with the measurements taken at point A on the basilar artery (fig. 6). From the diameter measurements taken at point C on the extracranial portion of the vertebral arteries, it was noted that the 5 cases in Pattern II, which had shown prolonged or biphasic spasm/narrowing intracranially also showed narrowing extracranially. None of the cases from Patterns I and III showed any extracranial changes (fig. 7 & 8).

Analysis of angiograms taken from the animals that had been subjected to repeated SAH showed that 5 out of the 6 had more pronounced spasm/narrowing of the basilar artery after the second SAH. Also, 3 out of 4 showed still further intensification of spasm/narrowing after the third SAH (fig. 9 & 10). Following each new SAH, the clinical symptoms worsened and the recovery time was longer.

Discussion

To date, although various in vivo experimental cerebral arterial spasm models have been developed, there is controversy about whether or not it is necessary to damage physically the wall of the cerebral vessel in order to produce spasm similar to that which occurs in human patients. Fein et al. state that the injection of fresh blood into the cranium produces spasm that lasts only one to three days, whereas the SAH models made by puncturing the internal carotid artery can result in spasm that lasts more than 7 days. Simeone et al. also report that mechanical trauma to an intracranial vessel is more effective in producing vasospasm than mere injection of blood. Landau and Ransohoff created SAH in monkeys by puncture of an intracranial artery and reported immediate spasm in all cases, 29% of which persisted after 8 days. On the other hand, Echelin et al. tried tearing or direct puncture of the trunk arteries of the circle of Willis and experienced a very high rate of morbidity and mortality which they explain is due to uncontrollable bleeding, seizure, respiratory arrest and sudden death. Moreover, they report that the extraordinarily high ICP and brain swelling resulting from the uncontrollable bleeding probably has more effect on spasm than the hemorrhage. Also, the size of the hemorrhage is not constant and there may be some additional influence from the
surgical procedure. Consequently, they thought this method inferior to the injection of fresh blood into the cistern.

Clinical studies by both Fisher and Mizukami confirm a correlation between the presence of subarachnoid clot as seen by computerized tomography within 4 days following SAH, and the subsequent incidence of vasospasm. In view of these latest findings and the previous experimental failures, we decided to adopt the cisternal puncture technique described by Kuwayama with the modifications described in the following paragraph.

The animal’s head-down position was maintained for 1 hour following SAH in order to hold the blood in the basal cistern. We found that this simple maneuver was most effective in producing prolonged or biphasic vasospasm in the vertebral and basilar arteries. The quantity of blood remaining in the basal cistern one week after the first SAH varied from only traces to definite clot. One week after the second injection, however, there was always residual clot in the prepon- tine cistern and surrounding the basilar artery in all of the animals. The reason for the persistence of blood following the second injection may be due to fibrous arachnoiditis formed by the first SAH interfering with CSF flow and perhaps rendering the area more receptive to clot formation.

In 1968, Brawley et al. created SAH in dogs and observed that the vasoconstriction was strongest at five minutes, recovering in about an hour and reappearing about 4-24 hours reaching a peak three days later. They named this phenomenon the “biphasic response.” Since then, many reports have noted the same phenomenon in various animal models. In our

FIGURE 5. Pattern III: (Vasodilatation). Top left — baseline. Top right — 1 hr after SAH. Bottom left — 1 day after SAH. Bottom right — 1 week after SAH. Note the arterial dilatation 1 hr post-SAH.

FIGURE 6. Changes in the vertebral artery (measurement B) diameters following SAH.
experiment, diffuse spasm/narrowing was observed in 8 of 10 animals one hour after injection of blood and in 5 out of these 8, the same symptom was confirmed after one week. Three animals showed relaxation of spasm intensity in angiograms taken one day following injection and yet after one or two weeks, the angiographic vascular narrowing reappeared. This may be the same response that Brawley observed, although the time difference was greater.\textsuperscript{12}

The etiological factors that are generally considered concerning cerebral arterial spasm are as follows—
1. Vasoconstrictor agents in blood or brain.
2. Mechanical stimulus or trauma to the brain vessels.
3. Vasomotor mechanisms.
4. A combination of the above.

The spasm/narrowing that was observed one hour after SAH in this experiment was in the region of the intracranial vertebral and basilar arteries in direct contact with the hemorrhage and this may be likened to the immediate narrowing known to occur in peripheral or basilar arteries following the application of blood.\textsuperscript{13, 14}

It has been thought that serotonin, noradrenalin or platelets in fresh blood are the main agents causing vasospasm immediately following SAH. In humans, angiography is almost never possible within an hour of SAH and, therefore, there is little evidence that this kind of spasm exists in man.

With regard to the spasm/narrowing that was observed one week after injection of blood, it is likely that serotonin or the other vasoactive agents spilled into the subarachnoid space lose their activity within 24 hours. The origin of the so-called late spasm, therefore, must be sought in such materials as decaying intermediates of blood and blood clots or in secondary...
Figure 10. Angiograms of case with 3 SAH's. Top (left to right) — baseline, one hour, one day and one week after 1st SAH. Bottom (left to right) — one hour after 2nd SAH, two weeks after 2nd SAH, one hour after 3rd SAH and one week after 3rd SAH. Note the intensification of intracranial spasm following successive hemorrhages and the diffuse spasm of the extracranial vertebrals one week after the 3rd hemorrhage.

alteration of the vessel wall with fluctuation of the vasomotor factors resulting from the diffuse early spasm immediately following SAH. Perhaps the two most important observations from this work are— a) the occurrence of spasm of the extracranial arteries one week following SAH strongly suggesting a central mechanism acting through the sympathetic nerves to the vessel wall and b) the increased intensity of intracranial vasospasm resulting from repeated SAH.

The clinical analogy to b) is the observation that recurrent hemorrhage typically causes precipitation of vasospasm and delayed ischemic insult presumably acting on vessels previously “sensitized” by the first bleed. One must also consider that further injections of blood increase the concentration of spasmogenic factors.

Finally, we feel we have resolved the controversy about how to create vasospasm in the experimental
animal. By injection of blood and allowing it to pool and clot in the subarachnoid cistern, we have successfully produced biphasic vasospasm in animals, with many features similar to the spasm observed in man, following SAH. The model is simple, reproducible and we hope of value to others in search of the answer to the pathogenesis of cerebral vasospasm.

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References
Angiographic study of vasospasm following subarachnoid hemorrhage in monkeys.
S J Peerless, A J Fox, K Komatsu and I G Hunter

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