Cerebral Vasospasm Model Produced by Subarachnoid Blood Injection in Dogs

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Abstract—Subarachnoid hemorrhage (SAH) was simulated in dogs by injecting blood into the cisterna magna. Time-dependent development of spasm of the basilar artery was angiographically determined. One week after SAH, the diameter of the basilar artery decreased by 15.5±5.4% and 46.4±3.0% in the single and double injection model, respectively. Thereafter, the artery diameter gradually returned to normal. The time course of diameter changes in the double injection model resembles that seen in the clinical setting, and the double injection model seems to be useful for the experimental study of cerebral vasospasm.

Cerebral vasospasm following subarachnoid hemorrhage (SAH) is one of the most serious, yet unsolved problems in neurosurgical practice. In order to clarify the pathogenesis of cerebral vasospasm and its appropriate treatment, various animal models of SAH have been devised. In dogs, it has been observed that an injection of blood into the subarachnoid space causes cerebral vasospasm, and repeated injections produce a more intense spasm (1, 2). However, there have only been a few reports that have followed the time course of vasospasm angiographically until its resolution (3, 4). Therefore, we undertook this study to clarify the relationship between subarachnoid injections of autologous blood and vasospasm and to closely follow time-dependent changes of basilar artery diameter after double injections of the blood.

Thirty-five adult mongrel dogs of either sex, weighing 10 to 15 kg, were used. All procedures were performed under general anesthesia induced by an intraperitoneal injection of 30-35 mg/kg of sodium pentobarbital and maintained by additional intravenous injections as needed. Body temperature (37°C) was kept constant with a heating pad, and the arterial blood pressure was continuously monitored. Arterial blood samples were withdrawn, and pH and blood gases were measured just before each angiography.

Dogs were divided into three groups. SAH was simulated by injecting blood into the subarachnoid space. On day 1, a No. 20 needle was inserted into the cisterna magna under fluoroscopic control. In Groups 1 (n=10) and 2 (n=15), 7 ml of the cerebrospinal fluid was removed, and 7 ml of fresh, autologous, unheparinized arterial blood was injected slowly. In dogs of Group 3 (n=10, control group), 7 ml of the saline was injected instead of the blood. The dogs were kept in a head-down position at 30° for 20 min to facilitate settling of the blood around the basilar artery. On day 3, dogs in Group 2 were anesthetized again, and 3 ml of fresh autologous blood was similarly injected into the cisterna magna. In Group 3, 3 ml of saline was injected again.

On day 1, baseline cerebral angiography was performed in all animals prior to injection of either the blood or the saline. A number 3 French catheter was introduced into the right femoral artery, advanced under fluoroscopic control to the C-3 or C-4 level of the left vertebral artery, and 3 ml of meglumine amidotrizoate (Angiografin, Schering AG, West Germany) or iopamidol (Iopamiron, Schering AG, West Germany) was used as a contrast medium. Angiographies were repeated on day 8 in Group 1 and on days 3, 5, 8, 15, 22, 29, 36, and 43 in
Groups 2 and 3. All angiographies were performed under the same magnification. The diameter of the basilar artery on the baseline angiogram was taken as a control vessel diameter. The basilar artery diameter was measured at the following points: (i) 1 mm below the basilar artery bifurcation, (ii) midpoint of the basilar artery, and (iii) 1 mm above the basilar-vertebral artery junction. The three values were averaged, and the results were reported as percent constriction (mean±S.E.) relative to each control vessel diameter. The Student's paired and unpaired t-tests were used to evaluate the significance of the results.

Arterial pH, pO₂ and pCO₂ were kept within the range of 7.32 to 7.40, 80 to 100 mmHg, and 35 to 40 mmHg, respectively. During blood injection into the cisterna magna, blood pressure remained unchanged or only slightly increased. On the other hand, when the contrast agent was injected during angiography, the blood pressure decreased transiently but soon returned to the level before injection of the agent.

Changes of diameter of the basilar artery in Groups 1 and 2 are shown in Fig. 1. One week after the blood injection, all the dogs in Groups 1 and 2 demonstrated angiographic cerebral vasospasm. In Group 1, the basilar artery diameter was reduced to an average of 84.5±5.4% on day 8 (Fig. 1). In Group 2, the artery diameter started to decrease on day 3, and the maximum decrease to 53.6±3.0% was attained on day 8, which was statistically significant (P<0.005) compared to the value in Group 1. Thereafter, the diameter gradually returned to normal. Typical responses in a double injection model (Group 2) are illustrated in Fig. 2. In Group 3, basilar arteries demonstrated no angiographic vasospasm throughout the experimental period.

Fisher et al. reported that in patients with SAH, the volume of the subarachnoid blood demonstrated by computed tomography well-correlated with an incidence of cerebral vasospasm (5) and suggested that a large
volume of blood around the basal arteries was a major factor for delayed cerebral vasospasm. Our experimental results that the degree of vasospasm seen in Group 2 was significantly more severe than that in Group 1 were consistent with their conclusion.

Clinically, it has been noted that cerebral vasospasm becomes evident angiographically two to three days after SAH and becomes progressively more severe, reaching a peak between the first and second weeks. Then, vasospasm gradually resolves within several weeks. In various models of experimental SAH reported previously, the degrees of vasospasm were not severe compared with those seen in clinically symptomatic patients (6–8). Zabramski et al. altered the volume of the blood and timing of subarachnoid injection in canine models, and they could successfully produce severe vasospasm by the three injection method (9). Also in our double injection model, the degrees of vasospasm were fairly severe and angiographically comparable to those seen in clinical conditions. In addition, the time course of cerebral vasospasm was also comparable to that recognized in patients with aneurysmal SAH. It is necessary to know the time course of basilar arterial spasm to study time-related functional changes of vascular endothelial and smooth muscle cells. Using our simple and reproducible method, angiographic basilar artery spasm is consistently produced. The canine basilar artery is one of the materials most frequently used for pharmacological studies (10, 11). The double injection canine model seems to be useful for further pharmacological studies on cerebral vasospasm.

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References
1 Chyatte, D. and Sundt, T.M.: Response of chronic experimental cerebral vasospasm to methylprednisolone and dexamethasone. J. Neurosurg. 60, 923–926 (1984)
2 Eldevik, O.P., Kristiansen, K., and Torvik, A.: Subarachnoid hemorrhage and cerebrovascular spasm. Morphological study of intracranial arteries based on animal experiments and human autopsies. J. Neurosurg. 55, 869–876 (1981)
3 Baker, K.F., Zervas, N.T., Spellman, J.P., Vacanti, F.X. and Miller, D.: Angiographic evidence of basilar artery constriction in the rabbit: a new model of vasospasm. Surg. Neurol. 27, 107–112 (1987)
4 Peerless, S.J., Fox, A.J., Komatsu, K. and Hunter, I.G.: Angiographic study of vasospasm following subarachnoid hemorrhage in monkeys. Stroke 13, 473–479 (1982)
5 Fisher, C.M., Kistler, J.P. and Davis, J.M.: Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized tomographic scanning. Neurosurgery 6, 1–9 (1980)
6 Gavras, H., Andrews, P. and Papadakis, N.: Reversal of experimental delayed cerebral vasospasm by angiotensin-converting enzyme inhibition. J. Neurosurg. 55, 884–888 (1981)
7 Sasaki, T., Wakai, S., Asano, T., Takakura, K. and Sano, K.: Prevention of cerebral vasospasm after SAH with a thromboxane synthetase inhibitor, OKY-1581. J. Neurosurg. 57, 74–82 (1982)
8 Varsos, V.G., Liszczak, T.M., Han, D.H., Kistler, J.P., Vielma, J., Black, P.M., Heros, R.C. and Zervas, N.T.: Delayed cerebral vasospasm is not reversed by aminophylline, nifedipine, or papaverine in a “two-hemorrhage” canine model. J. Neurosurg. 58, 11–17 (1983)
9 Zabramski, J.M., Spetzler, R.F. and Bonstelle, C.: Chronic cerebral vasospasm: effect of volume and timing of hemorrhage in a canine model. Neurosurgery 18, 1–6 (1986)
10 Toda, N. and Fujita, Y.: Responsiveness of isolated cerebral and peripheral arteries to serotonin, norepinephrine, and transmural electrical stimulation. Circ. Res. 33, 98–104 (1973)
11 Toda, N.: Hemolysate inhibits cerebral artery relaxation. J. Cereb. Blood Flow Metab. 8, 46–63 (1988)