Spasm of Basilar and Vertebral Arteries Caused by Experimental Subarachnoid Hemorrhage*

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In the present experiments on monkeys, marked spasm of the basilar and vertebral arteries, sometimes resulting in cessation of respiration and death, was produced: 1) When arterial blood was merely irrigated onto these vessels after opening the arachnoid widely over the cisterna pontis; 2) when subarachnoid bleeding surrounding these vessels was produced by rupture of a tiny pial vessel with a needle; 3) when subarachnoid hemorrhage into the basal cisterns occurred as a result of a blow to the animal’s head; and 4) following application to one of these vessels of a tiny pledget of cottonoid soaked in fresh blood.

Since the middle of the nineteenth century, many observers have suggested on empirical grounds, that spasm of cerebral vessels might play a role in epilepsy, migraine, temporary hemiplegia, hypesthesias, aphasias, and other transitory neurologic phenomena.

Although there is abundant evidence that both pial and intracerebral arteries are supplied with nerves, these vessels do not constrict more than about 8 to 10 per cent on stimulation of the cervical sympathetic nerves. Skin vessels on the other hand contract 80 per cent following similar stimulation of sympathetic fibres. Evidence that some dilatation of pial vessels occurs on stimulation of the vagus nerve, providing the facial nerve is intact, was supplied by Chorobiski and Penfield, and Cobb and Finesinger.

In contrast to the findings cited above, Florey reported in detail how marked spasms could be produced in individual pial vessels over the convexities of the cerebral hemispheres in cats by direct mechanical and electrical stimulation. Echlin confirmed the findings of Florey with photographic technique and extended them to include the larger pial vessels (basilar artery) at the base of the brain. He stated, “The aforementioned observations [on spasm] apply to arterial vessels of all sizes...the larger arterial branches, such as the middle cerebral, were somewhat more refractory than the medium-sized and smaller vessels. The basilar artery, on the other hand, constricted promptly to almost complete obliteration when stimulated in the usual manner with a blunt rod. The latter observation was made on 10 cats, in which the basilar artery was exposed through a burr hole in the base of the skull...”. Echlin concluded that mechanical stretch of the vessel was an adequate stimulus to produce spasm, independently of a neurovascular mechanism, and showed that such spasm occurs in essentially denervated branches of the middle cerebral artery of the cat. A distinct difference in the reaction of the pial vessels over the convexity of the hemispheres to mechanical stimulation was noted in various species. The cat’s pial vessels in this location contracted on mechanical stimulation, in the dog they were much more refractory, and in the monkey they were unresponsive. Lende has confirmed the finding that the pial vessels over the cerebral convexities in cats constrict promptly on mechanical stimulation, and Gurdjian et al. have corroborated the observation that the pial vessels in a similar location in monkeys do not respond to mechanical stimulation. Proof of cerebral vasospasm in hypertensive animals is also available. Further observations that the larger vessels of the circle of Willis in cats and monkeys contract vigorously on mechanical stim-
ulation have been reported by Harvey and Rasmussen, 20 Pool, 30 Pool et al., 32 Raynor and Ross, 37 and more recently by Corday et al. 7

That the larger pial branches of the circle of Willis in humans will also constrict following mechanical stimulation or stretch has been observed by Ecker and Rimenschneider, 15 Botterell et al., 1 Gillingham, 17 Johnson et al., 22 Pool et al., 2 Pool et al., 22 Penfield et al., 29 and others.

In recent years with the wide use of arteriography, evidence has accumulated that the large intracranial arteries in humans will go into spasm, especially in the presence of a ruptured aneurysm and subarachnoid hemorrhage. 12,13,22,25,26,37 Ecker and Rimenschneider, 15 by means of comparative angiograms, found evidence of spasm in 10 out of 11 patients with subarachnoid hemorrhage from an intracranial aneurysm which had ruptured less than 24 days previously. Angiograms on similar cases done more than 26 days after a subarachnoid hemorrhage failed to reveal spasm. They concluded, "The common element in the production of spasm in all cases of ruptured aneurysm seemed to be abrupt traction on the arterial wall." Johnson et al. 22 expressed a similar view that spasm was produced and maintained by the mechanical effect of the subarachnoid hemorrhage which resulted in spasm that sometimes lasted for weeks.

Raynor et al. 36 have provided evidence that the spasm of intracranial arterial vessels, which occurs following rupture of an aneurysm and subarachnoid hemorrhage, may be attributable not only to the mechanical factor of the rupture of the aneurysm, but also possibly to the direct effect of serotonin, a vasoconstrictor substance in blood. They have shown in cats that prolonged localized spasm of branches of the middle cerebral arteries occurred when serotonin was applied to the surface of the cortex. They also observed that small quantities of serum from clotted blood caused vasospasm comparable to that produced by serotonin. However, they were unable to produce spasm by applying fresh blood to the same vessels.

In the present investigation it has been found that fresh blood has a marked vasoconstrictor effect when applied directly to the basilar and vertebral arteries in the subarachnoid space of monkeys. It is, therefore, with this effect of fresh blood that the study is primarily concerned. However, preliminary observations have been made on the differential effect of serotonin and blood serum when applied in a similar manner to the same vessels.

**Method**

In 25 monkeys anesthetized with Nembutal intraperitoneally, the basilar and vertebral arteries were widely exposed through a craniectomy in the base of the skull. With the animals supine in a special head holder, an incision was made in the midline of the neck from the ramus of the mandible to the sternum. A tracheotomy was performed and a glass endotracheal tube was inserted. The anterior muscles of the neck as well as the trachea and esophagus were divided transversely and reflected upward, care being taken to avoid the major vessels on each side of the neck. The mandible was divided by a Gigli saw passed beneath the ramus of the mandible to the sternum. A tracheotomy was performed and a glass endotracheal tube was inserted. The anterior muscles of the neck as well as the trachea and esophagus were divided transversely and reflected upward, care being taken to avoid the major vessels on each side of the neck. The mandible was divided by a Gigli saw passed beneath the ramus of the mandible at its midpoint. The two halves of the mandible were retraced laterally with an automatic retractor. The muscle attachments to the inferior border of the mandible on the left side were divided and the tongue, larynx, esophagus, trachea and other structures retracted to the right side. The two halves of the mandible articulating at the temporomandibular joints could now be separated widely with the automatic retractor and an excellent exposure obtained of the base of the skull, anterior rim of the foramen magnum, and upper cervical vertebrae. A perforator opening was made in the base of the skull, and with rongeurs and a special, small (Spurling-Kerisohn) rongeur, a wide craniectomy was carried out to

![Fig. 1. Monkey No. 308. Spasm of the basilar artery 3 minutes after mechanical stimulation at + with the tip of a small blunt glass rod.](image-url)
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expose the dura mater overlying the basilar and vertebral arteries. With the use of dissecting glasses, the dura mater was opened to expose the vertebral and basilar arteries as shown in the photomicrographs. The animal was then placed so that an American Optical dissecting microscope could be mounted over the exposed arteries.

At this point a number of different procedures were carried out as outlined below. Photographs were taken of the vessels before and after wide opening of the arachnoid and before and after the vessels were stimulated mechanically, electrically, or with fresh blood, serum, or serotonin.

Results

Effect of Mechanical Stimulation of Basilar and Vertebral Arteries. In 25 monkeys local stimulation of the basilar or vertebral artery with a small blunt glass rod, or by means of traction exerted by a small metal suction tube, resulted in marked vasoconstriction (Fig. 1). The contraction was usually restricted to the area stimulated and never propagated for long distances as described by Chase in mesenteric vessels. However, contraction did occur for a short distance on either side of the area in contact with the stimulus. It was felt that this was because the maximum stimulation had been applied at the site of contact of the stimulus but that the vessel was stretched (and hence stimulated) over a wider area. The findings were essentially the same as reported following stimulation of the basilar artery in the cat but the constrictions were not quite so marked as in the latter animals. The duration of the local vasospasms in the monkey was usually about 3 to 10 minutes but sometimes lasted much longer.

In 3 monkeys a Schwartz clip was applied to the basilar artery for 5 minutes. On removing the clip a local, rather marked, dilatation of the vessel occurred (Fig. 2), rather than a constriction as had been expected.

Electrical Stimulation of Pial Vessels. Utilizing bipolar electrodes and a Grass stimulator with a frequency of 30 per/sec., 5 msec. duration, and a voltage of 5 to 10 v., the basilar or vertebral arteries were stimulated for 5 seconds. This type of stimulation, as in cats, caused a marked localized vasospasm of the vessel of 30 to 70 per cent of the prestimulation diameter, which lasted 5 minutes to 3 hours and sometimes longer (Fig. 3).

Vasospasm of Vertebral and Basilar Arteries When Irrigated With Arterial Blood. In 16 monkeys the arachnoid to either side of the basilar artery and between the vertebral arteries was opened widely with sharp-pointed scissors and the aid of dissecting glasses. Care was taken to avoid traction on the large vessels and no attempt was made to strip all the layers of arachnoid from surrounding the immediate wall of the basilar or vertebral arteries. Photographs were taken of the entire exposed field at this point. If vasospasm was present to any marked degree, time was usually allowed for the vessels to return to approximately their normal diameter. About 10 to 20 drops

Fig. 2. Monkey No. 283. (Left) Normal basilar and vertebral arteries. (Right) Two minutes after a silver clip had been placed on the basilar artery at + for 5 minutes. There is dilation at +.
of the animal’s fresh arterial blood were now allowed to flow directly onto the exposed arteries (from a syringe) or by cutting a branch of the neighboring external carotid artery. The hemorrhage was then stopped by applying a silver clip to the cut carotid vessel. The blood was allowed to remain in contact with the basilar and vertebral vessels for 180 to 5 minutes. It was then removed very gently by means of suction or with cottonoid pledgets. Great care was taken to avoid any mechanical stimulation of the exposed vessels.

Arterial blood applied in the manner described directly (subarachnoid) to the vertebral and basilar arteries and their branches consistently caused almost immediate, widespread, marked vasoconstriction of all exposed arterial vessels (Fig. 4). The larger arteries constricted 30 to 60 percent of their previous diameter. Blood flow in some branches of the basilar artery often became so sluggish that the individual blood corpuscles could be seen coursing slowly through them. Marked vasospasm usually lasted about 5 to 10 minutes but sometimes much longer. The vessels did not become refractory to this form of stimulation for they could be made to constrict on many occasions if the above experiment was repeated at 20-minute intervals. In the same and other monkeys, when fresh blood was irrigated onto the basilar and vertebral arteries before opening the arachnoid no vasospasm occurred.

In 3 monkeys, when vasoconstriction of the basilar and vertebral arteries and their branches occurred following their irrigation with fresh blood, respiration ceased within a few minutes and artificial respiration was required. One of the animals never recovered spontaneous respiration. In 1 monkey the arachnoid was stripped away from the wall of the arteries. Several layers of arachnoid were present and probably fused with the adventitia. Following this treatment the vessels in this animal failed to constrict when stimulated with fresh blood.

Vasospasm of the Large Pial Vessels of the Circle of Willis (Basilar and Vertebral) Following Subarachnoid Hemorrhage Produced by Direct Rupture of a Small Vessel. In 5 monkeys the dura mater was opened carefully over the pons and medulla to avoid rupture of the arachnoid as much as possible. In some animals tiny tears in the arachnoid were unavoidable. Time was now allowed for any spasms produced by the dissection to subside and photographs were taken. With a fine straight needle a subarachnoid, and to some degree a subpial, hemorrhage was produced by rupturing a small vessel in the subarachnoid space of the basal cisterns. In some animals a vessel between the two vertebral arteries was chosen and in others a small branch of the vertebral artery. In the same animal, 1 or more vessels were ruptured in stages. In this manner it was possible to observe the effect of a localized hemorrhage between the vertebral arteries on these vessels, or the effect of a localized hemorrhage on one portion of the basilar artery, or finally, a generalized subarachnoid hemorrhage on all the exposed vessels.

When the subarachnoid blood came in contact with the larger arteries, marked vasospasm (30 to 60 percent of their prehemorrhage diameter) developed almost
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immediately and lasted 10 to 40 minutes but sometimes longer (Fig. 5).

When the subarachnoid hemorrhage remained localized between the vertebral arteries, only these vessels became constricted. In other animals the blood came into contact with only a portion of the basilar artery and this portion of the vessel then went into spasm. In all animals when generalized subarachnoid hemorrhage took place, there was a widespread, marked vasoconstriction of the arteries.

**Vasoconstriction of Basilar and Vertebral Arteries Following Subarachnoid Hemorrhage as a Result of a Blow to the Head.** In 3 animals the vessels of the base of the brain were exposed in the usual fashion. The dura mater was incised with little if any opening in the arachnoid membrane. Photographs were taken. The animals were then suspended by the feet and concussive blows of varying severity delivered with a wooden mallet to the occiput or frontal region of the freely moveable head. In those instances in which concussion occurred without subarachnoid hemorrhage there was usually no observable change in the diameter of the basilar or vertebral arteries. However, on many occasions some spasm of the basilar or vertebral arteries, at times quite localized, was found (Fig. 6). It is believed that this spasm was probably the result of the trauma. However,
the possibility that the spasm may have been the result of mechanical stimulation on removing blood and fluid from the external surface of the arachnoid at the operative site cannot be ruled out entirely.

In all 3 animals, bleeding eventually occurred in the subarachnoid space around the basilar and vertebral arteries as the result of a severe blow to the head. In each animal there was marked and prolonged (20 minutes to 1 hour) associated spasm throughout the entire exposed part of the basilar and vertebral arteries. This vasospasm was so marked (30 to 60 per cent of the preconcussion diameter of the vessel) that no doubt remained regarding its origin. It was the result of the subarachnoid hemorrhage (Fig. 7).

Localized Vasospasm Following the Irrigation of 1 to 3 Drops of Fresh Arterial Blood onto the Basilar of Vertebral Arteries. In the experiments in which the basilar and vertebral arteries were irrigated with a considerable quantity (10 to 20, or more, drops) of fresh blood, mechanical methods had to be used to remove the blood before photography could be carried out. The question might be raised as to the possible role of mechanical stimulation as a factor in the production of the vasospasm in some instances. To eliminate this possibility the following experiments were undertaken.

In 12 monkeys the basilar and vertebral arteries were exposed in the usual manner and the arachnoid was opened, as described. The vessels were allowed to dilate if any constriction was present. Blood was now withdrawn at intervals from the brachial artery and immediately irrigated onto the exposed vessels. For irrigation a tuberculin

Fig. 6. Monkey No. 286. (Left) Normal basilar and vertebral arteries. (Right) After a blow to the head. Note that some spasm of the vertebral artery is present at the arrow.

Fig. 7. Monkey No. 276. (Left) Normal basilar and vertebral arteries. (Right) Three minutes after subarachnoid hemorrhage was produced by a blow to the animal's head. The basilar and vertebral arteries are markedly constricted.
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Fig. 8. Monkey No. 318. (Left) Normal basilar and vertebral arteries after opening the arachnoid. (Center) 1½ minutes after 2 drops of fresh arterial blood were applied to the vessels at +. Note the spasm at +. (Right) 1½ minutes after 5 drops of fresh blood were irrigated on the vessels. The entire basilar and vertebral arteries are constricted.

A syringe with 25-gauge needle was used. One to 3 drops of blood were dropped gently from a distance of 1 mm. onto a localized portion of the vessels. The vessels were not touched or otherwise stimulated. The experiment was carried out innumerable times at 10- to 20-minute intervals in each animal and the result observed and photographed through the binocular microscope.

If the blood was dropped between the two vertebral arteries so that it contacted only these vessels, then there was almost immediate constriction of these arteries (20 to 50 per cent of their diameter). When the blood was dropped onto a localized portion of the basilar artery, this vessel went into localized spasm where the blood had stimulated it (Fig. 8). If the blood flowed along the sides of the vessel, then the constriction was more widespread, being most marked where the greatest quantity of blood contacted the artery. If now the vessel was irrigated with 5 to 10 drops of blood the entire length of vessel in contact with the blood showed marked vasospasm (Fig. 9).

Focal Vasospasm Following Application of Blood on a Tiny Pledget to the Wall of a Vessel. In the experiments on the 12 monkeys described in the preceding paragraph it was found difficult to apply fresh fluid blood to a vessel and have it remain entirely localized so that it stimulated only a very restricted portion of the vessel. A cottonoid pledget, about 1 mm. square, was therefore soaked in fresh arterial blood and gently applied to the vessel wall for 1½ to 1½ minutes. Blood applied in this manner caused almost immediately a focal spasm of the vessel wall (20 to 50 per cent of the pre-stimulation diameter, Fig. 10), which lasted about 5 to 10 minutes and sometimes longer.

Comparative Vasospasm Following Irrigation or Application of Serotonin, Serum, or Blood onto the Basilar and Vertebral Arteries. In 5 animals the comparative effects of 4 potential vasoconstrictors were observed: serotonin, 1:1000 unbuffered; serotonin buffered to a pH of 7.3; blood serum; or fresh arterial blood. After opening the arachnoid in the usual fashion each solution was alternately applied to the basilar or vertebral arteries at 10- to 20-minute intervals. A strip of gauze was applied to the upper end of the operative exposure so that any large collection of fluid overlying the exposed vessels would be absorbed into the gauze. In this manner it was possible to carry out repeated irrigation of the vessels with different
solutions without touching the operative field. When serotonin, 1:1000 unbuffered, or buffered to a pH of 7.3 solution in normal saline or distilled water, or blood serum (refrigerated for 24 to 48 hours) was applied by irrigation (10 to 15 drops), or on a piece of cottonoid, a constriction of the wall of the vessel occurred in many instances (about 25 per cent) in each animal. However, the vessel did not constrict more than 20 per cent and in the great majority of instances not more than 5 to 10 per cent of its normal diameter. Constriction occurred more often when unbuffered serotonin in distilled water was used, but the results were quite variable in the different animals. In each of these same animals fresh arterial blood was applied to the wall of the vessel by irrigation, dropping, or pledget, and vasoconstriction took place which was consistently greater (30 to 50 per cent of the normal diameter of the vessels) than that observed with serotonin or blood serum.

**Discussion**

It seems well established that very little contraction of cerebral vessels takes place as a result of neural mechanisms. On the other hand it is now clear that spasm of pial vessels over the cerebral convexities in cats, and of the large pial vessels at the base of the brain in cats, dogs, and monkeys does occur after local mechanical stimulation. In humans, spasms of the large pial vessels of the circle of Willis have been observed with local stimulation and also following rupture of an aneurysm and subarachnoid hemorrhage. Raynor et al. have shown that the branches of the middle cerebral artery in the cat, like certain arteries in the periphery, contract when irrigated with serotonin or blood serum.

Finally it has been found in the present study that marked spasm of the basilar and vertebral arteries in monkeys takes place when these arteries are bathed in fresh arterial blood. The arterial spasm was generalized if 10 to 20 drops of fresh blood was irrigated onto the vessels after opening of the arachnoid, or if subarachnoid hemorrhage was produced by a blow to the animal's head, or by puncturing with a needle a small artery in the subarachnoid space. The vasospasm was localized if the blood was applied to a restricted area of the artery either by local irrigation of 2 drops of blood or by applying a 1-mm. square cottonoid pledget soaked in blood to the wall of the vessel. No vasospasm of the basilar or
vertebral arteries took place if blood was irrigated onto the surface of the arachnoid covering the vessels without opening the arachnoid. The hemorrhage must be subarachnoid. Perhaps this is why Raynor et al. failed to produce vasospasm of branches of the middle cerebral artery in cats when blood was applied to these vessels. In their experiments fresh blood was irrigated onto the surface of the cortex but no mention was made of opening the arachnoid.

In the present experiments when serotonin
1:1000 or blood serum was irrigated directly over the vertebral and basilar arteries, after opening the arachnoid, vasospasm frequently occurred. The findings, however, were variable and the vasospastic responses were less marked than when fresh blood was applied in a similar manner to the same vessels.

From the findings in this investigation it seems justified to conclude that fresh blood contains vasoconstrictor properties or substances which are capable of causing marked spasm of the basilar and vertebral arteries in monkeys. How great a role serotonin plays in this vasoconstriction is not yet clear and requires further study.

Direct proof that the large pial arterial vessels (basilar and vertebral) at the base of the brain in monkeys consistently go into severe, prolonged, spasm when bathed in subarachnoid blood requires a further re-evaluation of our thinking in relation to subarachnoid hemorrhage, as already emphasized by Pool and others, whether from a ruptured aneurysm, trauma, or other causes. Certainly in trauma to the head new conceptions regarding the effect of subarachnoid hemorrhage will be necessary; for such subarachnoid hemorrhage and the vasospasm that it may precipitate could, in part at least, be responsible for the prolonged coma and death, as well as certain other neurologic manifestations, that so often follow trauma to the head. These probabilities indicate the necessity for a continued search for: 1) the factors in fresh blood responsible for vasospasm, and 2) a means of rendering intracranial vessels less susceptible to the vasoconstrictor effect of subarachnoid blood.

Summary

1. Marked constriction of the basilar and vertebral arteries in monkeys occurs if these vessels are bathed in fresh subarachnoid arterial blood. No vasospasm takes place unless the blood is in the subarachnoid space.

2. The vasospasm may be generalized or local depending upon whether a localized or widespread area of the vessel is in contact with the blood.

3. In preliminary studies serotonin 1:1000 solution and blood serum frequently caused some vasoconstriction when applied to the large arteries at the base of the brain. The degree of spasm, however, was much less marked and less consistently present than when blood was applied in a similar manner to the same vessels. Further investigation with serotonin and blood serum will be required.

4. Local mechanical or electrical stimulation of the basilar or vertebral arteries resulted in marked vasoconstriction.

5. The proof that the basilar and vertebral arteries of monkeys go into marked spasm when bathed in fresh blood requires a further re-evaluation of our thinking in relation to the clinical role of subarachnoid hemorrhage in aneurysm, head trauma, and other conditions.

The author wishes to acknowledge the technical assistance of Lewis Brown and Caryl Schmer.

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