Prolonged Experimental Cerebral Vasospasm*

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The visualization of constricted cerebral vessels by angiographic studies of patients suffering from ruptured intracranial aneurysms is now accepted by neurosurgeons and radiologists. The fact that this cerebral vasocostriction, or vasospasm, has often disappeared by the time of follow-up studies indicates that the phenomenon was not due to a permanent pathological change in the vessel walls. Narrowing of cerebral arteries has been reported in a high percentage of patients with ruptured intracranial aneurysms, particularly when the patients are studied shortly after the hemorrhage.

Several retrospective studies have indicated a significant correlation between mortality or morbidity and the presence of cerebral vasospasm. Fletcher, et al., found that the incidence of coma or stupor, seizures, hemiparesis, and papilledema increased two- to fivefold when spasm was present in the angiogram. Other clinical studies have demonstrated that spasm may occur postoperatively following successful intracranial obliteration of any aneurysm. Alcock and Drake noted vasospasm postoperatively in 27% of the patients who recovered satisfactorily from intracranial surgery for aneurysms, whereas 71% of their patients with unsatisfactory results demonstrated postoperative vasospasm. Smith, and Birse and Tom have demonstrated ischemia of the cortex and edema of the white matter in the territory supplied by the aneurysm-bearing vessel, suggesting that the vasospasm led to cerebral infarction.

The phenomenon of cerebral vasospasm is respected to the extent that neurosurgeons feel that, when demonstrated, it is a definite contraindication to surgery. Despite this there is no proven treatment directed to relief of vasospasm, nor is the mechanism of initiation, propagation, and prolongation of the pathological vasocostriction understood. The authors felt that an experimental model of cerebral vasospasm comparable to the clinical phenomenon was required before physiological understanding and rational treatment could be accomplished.

Materials and Methods

The technical aspects of this work were begun at the Boston City Hospital in the laboratories of Dr. Vernon H. Mark and have been continued in the Radiology-Physiology laboratories in the Temple University Health Sciences Center.

Large Rhesus monkeys were selected as the experimental animal after it had been determined that satisfactory cerebral angiograms of the required quality could not be taken in other common laboratory animals.

The animals were anesthetized with intramuscular Sernylan, a cataleptic agent, and they were not intubated unless controlled respiration or general anesthesia were to be used in the experiment. Intracranial pressure was measured through a catheter inserted in the subdural space which led to a Statham pressure transducer fed into a Grass polygraph. Systemic arterial pressure was similarly measured through an intra-arterial catheter. When the electroencephalogram was monitored, bipolar recordings were taken via electrode pairs screwed into the skull to avoid impedance variation by brain pulsation. Recently bilateral carotid blood flow has been measured by a Statham two-channel electromagnetic flow meter, which also records on the polygraph. Flow probes were gently placed about each common carotid artery with or without occlusion of the external carotid artery.

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The animal was placed on an operating table where biplane high-speed (up to 540 frames per sec) cineangiograms could be taken as well as serial plane film angiograms at a rate of 6 per sec. A variety of methods for introducing the angiographic contrast material into the cerebral circulation were tried. The most satisfactory technique required passage of an Odman radio-opaque catheter from the femoral artery up the aorta to the innominate artery; injection then opacified both common carotid arteries. The catheter could be advanced to fill the right carotid only. The catheter was connected to a Viamonte-Hobbs injector which delivered a given amount of contrast medium at a known rate and automatically activated the x-ray apparatus after a predetermined time delay. Ordinarily, 3 cc of contrast medium were administered by a 0.3 sec injection. Thorotrast++ was the medium of choice when physiologic studies were performed because of its known lack of vasoactive properties. Exposure factors for serial angiograms at 6 per sec were 100 mA, 65 kV, at 1/30 sec. Image amplified fluoroscopy allowed accurate catheter placement and satisfactory head positioning.

After baseline measurements were made, control angiograms were taken prior to attempts to alter cerebral vasomotor tone. A small anterior craniectomy was made at the lateral margin of the sphenoid wing. The dura was reflected gently from the floor of the middle fossa to its attachment near the anterior clinoid process.

A 5 mm incision was made in the dura after which the internal carotid artery and its bifurcation into the anterior and middle cerebral arteries could be easily visualized. When the retractor was removed, the dura fell back into place and a relatively physiologic relationship between the cerebral vessels and the subarachnoid space remained. When the effect of vasoactive chemicals was to be studied, a fine catheter was left in the subarachnoid space through the dural incision and was brought out the temporal craniectomy.

The cerebral vessels were then subjected to a variety of chemical and physical stimuli such as mechanical stroking, local application of heat, electrical and radiofrequency current; the effects were studied by cerebral angiography. The definitive procedure consisted of puncturing one of the vessels in question with a 30-gauge needle. This produced a brief period of arterial bleeding, which usually stopped spontaneously when the retractor was removed. The animals were followed up to 9 hours during the acute experiments and up to 7 days in a smaller number of chronic experiments. In the chronic experiments the principal study was repeat serial angiography.

**Results**

*Normal Cerebral Angiogram.* The normal cerebral angiogram in the Rhesus monkey is shown in Fig. 1. The vessels demonstrated angiographically have been correlated with acrylic casts made in our laboratories by Dr. Akbar Bonakdarpour.++ The similarity to the human cerebral vascular anatomy is obvious; the only major difference is the formation of a single vessel by the conjunction of the two anterior cerebral arteries, rather than paired pericallosal vessels.

*Action of Chemicals in the Subarachnoid Space near the Bifurcation of the Internal Carotid Artery.* Fresh blood injected into the catheter in the subarachnoid space immediately after withdrawal from the femoral artery occasionally produced focal constriction of the vessels in the immediate vicinity of the catheter tip, extending less than 10 mm. When the blood was fresh, this constriction lasted only a maximum of 10 minutes. When arterial and venous blood were allowed to decompose by standing for 2 hours after vigorous agitation, the duration of spasm was more transient. A subarachnoid injection of as much as 2 cc of blood caused no significant change in the physiological parameters measured, except for a slight increase in intracranial pressure due to the added volume.

When more intensely vasoactive substances such as 1% serotonin or 0.1% epinephrine were injected, an intense diffuse vasoconstriction was demonstrated on angiography with as little as 0.2 cc of these substances (Fig. 2). Lesser concentrations of these agents were not used because our main interest was to demonstrate maximal response angiographically. The duration of this intense diffuse spasm was roughly 5 minutes.
after which vessel caliber returned to normal. A marked and almost immediate rise in systemic arterial pressure, and to a lesser extent intracranial pressure, followed the injection of small amounts of these vasoactive substances into the subarachnoid space, indicating rapid absorption into the systemic circulation. This was corroborated by dilation of the larger vessels leaving the aortic arch as has been previously described. There was no tendency for focal constriction to be produced by the injection of these potent vasoactive substances but, rather, a diffuse bilateral spasm. Angiographic contrast materials had no vasoactive properties when injected in the subarachnoid space.

Effects of Mechanical Stimulation. Stroking of the carotid artery or one of its branches with a metal instrument occasionally produced very transient spasm which could only be demonstrated if the angiogram was performed almost immediately after stimulation. Bipolar electric stimulation of the involved vessels usually produced spasm lasting for a few minutes. Radiofrequency stimulation had no effect.

Effects of Direct Puncture of Large Cerebral Vessel. When the internal carotid artery or one of its branches was punctured with a 30-gauge needle, immediate intense vasoconstriction was usually demonstrated in the punctured vessel and its peripheral branches. Often the vasoconstriction involved the internal

Fig. 1. Control cerebral arteriogram with tracing of the circulation on the left side, Rhesus monkey, anteroposterior view.

Fig. 2. Left circulation tracing and angiogram. Diffuse bilateral spasm particularly noticeable in distal middle cerebral arteries after subarachnoid installation of 1% serotonin.
carotid artery proximal to the puncture, producing the characteristic narrowing of this vessel as it leaves the cavernous sinus.

Figure 3 is a control angiogram. Figure 4 was taken immediately after the middle cerebral artery was punctured just distal to its origin. A small amount of extravasated contrast material indicates the point of puncture (extravasation was occasionally seen when the angiogram was taken immediately after puncture). Note the marked distal spasm of the middle cerebral artery without filling of its branches, whereas the branches of the middle cerebral artery are demonstrated on the opposite side. Figure 5 demonstrates persistent cerebral vasospasm 2 hours after the initial puncture. Although the spasm is partially relieved, the distal branches of the middle cerebral do not fill as on the opposite side. Figure 6 shows that 4 hours later the vessel caliber has returned further but distal perfusion is still limited. Figure 7 taken 9 hours after the initial puncture, shows that the middle cerebral artery, although still quite narrowed, now permits distal perfusion comparable to the normal side.

Total Duration and Intensity of Cerebral Vasospasm. Attempts to maintain animal survival for repeated angiography on subsequent days after vessel puncture initially were somewhat disappointing. Eventually im-

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Fig. 3. Control cerebral angiogram with tracing of the circulation on the left side, in another monkey.

Fig. 4. Small arrow denotes marked focal constriction of middle cerebral artery just beyond the extravasation at the puncture site. The large arrow indicates absence of perfusion of distal branches of middle cerebral artery when compared to the opposite side.
Fig. 5. Arrow denotes persistent marked spasm of middle cerebral artery two hours after puncture.

Fig. 6. Arrows indicate some alleviation of spasm 4 hours after puncture.

Fig. 7. Nine hours after puncture the middle cerebral artery is still in spasm (small arrow). The large arrow indicates early return of perfusion to distal branches of middle cerebral artery.
provements in technique and anesthesia were made so that survival by certain monkeys for up to five separate experiments was possible. The lethal dose of contrast material in the cerebral circulation of the monkey was not known, but the animals usually tolerated Thorotrast in doses not exceeding 1 cc per lb for the entire experiment. Even with careful control of total contrast material dosage, many animals died on the first postoperative day, particularly when severe cerebral vasospasm was produced.

The control angiogram in the lateral view (Fig. 8) demonstrates that the course and distribution of the anterior and middle cerebral arteries of the monkey are comparable to those in man. The anterior cerebral artery was punctured just proximal to the anterior communicating artery where intense focal vasospasm was demonstrated shortly after the puncture (Fig. 9). Increased vasoconstriction was often noted several hours after the puncture. Reexamination 4 days later demonstrated even more intense diffuse vasospasm of the internal carotid artery and the middle cerebral arteries; on repeated injections the anterior cerebral arteries filled poorly (Fig. 10). The same animal studied 7 days after the initial puncture was relatively alert (Fig. 11) and the cerebral vessel caliber had almost returned to normal.

Postmortem examination of the brain and
Prolonged Experimental Cerebral Vasospasm

Four days after this same puncture internal carotid artery and middle cerebral artery are still in marked spasm, and anterior cerebral artery barely fills.

FIG. 10. Four days after this same puncture internal carotid artery and middle cerebral artery are still in marked spasm, and anterior cerebral artery barely fills.

Seven days after this same puncture the arterial caliber has virtually returned to normal.

FIG. 11. Seven days after this same puncture the arterial caliber has virtually returned to normal.

cerebral vessels usually demonstrated the effects of staining from subarachnoid blood particularly on the side of the punctured vessels. The site of puncture was generally observed as a small discoloration in the vessel wall; when such a vessel was opened, there was no evidence of subintimal dissection or hematoma. There was no grossly observable brain swelling.

In no instance was an organized intracerebral or extracerebral hematoma produced by this technique. There was no correlation between the degree of vasospasm and the amount of blood or xanthochromia in the cerebrospinal fluid.

Effects on the Electroencephalogram. Bipolar recordings were taken from screw electrodes in the skull over the distribution of the middle cerebral artery in each side. Interpretation of the electroencephalogram was difficult in many cases because of the asymmetry induced by the extradural retraction of the temporal lobe. In some instances, however, there was marked flattening and loss of background activity after puncture of the middle cerebral artery during the maximal spasm. The amplitude of the recording usually returned to a point comparable to that on the opposite side, but with increased slow-wave activity, even though vasospasm was still present.

Intracranial Pressure and Systemic Arte-
rival Pressure. There was a mild and unsustained increase in systemic arterial pressure after puncture of the vessel. The intracranial pressure rose abruptly at the time of the puncture and very gradually recovered but not to baseline levels. A sustained but mild increase in intracranial pressure was maintained after the puncture.

Cerebral Blood Flow and Cineangiographic Measurement of Circulation Time. Studies of cerebral blood flow based on electromagnetic flow meter measurements on the common artery were not considered reliable. Because of the prominence of the external carotid circulation in the monkey and because of external-internal carotid anastomoses, the electromagnetic recording of cerebral blood flow is not reliable unless the external carotid system can be completely excluded from the circulation. Under certain circumstances, including the administration of epinephrine, we have observed angiographic evidence that the external carotid system dilates independently of the internal carotid system. Effects of this sort will obscure the measurement of total blood flow to the brain.

Biplane cineangiograms at a rate of up to 540 frames per sec were made; spasm in the major cerebral vessels was observable, but the inherent clarity in these 16 mm films was disappointing. High speed cineangiograms are motion picture photographs of an image-amplified fluoroscopic screen. The resolution is, therefore, limited by the haziness of the screen. It became obvious after the first 20 experiments that the subtle alterations in vessel caliber and circulation could not be measured with this technique.

High-speed serial angiograms at 6 per sec did provide adequate resolution demonstrating changes in vessel caliber and altered circulatory dynamics. Particularly visible were alterations in circulation time through narrow vessels, the development of colateral flow after spasm, and changes in the character of opacification. The physiological significance of these local and regional angiographic findings and the technique of their serial calculation will be the subject of a future report.

Arterial puncture experiments were performed in 73 animals. Twenty experiments, which involved predominantly the use of cineangiography, were discarded from the series after it was concluded that this technique could not accurately demonstrate changes in these small vessels. Five other experiments were excluded because of technical problems or failure of the animals to survive the early stages of the procedure. Among 48 experiments in which satisfactory pre- and post-puncture angiograms could be obtained, 31 demonstrated definite evidence of arterial narrowing 1 hour or longer after puncture. The interpretation of arterial vasospasm was based on significant narrowing easily visible by the naked eye. Spasm was accepted only when both investigators, a radiologist (K.R.) and a neurosurgeon (F.S.), agreed. In the acute experiments the vasospasm was observed throughout the duration of the animal's survival. Interestingly, the percentage of monkeys who developed significant spasm after puncture is comparable to the incidence of angiographic spasm in patients with freshly ruptured cerebral aneurysms.

Discussion

Florey in 1925 observed that a pial artery would constrict when stimulated mechanically.10 Echlin's pioneering observations on pial artery activity concluded that mechanical stress of the vessel wall was adequate stimulation to produce constriction, but vasoconstriction so produced was never propagated for very long distances. The vasospasm induced by stretching was, therefore, a more local phenomenon producing a beaded appearance of the vessel. In Echlin's preparation the maximal duration of narrowing from a single stimulus was 12 min with an average duration of 3 min. The constriction sometimes did not reach its maximum until 1 min after stimulation. In his experiments the basilar artery seemed to be more "active." In our experiments the verteobasilar system did not contribute as actively to generalized vasospasm as did the carotid system. This concurs with clinical angiographic findings in patients with ruptured cerebral aneurysms. In patients who died following ruptured cerebral aneurysms, Smith16 observed infarction only in the distribution of the carotid system, not in the verteobasilar system.

This differential activity of the two major cerebral circulation systems is only speculative; we did not puncture verteobasilar
system vessels during our series of experiments. Differential reactivity of pial vessels was also described by Echlin and others in reference to the species of his experimental preparations. He concluded that the cat's pial vessels were most sensitive to mechanical and electrical stimulation, that the dog's pial vessels were less sensitive than the cat's, and that monkey's pial vessels were more refractory to direct stimulation than those in either the cat or dog.⁶

Raynor, and others¹,¹⁰,¹¹,¹³ produced transient pial artery constriction with the local application of serotonin. More recently, Echlin¹ observed both vertebral and basilar arteries in monkeys as these vessels were bathed with fresh blood. The maximal duration of the resultant spasm was apparently around 60 min, but the usual duration was 5 to 10 min. Lende¹³ was able consistently to produce local pial spasm with electrical stimulation. But the maximal duration of this spasm following a single stimulus was around 30 min.

We studied the intracranial carotid, anterior and middle cerebral artery systems because these vessels seem to be most active clinically in the vasoconstriction following aneurysmal rupture. The behavior of pial vessels is probably quite different from that of the larger arteries at the base of the brain.

Du Boulay¹ studied the angiograms in 137 patients with ruptured intracranial aneurysms. From repeated angiography he concluded, "relaxation of spasm after subarachnoid hemorrhage takes from one to four weeks and is often complete in the third week." The frequency of follow-up angiography in his series, however, was not sufficient to determine precisely the time of relaxation of the spasm, so that the spasm duration may appear artificially long. He did note that in patients studied within a few hours of the hemorrhage, the spasm may be very severe and widespread. This impression, in general, has been confirmed in our series of follow-up studies on monkeys. The intense generalized spasm which sometimes follows vessel puncture, with a variable latency, has a devastating effect on cerebral perfusion. This ischemic interval may well account for the loss of consciousness that follows rupture of an aneurysm.

To separate this characteristic persistent vasospasm that follows rupture of a cerebral aneurysm or puncture of a major cerebral vessel from the more localized spasm of short duration produced by other experimental techniques, we have used the term "prolonged cerebral vasospasm." Arbitrarily this refers to the narrowing of a cerebral artery for a period significantly longer than 1 hour following a single stimulus. We have insufficient understanding of this phenomenon to permit us to hypothesize intelligently on the mechanisms of its initiation and prolongation. The function of fine nonmyelinated perivascular nerves on larger cerebral arteries is not understood, and their neuroanatomical connections are not known. The popular theory that vasoconstrictor chemicals in the extravasated blood are responsible for this vasospasm remains unproven.⁷,²⁰,²¹

From these studies and the particular association of prolonged cerebral vasospasm with ruptured cerebral aneurysms, it seems apparent that a penetrating insult to the wall of a major cerebral vessel is sufficient to induce long-standing constriction. It does not seem reasonable that blood products can induce vasoconstriction that lasts for several days or several weeks. Prolonged severe cerebral vasospasm following intracranial bleeding is rare except when a ruptured cerebral aneurysm is the cause. Since it is not possible to produce an aneurysm on cerebral vessels experimentally, we cannot study the role of the aneurysm itself in the prolongation of spasm.

Summary

1. Cerebral angiography in Rhesus monkeys is a feasible way to study the anatomy of the cerebral vascular system.
2. High-speed serial angiography was used to obtain physiological flow data in addition to changes in vascular anatomy. Cineangiography with currently available equipment, however, provided insufficient resolution to be of use in interpreting flow and caliber changes in large monkeys.
3. Angiography demonstrates changed cerebral vessel caliber when these vessels were subjected to mechanical stimulation, electrical stimulation, and the application of chemicals of known vasoconstrictive properties. The injection of potent vasoactive chemicals in the
subarachnoid space produced transient generalized arterial constriction.

4. The puncture of a major vessel in the circle of Willis produced an immediate and durable vasospasm, both localized and generalized, which persisted throughout the duration of the experiments, limited usually by the animal's survival. Spasm lasting over 4 days before subsequent relaxation was demonstrated following a single puncture.

5. Since prolonged vasospasm was observed in over 65% of a series of 48 satisfactory experiments on monkeys, we feel that this technique provides a model for the study of the phenomenon of prolonged cerebral vasospasm and its effect on the cerebral circulation. It may serve as a tool for investigation of methods to restore normal flow.

References


