This study does not establish the mechanism by which CBF is regulated during changes in arterial pressure. We conclude, however, that the failure of CBF to increase during increases in arterial pressure is not the result of baroreceptor-induced cerebral vasoconstriction. These findings favor the concept that neural control of CBF is important1–3, 6–9 and support a predominant role of local factors.

Acknowledgment

We thank Donald Piegors and Dennis Beach for technical assistance; James Ehrhardt, Ph.D., for assistance with isotope separation; Oscar Lim for assistance with computer programming; and Violetta Pusack for secretarial assistance.

References


A Model for Spasm of the Anterior Cerebral Artery

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SUMMARY A model for production of spasm of the anterior cerebral artery in primates is presented. The model consists of injection of 0.35 cc of fresh blood into the chiasmatic cistern through the optic canal after orbital exenteration. Clinical and angiographical follow-up is possible. The clinical appraisal of acute and chronic changes can be accomplished in the awake animal.

THE PATHOPHYSIOLOGICAL MECHANISMS of spasm of the cerebral arteries are not well understood. A variety of theories have been proposed to explain a confusing, and sometimes contradictory, body of clinical and radiographical evidence.1–12 The complexity of the problem is borne out by the large number of proposed models.13–20 Experimental vasospasm is produced either by mechanical trauma to a vessel or by application into the subarachnoid space (SAS) or directly on the vessel of a variety of spasmodenic agents in a wide range of volumes and concentrations. The applicability of the proposed models to the naturally occurring spasm in man remains sub judice.14 In particular, no experimental method is available to investigate the immediate as well as the prolonged clinical effects of subarachnoid hemorrhage (SAH) and subsequent vasospasm in the awake animal.

A method for the production and evaluation of cerebrovascular spasm in primates is proposed. The model, which is a derivation of the Hudgins and Garcia approach for creating experimental cerebral infarction,20, 21 has two distinctive and advantageous features: (1) production of segmental vasospasm in the anterior circle of Willis using a small amount of spasmodenic agent, and (2) the possibility of clinical appraisal of acute and chronic changes in the awake animal.

Methods

A total of 29 rhesus monkeys weighing 5 to 7 kg were used. The experimental protocol included two phases: (A) placement of an indwelling catheter into the chiasmatic cistern, and (B) introduction of spasmodenic agent into the cistern followed by clinical and angiographical evaluation.

Phase A

The anesthetized animal was appropriately positioned in a standard primate headholder. The left eye was enucleated along with all muscle attachments and orbital fat, and exenteration of the orbit was accomplished using the operating microscope. The optic nerve was severed, and bleeding from the ophthalmic artery was controlled with bipolar coagulation. Using sharp curettes, the optic canal was enlarged until the ophthalmic artery was controlled with bipolar coagulation. The anesthetized animal was appropriately placed into the operating room and positioned in the headholder. The left eye was enucleated using a sharp curette, and the optic canal was enlarged using bipolar coagulation. The optic canal was then closed using a 7-cm Raimondi peritoneal catheter.* The catheter was placed into the chiasmatic cistern. The clinical and angiographical evaluation was performed following placement of the catheter.
catheter was carried out under fluoroscopic and radiographic control and efforts were made to place its tip just across the midline, close to the right anterior clinoid process. The catheter was anchored in the orbital portion of the optic canal using a gelatin sponge impregnated with alpha cyano-acrylate glue. The rest of the tubing was coiled in the orbit and the lids were sutured together, leaving the catheter opening in an easily accessible position. A recovery period of one week was allowed before Phase B and, during this period, the animal was treated with antibiotics. In two animals, meglumine iocarmate was injected into the catheter to confirm its placement by outlining the chiasmatic cistern. When correctly placed, cerebrospinal fluid (CSF) flowed freely from the catheter.

Phase B

Whole, fresh, arterial blood was the spasmogenic agent employed. Blood was obtained in the awake animal from an angiographical catheter indwelling in the femoral artery since the previous day. The volume of blood introduced through the catheter into the cistern was 0.35 cc with due consideration given to the catheter dead space.

Clinical evaluation in the acute phase, starting soon after the cisternal injection of blood, was done in 13 awake animals without concomitant angiographical control. A standard primate restraint chair was used for this purpose. Animals were checked during an eight-hour period of time. Magnification (X3) angiography of the carotid circulation was carried out by transfemoral catheterization of the right common carotid artery, under intravenous sodium thiamyl anesthesia in 12 animals. Meglumine diatri-
FIGURE 2. Control before (1) and 30 (2) and 160 (3) minutes after cisternal blood injection. In control angiogram, projection is slightly different than in post-injection films. Note marked spasm at 30 minutes and rebound dilatation at 160 minutes. The latter is particularly evident in ACA.

Zoate** (2 cc) was used for each angiographical examination. A maximum of eight injections (Viamonte-Hobbs pressure injector)** were made during a day. The sequence of the angiograms, taken after the cisternal injection of blood, varied. Fifteen, 30, 60 and 120-minute studies were made in all animals, whereas studies ranging from several hours to several days were carried out according to special needs. In particular, studies were performed in five animals, one to four days after blood injection, to evaluate biphasic (early and late) vasospasm.

In both groups of animals with and without angiograms, intra-arterial blood pressure and electrocardiograms were recorded during the acute stage of the experiment. Also, blood gases (PaO₂, PaCO₂, and pH) were measured with samples taken immediately before and after cisternal injection of blood, and before and after each angiographical study. CSF was obtained on seven consecutive days from six of 13 animals used for clinical evaluation of acute spasm. Color, cell count, and protein concentration were noted for each sample.

Chronic clinical evaluation was carried out in both groups by checking for obvious neurological deficits every day up to a maximum of 15 days. After this period the animals were killed and gross postmortem study of the chiasmatic cistern, the circle of Willis and the brain followed.

Four monkeys without cisternal catheter were used exclusively for controlling postangiographical physiological changes. These animals were not killed.

Results

Clinical evaluation of the acute phase of cerebral vasospasm was performed in 13 awake animals. Every monkey screamed during the initial injection, became lethargic or somnolent within 30 minutes, and recovered to its preinjection active state within 60 to 90 minutes. Three animals, in addition to becoming lethargic, had a left hemiparesis within 30 minutes of the injection, which cleared within two hours. Over the following days, these 13 animals remained neurologically normal. This intact neurological status was also noted in the animals which had had angiography and for which no acute clinical testing was possible.

The angiographical evaluation of the acute vasospasm was carried out in 12 animals. In all cases, segmental vasospasm of the A1 segment of the right anterior cerebral artery (ACA) was observed. The spasm commenced at 30 to 60 minutes after cisternal injection, and persisted for 30 to 60 minutes. In most cases, the vessel was totally back to normal within two hours (fig. 1). One animal showed a postvasospastic (rebound) dilatation of the ACA (fig. 2). In each case, the demonstration of vasospasm was unequivocal with a reduction in vessel caliber of 30% to 50%. In two animals, the right A1 segment in the control angiogram appeared smaller than the average caliber of 2.5 mm seen with X3 magnification angiography. Here, the experimentally induced spasm was less evident. In both cases, postmortem study revealed anatomical variations in which the right A1 was smaller than the left.

It should be noted that control angiograms of up to eight consecutive injections performed on four separate test animals failed to produce vasospasm. Also, in agreement with previous reports,27-29 we observed no lasting clinical ill effects in these control monkeys. We confirmed the findings already well documented by others28-30 of bradycardia and lowering of the blood pressure immediately following contrast medium injection. This response was not observed with cisternal blood injection alone, whether in the awake or anesthetized animal. In our animals, changes in PaO₂, PaCO₂ and pH in the arterial blood were negligible in connection with both angiography and the production of experimental SAH.

**Renografin 76, Squibb, Princeton, New Jersey.
††Barber-Colman Company, Rockford, Illinois.
Angiographical evaluation of biphasic spasm was done in five animals. Following the initial production and regression of acute spasm, angiograms were carried out at 24, 48, 72 and 96 hours. In only one instance was a return of spasm noted, at 72 hours (fig. 3).

The findings with regard to the CSF are compatible with those of SAH in man. In all cases, within six hours after cisternal injection of blood, CSF removed from the cisterna magna revealed an increase in the number of red blood cells, white blood cells and protein concentration. The increase in white cells was primarily an increase in the number of polymorphonuclear cells. The CSF became xanthochromic at 24 hours and remained so for seven days.

Gross postmortem examination in the animals which were
killed showed no significant abnormality in the chiasmatic cistern, the vessels about the circle of Willis, and the brain sections.

Acknowledgment

The technical assistance of Clifford A. Seay and Mary E. Girton is acknowledged.

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Stroke. 1976;7:243-247
doi: 10.1161/01.STR.7.3.243

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