Experimental vasospasm, acute and chronic, due to blood in the subarachnoid space

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This investigation on monkeys provides arteriographic and other evidence that blood, in the absence of evident mechanical stimulation or injury to intra-dural arteries, will, when injected into the anterior cervical subarachnoid space through a catheter, consistently cause acute and chronic vasospasm of the intra-dural arteries, presumably where they are contacted by blood. Evidence indicates that vasoconstrictor agents or factors in fresh blood cause the vasospasm, since similar subarachnoid injection of saline or clear serum did not cause vasoconstriction. Other circumstances involving mechanical or other factors, such as vessel injury, may contribute to the length and severity of the vasospasm, but whether they have an etiological role needs further study.

KEY WORDS: vasospasm, subarachnoid space, intradural arteries

It is now established that prolonged, often delayed vasoconstriction of the intradural arteries may accompany subarachnoid hemorrhage from a ruptured aneurysm. The vasoconstriction, although often bilateral and diffuse, is commonly more marked ipsilateral to the aneurysm and may involve especially the ruptured vessel or a segment thereof close to the rupture.

Wilkins, et al., have stated: "It has been postulated that preoperative intracranial arterial spasm originates locally as a result of arterial distortion and irritation by aneurysmal rupture and perivascular clot formation and is propagated to other areas by the nerves and smooth muscle fibers of the involved cerebral arteries. Our recent clinical experience with intracranial arterial spasm, as analyzed in the present paper, adds further support to this concept."

Simeone, et al., using an angiographic technique (as introduced by Allcock) were the first to demonstrate experimentally that acute and prolonged vasospasm can be produced by puncturing a major branch of the circle of Willis with a needle which caused "a brief period of arterial bleeding." Evidence that vasospasm is both acute and recurrent ("biphasic") was presented by Brawley, et al., following evulsion of the anterior cerebral artery. These two sets of experiments have each ingeniously duplicated from a mechanical and a hemorrhagic aspect what may happen in rupture of an aneurysm, but Simeone, et al., concluded that the cause of vasospasm is mechanical and Brawley, et al., that it is due to substances released from blood.

Using the technique of Simeone, et al., we obtained evidence in preliminary acute experiments that bloodless transfixion of a branch of the circle of Willis usually leads to transitory, largely local, spasm, whereas puncture with hemorrhage is followed by more prolonged and more diffuse vasocon-
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striction, similar to that resulting from subarachnoid injection of blood. In recent experiments, acute and pro-
longed, often recurrent vasoconstriction has been recorded arteriographically after the in-
jection of subarachnoid blood by catheter via an anterior cervical approach, into the cisterna magna or into the cisterna interchiasmatica by needle technique (as described by Lougheed and Tom).

Finally, there is experimental evidence that spasm may be more marked and more prolonged when puncture of or injury to a branch of the circle of Willis is combined with one or more subarachnoid injections of blood than when the latter alone is per-
formed.

Methods

In 36 monkeys anesthetized with nembutal intraperitoneally and placed in the supine position in a special headholder under sterile technique, the dura mater was exposed over the anterior surface of the spinal cord via an anterior approach through the bodies of the cervical vertebrae C-3 to D-2. A catheter (diameter 0.017 in.), bent to almost a right angle with the stylet inserted to just beyond the bend, was passed, under the microscope, cephalad about 1/8 inch, in the midline, into the subarachnoid space through a hole in the transparent arachnoid. Before insertion into the subarachnoid space, a ligature was tied about the catheter and stylet and later fast-
tened to the dura with two silver clips to hold it in place, the stylet withdrawn, and the dura closed. It was impossible for this inves-
tigator to insure insertion of the catheter into the subarachnoid space except under the microscope.

The right brachial artery was now ex-
posed low in the arm and a catheter inserted and tied in place. Serial arteriography was per-
formed following the insertion of the cervical catheter and immediately before each subarachnoid injection of blood, and there-
after at 3 to 5 min, 1, and usually 2 to 3 hrs, and then at 24, 48 and 72 hrs. In a smaller series, daily angiograms were per-
formed for 1 week or longer. Lateral films were taken in all cases and frequently anteroposterior films as well. The arterial catheter was always withdrawn and the brachial artery ligated at the end of each day's experiments and reinserted on subsequent days. It was common in subsequent experiments in 24 hrs or more to find a firm clot in the brachial artery. After opening the artery with dissecting scissors immediately above the site of the previous ligature, it was usu-
ally easy to milk out the clot, establish a completely free flow of blood, and reinsert the catheter. With care this procedure could be repeated at daily intervals for a week or more without danger of embolism.

In 30 monkeys, 2 to 5 cc of fresh blood were withdrawn from the brachial artery and immediately injected forcefully (and in some slowly) into the subarachnoid space through the cervical catheter which in 20 instances was then immediately withdrawn. In one other animal, the injection was in the tho-
racic region through a laminectomy and one via a suboccipital craniectomy and cervical laminectomy. In four additional animals, blood was inadvertently injected into the subdural space via an anterior cervical ap-
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racic region through a laminectomy and one via a suboccipital craniectomy and cervical laminectomy. In four additional animals, blood was inadvertently injected into the subdural space via an anterior cervical ap-
proach. In three instances the subarachnoid catheter was left in place for several days. In five monkeys the catheter was reinserted into the subarachnoid space 24 hrs or more after the initial procedure and further injections made of blood, blood with acid dextrose solu-
tion (ACD), blood with ethylenediaminetraacetic acid (EDTA), or saline. Serial angiograms were performed in all instances before and after any injections. Local anes-
thesia was usually used in the chronic exper-
iments.

Autopsies were carried out on all animals, and the brain and upper cervical cord re-
moved after fixation with formalin injected via the brachial or, at times, carotid arteries.

Other experiments were done as described below following transfixion, puncture, or other stimulation of cerebral vessels with and without subarachnoid hemorrhage. Ar-
terograms were performed in some animals by using the right carotid artery.

Results

Acute Vasospasm following Injection of Fresh Blood into the Cervical Subarachnoid Space

In experiments on 30 monkeys, acute bi-

lateral diffuse vasoconstriction of the arteries of the circle of Willis and their branches oc-
curred in all animals following a single forceful or slow injection of 2 to 5 cc of fresh arterial blood into the subarachnoid space through a catheter inserted microscopically via an anterior cervical approach (Figs. 1 and 2). The spasm, although diffuse, was often more marked in the posterior circulation where the basilar artery frequently became almost invisible. The severe degree of spasm was present within 3 min and remained intense for usually less than 30 min, but some spasm was common for many hours, and in eight animals remained quite severe for the 3-hour duration of the acute experiment. Acute vasospasm was always present if the blood was in the subarachnoid space but not when the blood was injected subdurally.

In acute experiments on 10 monkeys, a second injection of 1 to 5 cc of fresh blood was carried out within 1 hour following the first one, at a time when the initial acute vasospasm had largely or completely disappeared. In all animals, severe diffuse vasoconstriction of the major intradural arteries recurred and persisted, for up to $\frac{1}{2}$ hr in most animals, but often longer. The spasm was more pronounced and apparently lasted longer following the second injection of blood in some but not all of these animals. Several of the animals stopped breathing and all died within 24 hours. The clinical course may have been influenced by the use of tracheotomy and the later development of an excess of pulmonary secretion in these early experiments.

Subarachnoid Injections of Fresh Blood in the Posterior Cervical and Thoracic Region

In two additional animals, 1 cc of fresh blood was either injected slowly into the subarachnoid space in the posterior cervical region (Monkey 500) or 7 cc slowly in the thoracic region (Monkey 501). In each, a laminectomy was performed and the catheter inserted with microscopic technique (as de-
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Subarachnoid Injection of Blood Anticoagulated with ACD and of Saline with ACD

In two other animals (Monkeys 492 and 493), 5 cc of saline (normal human) containing acid citrate dextrose solution (ACD) were injected into the subarachnoid space via the anterior cervical approach. In 3½ min, all major intradural arteries were quite markedly dilated. Then 4 min later, 5 cc of fresh monkey blood anticoagulated with a similar quantity of ACD was similarly injected and within 3½ min caused quite marked constriction of all intradural arteries. At 34 min this diffuse vasospasm was even more intense and persisted in angiograms at 1 and 2 hrs. At 24 hrs diffuse spasm was still

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Fig. 2. Monkey 491. Upper Left: Normal right brachial arteriogram after insertion of cervical catheter. Upper Right: At 3 min following the subarachnoid injection of 5 cc of blood there is intense diffuse vasoconstriction. Center Left: At 1 hr, acute spasm is much less. Center Right: At 24 hrs after the injection chronic spasm is present and somewhat greater than at 1 hr. Lower Left: At 7 days after the subarachnoid injection of 5 cc of blood, some vasoconstriction is still present in the anterior circulation. Lower Right: At 10 min after lower left arteriogram and 3½ min following the injection of 5 cc of normal saline into the subarachnoid space, there is marked diffuse vasodilatation.
present, but not so marked, and had almost disappeared in 3 days. In two more animals, injections of blood anticoagulated with similar quantities of ACD and kept refrigerated for 12 days were followed by similar acute and "chronic" vasospasm at 24 to 48 hrs. The quantity of ACD used with blood or saline was equivalent to that employed routinely in the blood bank for anticoagulation of human blood.

Vasodilatation and Relief of Vasospasm Following Subarachnoid Injection of Saline

To determine if the mechanical effect of the injection of blood might be responsible for the resulting acute vasospasm, in five normal monkeys, 2 to 5 cc of normal (human physiological) saline, and in three additional instances, 5 cc of serum (clear human or monkey) was forcefully injected into the anterior cervical subarachnoid space in a manner identical to that used with blood. In none of the animals did any vasoconstriction of intracranial arteries occur. In fact, saline consistently produced vasodilatation of the normal vessels of the circle of Willis and their branches. In three other animals in which vasoconstriction had resulted from the subarachnoid injection of 2 cc of fresh blood, a subsequent injection of 5 cc of saline caused an immediate diffuse vasodilatation of the intradural arteries above the caliber of normal vessels (Fig. 2 upper left). A second injection produced an even greater vasodilatation. The dilatation varied in duration but was still present after 24 hrs in two animals in vessels chronically constricted for more than 24 hrs by an injection of blood. A subsequent injection of 5 cc of fresh blood converted the vasodilatation to vasoconstriction of the major branches of the circle of Willis but not always the peripheral (cortical) ones. The reason for the dilatation with saline is not yet clear and requires further study using normal physiological (monkey rather than human) saline with careful control of the pH and electrolytes used.

Chronic Vasospasm

In 16 of 18 monkeys studied with serial angiography in which a single, anterior cervical subarachnoid injection of fresh blood had been made, diffuse chronic vasoconstriction of the intradural arteries was demonstrated at 24 to 72 hrs post injection (Figs. 1 and 2). In 14 of these 16 animals, vasospasm was greater at 24 to 72 hrs than at 35 to 48 min, at which time the intense acute spasm had subsided in varying degrees. Of nine monkeys followed, seven continued to show diffuse vasospasm for 3 to 7 days, but this had almost disappeared by the 14th day in the two animals studied for this period. In four of this group spasm was somewhat more marked at 48 to 72 hrs than at 24 hrs.

In six additional animals mentioned in the acute experiments, in whom fresh blood, or fresh or old blood anticoagulated with ACD, had been injected into the anterior or posterior cervical or thoracic subarachnoid space, chronic diffuse vasoconstriction was present in all at 24 to 48 hrs after injection.

Thus, chronic diffuse vasoconstriction of the intradural arteries appears to have been demonstrated in 22 of 24 animals.

Angiograms at 24 hrs after the subarachnoid injection of blood in the anterior cervical region usually revealed some narrowing of the vertebral arteries, perhaps the result of local hemorrhage or edema but possibly due to propagated spasm. Questionable vasoconstriction of the carotid arteries was also noted in angiograms of several monkeys at 3 to 24 hrs following their exposure during exploration of the basilar artery or anterior cervical exploration.

Clinical Manifestations following Subarachnoid Injections of Blood

In 20 monkeys, in the acute experiments, only a single subarachnoid injection of blood was made under general anesthesia. Eighteen of these animals survived 24 hrs to 7 days, probably due to improved technique. In few of them were major neurological abnormalities noted despite the presence of marked vasospasm. The majority were quite active about their cages and eating well within 24 to 36 hrs after the acute experiments, although a few remained drowsy and later showed questionable mild paresis as a possible result of the subarachnoid blood. Sufficient data are not available to draw firm conclusions regarding the clinical effect of vasospasm in this group.

Electroencephalograms and electrocardiograms were performed on many of the animals during the acute and chronic phases of the experiments but the findings were not conclusive and will not be reported here.
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**Autopsies**

When 2 to 5 cc of blood were injected into the anterior cervical subarachnoid space, autopsies at 24 hrs revealed blood evenly distributed throughout the basal cisterns contacting all the major vessels of the circle of Willis and extending symmetrically along the middle cerebral arteries in the Sylvian fissures and along the anterior cerebals between the hemispheres. Where larger quantities of blood (10 cc) had been used in acute experiments, blood was also present widely over the cerebral convexities, but the major quantity was in the basal cisterns. At 24 hrs to 7 days the findings were similar except that the quantity of blood became progressively less, especially over the cerebral convexities. In four animals the injected blood was in the subdural space, and these were the only monkeys that did not develop either acute or chronic vasospasm arteriographically.

**Preliminary Observations on the Effect of Transfixion, or Puncture with Hemorrhage, of Intracranial Arteries**

In 10 monkeys through a frontal craniectomy, the anterior or middle cerebral or carotid artery was transfixed with a 30-gauge needle, and serial angiograms performed. In those animals where no hemorrhage occurred, there was local spasm of the vessel transfixed with some decreased flow in this vessel, which had largely disappeared at the end of the acute experiment in 2 hrs in six monkeys. In four of these animals angiograms were obtained at 24 hrs and revealed no evidence of spasm, but there was observable brain edema.

In these 10 monkeys, after 24 to 36 hrs, the same or a neighboring artery was punctured with local or diffuse subarachnoid hemorrhage. Serial angiograms showed local and unilateral acute spasm when the hemorrhage was localized (as revealed at autopsy) and diffuse spasm when the subarachnoid hemorrhage was diffuse. All of these animals died within 24 hrs after the hemorrhage.

**Transfixion and Puncture of the Basilar Artery**

Bloodless transfixion (with a 30-gauge needle) of the basilar artery through a cranietomy in the base of the skull in two monkeys caused local observable spasm. In bra-

**Discussion**

The three most commonly considered etiological factors in cerebral vasospasm are a vasoconstrictor agent or agents in blood, mechanical stimulation or injury of intradural arteries, and a vasomotor mechanism, or a combination of all three.

Fig. 3. Monkey 518. Arteriogram 24 hrs after bloodless transfixion of the basilar artery with a 30-gauge needle. There is no local or diffuse spasm. The needle is not seen in the arteriogram but is still in place transfixing the basilar artery as confirmed at autopsy.
In the first part of this investigation, subarachnoid injections of fresh blood (or old anticoagulated), in the absence of apparent mechanical stimulation or injury to intracranial vessels, consistently caused acute and, in 22 of 24 monkeys, also chronic diffuse vasospasm of the intradural arteries. These findings are in keeping with other reports of acute or chronic spasm following injection of blood into the subarachnoid space by different routes. The apparent recurrent nature of the phenomenon agrees with the observations of Brawley who evulsed the anterior cerebral arteries. The latter procedure, however, does not rule out the role of vessel trauma as an etiological factor. In humans, angiograms are seldom performed during the first half hour following a subarachnoid hemorrhage and hence the acute phase of spasm is rarely recorded. The question of whether the chronic vasospasm is "prolonged" or "recurrent" is perhaps academic. However, vasospasm does appear to occur in two phases, an acute and a chronic one, i.e., is "biphasic." The intense, acute phase usually lasts about half an hour but may persist to some degree and again becomes marked in angiograms at 24 to 72 hours. Both the acute and chronic vasospasm, although diffuse, was frequently more marked in the posterior circulation, which was usually bathed in a large quantity of blood injected almost directly into the basal cisterns through an anterior cervical approach.

The experiments were planned so that no direct injury to intracranial vessels occurred that might account for their vasoconstriction, as may happen when an intradural artery is directly punctured or evulsed, or when injections are made by needle into the chiasmatic cistern. Also, the injected blood was quite symmetrically distributed intracranially rather than more locally as in rupture of an aneurysm or puncture of a vessel. The possibility that injection of blood into the anterior cervical subarachnoid space could distend the basal cisterns, stretch or in some way indirectly stimulate the large vessels and cause acute spasm, likewise appears ruled out: since similar injections of saline or clear serum did not produce any vasospasm. The former in fact consistently caused vasodilatation of normal arteries as well as of those acutely or chronically constricted by a previous injection of blood. The rapid dilatation of vessels chronically constricted by blood does indicate that "constriction" was not due to edema of the vessel wall. No detailed work has been done on other agents that may relieve vasospasm.

In the acute and chronic experiments, constriction took place apparently where blood came in contact with intradural arteries. The findings regarding acute spasm are in accord with those where blood or blood products produced acute temporary vasoconstriction when directly applied to peripheral vessels, to smooth muscle, or to the basilar artery, and with others where vasospasm of the basilar artery followed application of blood, packed red blood cells or platelets 12 days old, each anticoagulated with ACD; but not when anticoagulated with EDTA (ethylenediaminetetra-acetic acid). Whether this vasoconstriction is the result of serotonin, noradrenaline, or some additional agent is undecided. The chronic vasospasm in these studies, like the acute one, is also difficult to explain on the basis of injury or mechanical stimulation and would seem most likely to be the result of factors in blood or of substances slowly released during its fibrinolysis. A possible inflammatory factor should also be kept in mind. The chronic vasoconstriction does not appear due to a variability in vessel diameter that might occur normally with sequential arteriograms since it was present in almost all animals (22 of 24). Also, serial brachial angiography (as employed) in normal monkeys, unlike humans, showed little variability in the filling of the posterior or anterior circulation. The presence of some constriction of the vertebral arteries noted at 24 to 72 hours, may have contributed in some degree to the very poor filling of the basilar artery at this time, but does not explain the vasoconstriction in the anterior circulation, nor the marked spasm of the posterior circulation in almost all the acute experiments, nor the acute and chronic diffuse vasospasm that occurred following subarachnoid injections of fresh blood in the posterior cervical or thoracic regions.
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These observations that blood rather than vessel injury was responsible for the vasospasm were supported by preliminary control ones in which needle transfixion of a large branch of the circle of Willis without hemorrhage was usually followed by transitory local constriction, whereas puncture of the same vessel with hemorrhage produced relatively local spasm when the hemorrhage was local and more diffuse spasm when the hemorrhage was diffuse. Many of the monkeys in this group with local or diffuse hemorrhage and vessel injury developed local pathological and neurological abnormalities that could not be correlated with the degree of spasm present. Such abnormalities were rare in those monkeys with spasm from subarachnoid injection of blood alone, but were common when the catheter tip lay partly in the subdural space or was partially obstructed, as noted when injections were made 24 hrs or more after insertion of the catheter. The evidence that vasospasm is more pronounced when subarachnoid hemorrhage is combined with vessel injury, cannot be answered in this study. However, other factors in addition to vasospasm must be considered as a possible cause of the neurological deficit and high morbidity that may follow subarachnoid hemorrhage from rupture of an aneurysm, or needle puncture with hemorrhage. These include pathological changes in the vessel wall, intra-arterial accumulation of platelets and blood products with partial thrombosis, slowing of the circulation, embolic phenomena, or even thrombosis of the damaged artery and brain edema. In addition, blood may extravasate into the brain tissue as well as locally along the ruptured vessel in the subarachnoid space, giving rise to focal brain pathology. When vasospasm is superimposed on such pathology, the morbidity and mortality is probably much increased. This appears in keeping with the observation of many neurosurgeons that severe vasospasm is often a bad prognostic sign. On the other hand, the absence of such associated pathology may explain why some patients with severe subarachnoid hemorrhage and diffuse vasospasm survive without neurological deficit.

There is no doubt that local mechanical (or electrical) stimulation of the large vessels of the circle of Willis in humans and in acute experiments in animals will usually cause an acute marked constriction of the vessel stimulated. This is likewise true when fresh blood is applied to a local area of the basilar artery. These constrictions have appeared localized and nonpropagated. There is experimental evidence that under certain circumstances such acute local spasm may be propagated but only for a very brief period. Also, injury to the basilar artery that may accompany forceful application of a silver clip results in local nonpropagated dilatation at that site in acute experiments when the clip is removed. Whether chronic local injury of an intradural artery per se can precipitate severe propagated spasm and prolonged diffuse vasoconstriction of more than mild degree is possible but apparently has not yet been proved.

Certainly, the intradural arteries are richly supplied with nerves and a vasomotor mechanism exists, but so far the indications are that it plays a minor part in the maintenance or propagation of vasospasm. Stimulation of the sympathetic nerves in the neck causes a very slight vasoconstriction of the cortical vessels. Following chronic denervation of cortical arteries in the cat, acute vasospasm still occurs unchanged on mechanical or electrical stimulation.

Recent work by Pool and collaborators may throw new light on this subject for they have shown that the noradrenergic fibers in the adventitia of the basilar and vertebral arteries in monkeys, as in the periphery, are depleted by spasm and catecholamine releasing agents and disappear entirely after bilateral superior cervical sympathectomy. Their findings suggest that intracranial arterial spasm is mediated through the alpha receptors on the vessel wall and that spasm is blocked by local application of alpha adrenergic blocking agents. On the other hand, after surgical sympathectomy they found that the vasoconstrictive response of the intracranial arteries to known vasoconstrictive substances, and to the application of blood (as with mechanical or electrical stimulation), is not altered.

Conclusions

Evidence has been presented that fresh blood injected into the subarachnoid space of

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monkeys consistently causes marked acute vasospasm of the intradural arteries, and usually chronic vasospasm as well.

The evidence indicates that the acute vasospasm is due to vasoconstrictor agents or factors in fresh blood, and the chronic phase to factors in blood or to agents slowly released during its subsequent fibrinolysis.

Subarachnoid injection of saline or clear serum in a similar manner did not produce acute vasoconstriction. The former caused diffuse vasodilatation of normal intradural arteries and of those acutely or chronically constricted by injections of blood.

Vessel injury may contribute to the severity and duration of cerebral vasospasm in ruptured aneurysms or following puncture of an intradural artery, but the role of vessel injury and of vasomotor mechanisms in the etiology of prolonged and possibly propagated vasospasm requires further study.

Following injury to or rupture of a major branch of the circle of Willis, other factors, in addition to vasospasm, may be important in the determination of subsequent morbidity and mortality.

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