Experimental Subarachnoid Hemorrhage from a Middle Cerebral Artery

Neurologic Deficits, Intracranial Pressures, Blood Pressures, and Pulse Rates

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SUMMARY Devices to produce experimental subarachnoid hemorrhage (SAH) can be implanted in animals. After SAH is produced by the puncture of a middle cerebral artery (MCA) in awake cats, neurologic deficits develop that are not as severe as those caused by MCA occlusion. Biphasic increases of epidural pressure occur and are related to the extent and distribution of the hemorrhage. Ischemic changes are more severe if the flow of blood through the MCA is interrupted.

MANY EXPERIMENTAL models of subarachnoid hemorrhage (SAH) have been developed since Bagley first described the subarachnoid injection of blood in animals. Generally, one of two models have been used: a) injection or topical application of blood or blood products in the cerebrospinal fluid (CSF) spaces, and b) rupture or puncture of an intracranial artery. The injection of blood into the CSF is unlike the clinical situation caused by the rupture of an intracranial aneurysm in humans. Previous models of experimental intracranial arterial hemorrhage also have been unlike the clinical situation, in that the models have required anesthesia and craniectomies for production of the hemorrhage so that changes of intracranial pressure (ICP) necessarily have been modified.

For the present study, experimental SAH was produced in cats with intact skulls using modifications of a device previously developed for occlusion of a middle cerebral artery (MCA) implanted transorbitally several days before the hemorrhage. The neurologic deficits and pathologic findings observed after SAH were related to changes of epidural pressure (EDP), mean arterial blood pressure (MABP), and pulse rate (PR).

Methods

Experimental Models of SAH

Implantation of Devices for Producing SAH

Unselected adult cats of either sex, weighing 2.5 to 5 kg, were anesthetized with phencyclidine hydrochloride, 1 mg/kg injected intramuscularly, and sodium pentobarbital, 20 mg/kg injected intraperitoneally. The contents of the left orbit were removed, the optic foramen was enlarged, and with an operation microscope the proximal part of the left MCA was visualized.

Three types of implanted devices were developed for the experimental production of SAH:

1. Puncture device. To produce puncture of the MCA intracranially, a needle was introduced through a Teflon tube fixed to the artery and extending through the orbit. The tube was fixed to the artery in the following manner: two knots were placed approximately 2.5 mm apart in a 7-0 silk suture previously treated with silicone. The suture was placed around the proximal part of the exposed MCA with the artery between the two knots. The ends of the suture were passed into an 18 gauge Teflon tube 45 mm long through two small holes approximately 0.5 mm from the end of the tube (fig. 1A), which was cut concavely to fit against the MCA. The tube then was fixed to the orbit in the following manner: two knots were placed approximately 2.5 mm apart in a 7-0 silk suture previously treated with silicone. The suture was fixed by a knot just outside the exit hole, which was sealed with Silastic adhesive. The opening in the dura and the enlarged optic foramen were closed with Silastic sheeting and sealed with oxidized cellulose and Eastman 910 contact adhesive.

2. Tearing device. In a modification of the device just described, the suture placed around the MCA was not knotted. It was passed through the intracranial end of the tube (fig. 1B), and, at the extracranial end of the tube, the exit hole for the suture was sealed and the device implanted as described. After implantation of the device the empty orbit was filled with epoxy cement and the skin was closed
3. Withdrawal puncture device. Another modification of the puncture device consisted of placing a sharp needle approximately 0.1 mm in diameter perpendicularly into the MCA through the arachnoid. A suture was attached to the needle and passed through the Teflon tube (fig. 1C).

Puncture devices were implanted in more than 20 cats, tearing devices in more than 5, and withdrawal devices in more than 16.

Following implantation of a device the cats were allowed to recover from the anesthetic and surgical procedures and food and water were made available. Each cat was examined at regular intervals to be certain that there was no evidence of a neurologic deficit, leak of CSF, or intracranial infection caused by implantation procedures. Five to seven days later experimental SAH was produced. With the puncture device the needle was moved forward until restricted, then withdrawn several millimeters. With the tearing device the suture was pulled tightly until the MCA was ruptured. With the withdrawal device the needle penetrating the MCA was withdrawn. The needles and sutures were left in the tubes to prevent leakage.

For observations of neurologic status after SAH, three cats had puncture devices implanted and withdrawal devices were placed in three other cats. Five to seven days after implantation SAH was produced without sedation or anesthesia. Three to seven days after SAH each cat was killed with sodium pentobarbital, the left carotid artery was exposed, and 0.5 ml of India ink was injected with moderate hand pressure. The brain was removed and inspected; after fixation coronal sections were made at the levels of the tips of the temporal lobes, the optic chiasm and the posterior mammillary bodies.

For observations of epidural pressure, mean arterial blood pressure and pulse rate following SAH, puncture devices were implanted in 15 cats and tearing devices in five. At the same time, a shallow stainless steel cylinder with a thin Silastic membrane was implanted in a burr hole in each parietal region for measurement of EDP. Five to seven days later each cat was sedated with phencyclidine, procaine hydrochloride, 2%, was injected into the skin over a femoral artery, and a short incision was made through the anesthetized area. A polyethylene catheter was passed into the abdominal aorta for measurement of MABP and PR.

The volume of water required to produce a recorded value of 5 mm Hg for EDP on a polygraph was injected into each stainless steel cylinder from a microliter syringe attached to a sidearm. For each subsequent measurement of EDP the device was evacuated and the same volume of water was injected. Although EDP values were recorded as absolute mm Hg the devices thus were standardized to an original value of 5 mm Hg, which is close to the usual EDP of cats.

SAH was produced in 14 of the 15 cats by puncture and in five cats by tearing; one cat with a puncture device served as a sham-operated control. Measurements of EDP, MABP and PR were made at intervals for up to 48 hours after SAH. Respiration was not assisted, additional amounts of phencyclidine were injected as necessary for sedation. After 48 hours of observation the animals that survived were killed with potassium chloride. In all cats India ink was injected into the left carotid artery, the brain was removed and examined, and histologic sections were made.

Results

Production of SAH

With the puncture devices the first advance of the needle nearly always produced SAH detectable by changes of behavior or increases of EDP. Following puncture or tearing
a small amount of blood occasionally extruded through the extracranial side-hole of the tube for a few seconds to a few minutes. The extent and distribution of blood varied considerably after SAH. In most cats the hemorrhage was chiefly on the left side, particularly at the base of the temporal lobe, in the proximal portion of the Sylvian fissure, around the optic chiasm and pituitary gland, in the interpeduncular cistern, and along the ventral surface of the brain stem. At times hemorrhage was restricted to a small area around the left MCA. Rarely, blood covered the entire surface of the brain, filled the incisura and the cisterna magna, and/or extended to the right side. No leakage of blood from the cranium through the dura to the orbit was found. Cerebral ischemia and infarction were detected in approximately one-third of the cats with SAH.

Neurologic Deficits after SAH

There were no dramatic events, such as collapse or seizure activity, at the time of production of SAH in six cats. However, the behavior of the cats changed: they would not walk spontaneously, but remained sitting with slight drooping of the head and partial closure of the eyes. Five of the six cats arose several seconds to several minutes later, and began to walk slowly, only to stop and sit again after a few steps. The walking-stopping behavior continued for three to ten minutes. This restless behavior had the appearance of being induced by some uncomfortable or distressing event.

In four of the six cats postural disturbances (deviations of the head and neck) and circling movements began three to ten minutes after SAH. The direction was toward the side of the affected MCA in two cats and toward the opposite side in one; in the other cat the direction varied. Deviations and circling generally disappeared from ten minutes to one hour after SAH.

In three of the four cats with early circling, limb weakness in the opposite side from the affected MCA became evident, particularly in the forelimb. Weakness was not as great as that usually caused by MCA occlusion and persisted for only ten to thirty minutes, except for one cat in which weakness persisted for seven days. In all cats deficits of stepping and placing responses were absent or minimal.

Twenty minutes to two hours after SAH active movement gradually subsided, and the appearance of the cats was one of lethargy and distress.

At autopsy obvious SAH was present in all six cats, but the left MCA and its branches were well filled with India ink indicating a continuing flow of blood in the damaged arteries. Ischemic changes were found in two brains; in both there were changes in the deep structures of the left cerebral hemispheres, and in one (the cat with the persistent neurologic deficit) there were changes in the parietal cortex.

Changes of EDP, MABP and PR after SAH

In all 19 cats with SAH, EDP increased bilaterally within 10 to 30 seconds. In twelve, including the five in which the MCA was torn, EDP increased to a peak of greater than 50 mm Hg within 18 to 100 seconds (fig. 3). EDP then decreased but never to values lower than the standard of 5 mm Hg (figs. 4, 5).

A later increase of EDP occurred in 16 cats. In six, including four of the five with a torn MCA, increases began from 30 minutes to 4 hours after SAH, continued for three to eight additional hours, and exceeded 30 mm Hg (fig. 4). Three cats died during the increases of EDP. In ten cats increases of EDP occurred 30 minutes to 12 hours after SAH but did not exceed 30 mm Hg (fig. 5).

Side-to-side gradients of EDP greater than 5 mm Hg were noted in four cats during the initial increases of EDP immediately after SAH. In three of these the EDP was greater on the left side. Only one cat had a side-to-side difference during later increases of EDP.

Changes of MABP of greater than 10% were observed during the initial increases of EDP in 16 of 18 cats. In nine cats MABP increased (fig. 4); in six MABP decreased; and in one there was a decrease after a transient increase (fig. 5).
Decreases of PR occurred in 13 of the 19 cats; no increases were observed.

In three of five cats with later increases of EDP greater than 30 mm Hg, MABP decreased in two (fig. 4) and increased in one. In the other 13 cats fluctuations of MABP and PR occurred. No consistent changes of EDP, MABP or PR were recorded in the cat with the sham operation.

In all five cats in which the MCA was torn there was extensive SAH. Moderate to large areas of ischemia and infarction were found in the distribution of the affected MCA.

Eight of the 14 cats in which the MCA was punctured had extensive SAH. Three of these had ischemic changes and one had a large infarct. In the other six SAH was restricted to the site of the punctured MCA; three had ischemia but in two the ischemic regions were confined to the basal ganglia (table 1). A small area of ischemic change was detected in only one of the three cats without late increases of EDP. Other relationships among SAH, EDP, and infarction are indicated in the table.

**Discussion**

**Production of SAH**

The implantable devices described in this paper were developed to model SAH occurring from the rupture of an aneurysm of the proximal part of the MCA. Each device has specific advantages and disadvantages. With the puncture device, there is no damage to the MCA before the production of SAH. Arachnoidal tissue is damaged, however, and there is some evidence that the arachnoidal bands at the base of the brain may influence vascular constriction after SAH.\(^{23,25}\) With the withdrawal device (previously described only with craniectomy)\(^{18}\) arachnoidal tissue is largely undisturbed, but penetration of the MCA with the needle possibly could damage the vessel and interfere with the flow of the arterial blood. However, injection of India ink in the present study showed that blood flow was maintained.

A biphasic occurrence of cerebral vasospasm, similar to the clinical course of vasospasm after SAH in humans, has been described only with experimental models in which SAH has been produced by injuring cerebral vessels.\(^{12,14,16}\) These animal models have required craniectomy with complicated surgical procedures; and the experimental results may have been influenced by cerebral damage, by an open cranium or by drainage of CSF at the time of production of SAH.

Previous studies of neurologic deficits developing after SAH have been restricted to observations made after recovery from anesthetic and surgical procedures.\(^{5,8,9,29}\) In one report describing acute neurologic deficits,\(^{15}\) the deficits were not caused by SAH alone but also by interruption of
the anterior cerebral artery. The major differences between neurologic deficits of SAH and MCA occlusion\(^\text{25}\) are in the signs of focal weakness, postural disturbances and circling.

With SAH, focal deficits appear later, are less severe and resolve more quickly than with MCA occlusion. Moreover, after SAH the deficits are not necessarily lateralized to the appropriate side. Deficits and ischemic changes after SAH may be related to decreases of regional CBF caused by early vasospasm.\(^\text{14, 16, 18, 26-28}\) Ischemic changes and infarction have been described in Rhesus monkeys in which vasospasm has been demonstrated angiographically.\(^\text{17}\)

### Changes of EDP, MABP and PR after SAH

There have been many reports of changes of ICP, blood pressure and PR after SAH.\(^\text{5, 8, 9, 10, 14, 16, 28}\) Increases of ICP after SAH are related to the extent and distribution of the hemorrhage. From studies of volume-pressure relationships and the mechanisms of compensation for increases in intracranial volume,\(^\text{21, 22}\) it appears that increases of ICP occurring immediately after SAH might be caused not only by extravasated blood\(^\text{24}\) but also by increases of intravascular cerebral blood volume\(^\text{4-18}\) resulting from vasomotor responses activated by the mechanical or chemical effects of blood in the subarachnoid space. Changes of MABP and PR observed during initial increases of EDP suggest that systemic vasomotor responses also occur.

Decreases of ICP after initial increases can be attributed to the arrest of active hemorrhage and to compensation for the increased intracranial volume.\(^\text{30, 32}\) Other studies of SAH have reported decreased values for CBF during a plateau period following the immediate changes.\(^\text{5, 16, 18, 27, 28}\) Later increases of ICP probably are the result of cerebral edema,\(^\text{7, 18, 29}\) perhaps caused by ischemia, and hypoxia, toxic effects of extravasated blood, disturbances of flow or absorption of CSF.\(^\text{1, 2, 4, 24}\)

Side-to-side gradients of EDP such as those that occur after MCA occlusion\(^\text{21, 22}\) were observed only infrequently, and early after SAH, pc haps because of distortion of the brain from the intracranial bleeding. Thus, cerebral edema after SAH may be generalized rather than focal. Increases of EDP after SAH were not accompanied by changes of MABP and PR similar to those observed with MCA occlusion,\(^\text{21}\) indicating that the vasomotor Cushing response may be dependent upon pressure differentials influencing tentorial herniation and brain stem ischemia.

SAH produced relatively lesser increases of EDP and smaller areas of ischemic change on histopathologic examination than MCA occlusion.\(^\text{25}\) However, tearing the MCA, which results both in SAH and in interruption of blood flow through the artery, produced greater increases of EDP and larger areas of ischemic change than did MCA occlusion alone. Perhaps cerebral vasospasm caused by SAH can prevent the development of increases of blood flow through collateral channels to the region of distribution of the interrupted MCA; alternatively, extravasated blood in the subarachnoid space may have a direct effect on underlying ischemic brain to produce an impairment of local CBF and cerebral edema.

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### References

Relationships Among Intracranial Pressure, Blood Pressure, and Superficial Cerebral Vasculature After Experimental Occlusion of One Middle Cerebral Artery

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SUMMARY A cranial window conforming to the contours of the underlying cerebral cortical surface was implanted successfully in 18 cats. Subsequently the left middle cerebral artery (MCA) was occluded inside the sealed cranium and changes in the superficial cerebral vasculature were related to measurements of intracranial pressure (ICP), measured extradurally, and to the resulting infarcts.

Vascular changes early after MCA occlusion were not predictive of the outcome of the occlusion, except for aggregation of formed elements of the blood in arterioles, which was a bad prognostic sign. Secondary reactive hyperemia was not beneficial; increases of ICP suggested that hyperemia led to increased cerebral edema as well as to swelling.

Each animal had an occluding device, a transparent window for observation of surface vessels, and a device for measurement of epidural pressure (EDP) implanted in an otherwise intact skull. The relationships among changes in the superficial cerebral vasculature, EDP, mean arterial blood pressure (MAP), pulse rate (PR), and blood gases were observed for up to five days after MCA occlusion.

Methods

Implantation of Devices for MCA Occlusion and EDP Measurement

Twenty-one unselected adult cats were used for the study. Each cat was anesthetized with phencyclidine hydrochloride, 1 mg per kg injected intramuscularly, and sodium pentobarbital, 20 mg per kg injected intraperitoneally. The techniques for implantation of the devices for occlusion of the left MCA and for measurement of EDP have been described in detail previously.18-20

In brief, the left MCA was exposed transorbitally and

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