Immediate Effects of Cerebral Ischemia: Evolution and Resolution of Neurological Deficits After Experimental Occlusion of One Middle Cerebral Artery in Conscious Cats

BY TORU HAYAKAWA, M.D., AND ARTHUR G. WALTZ, M.D.*

Abstract:
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Acute occlusion of the left middle cerebral artery (MCA) was accomplished without anesthesia and inside an intact cranium containing cerebrospinal fluid (CSF) in ten cats five to nine days after implantation of an occlusive device through the orbit. Immediate neurological deficits included forced ambulation, circling, and tonic deviation of the head and neck toward the side of the occluded artery; weakness of the opposite limbs; and an apathetic or akinetic state. Two cats died within 24 hours. The other eight cats improved, but secondary deficits developed in two, causing death. In two of the remaining six cats no deficits were apparent seven days later. The cerebral infarcts regularly involved the basal ganglia, internal capsule, and cortical regions, and were larger and less variable than those produced by MCA occlusion through an open optic foramen or craniectomy with cranial decompression by drainage of CSF. This model of acute focal cerebral ischemia may be of value for studies of physiological and biochemical factors uninfluenced by sedatives, anesthesia, or recent surgical procedures.

Additional Key Words
- cerebral infarction
- cerebral blood flow
- intracranial pressure
- cerebral edema

Methods

IMPLANTATION OF THE OCCLUSIVE DEVICE

Ten unselected adult cats were anesthetized with phencyclidine hydrochloride, 1 mg per kilogram injected intramuscularly, and sodium pentobarbital, 20 mg per kilogram injected intraperitoneally. The head of each cat was immobilized in a head holder, and the left MCA was exposed transorbitally. Modifications of the surgical procedure described previously included an approach through the palpebral fissure, with excision of the margins of the upper and lower eyelids and conjunctiva; dissection along the lateral aspect of the globe, without removal of the cornea or lens; and section of the muscular cone and optic nerve close to the optic foramen for removal of the contents of the orbit. Care was taken not to enter the nasopharynx during dissection; after exenteration of the orbit, the temporal muscle at the inferolateral aspect of the orbit remained intact.

With the aid of an operation microscope the MCA was freed from the enveloping arachnoidal tissue and a silicone-treated 6-0 silk suture was looped carefully around it approximately 2 mm from the bifurcation of the internal carotid artery, proximal to the point where the MCA gives rise to major branches and enters the Sylvian fissure (fig. 1A). The suture was manipulated into a loose single knot and the ends were put into an 18-gauge Teflon tube, 4.5 cm long, through two small opposing holes approximately 0.5 cm...
Photographs taken through operation microscope during implantation of occlusive device. (Emphasis added for clarity so A, B, and C.) A. Suture looped around left MCA. B. Single knot tied in suture; ends of suture put into tube. C. Tube apposed and single knot secured around MCA. D. Optic foramen sealed.

mm from the end of the tube (figs. 1B and 2). The ends of the sutures were pulled from the tube through a single small hole 5 mm from the opposite end (fig. 2). A Teflon stylet, supplied with the Teflon tube as a commercially available intravenous catheter, was inserted into the tube and adjusted by observation through the operation microscope until the end of the stylet was flush with the end of the tube; the stylet then was fixed to the tube at the opposite end with quick-setting epoxy cement (fig. 2). The stylet limited the flexibility of the tube and provided a solid base for apposition to the MCA, yet the suture could be moved inside the tube. The occluding device was positioned precisely, just touching the MCA, and fixed to the wall of the orbit with epoxy cement; then the ends of the suture exiting through the device were

Schematic drawing of implanted occlusive device.
pulled carefully, with observation through the operation microscope, until the single knot was secure but not tight around the MCA (fig. 1C). The openings in the dura and the enlarged optic foramen were closed with silastic sheeting and sealed with oxidized cellulose and Eastman 910 contact adhesive (fig. 1D). The empty orbit was filled with epoxy cement and the skin incision was closed around the occlusive device. The protruding ends of the suture were connected to heavier string, and the side hole of the occlusive device was sealed with silastic adhesive to prevent leakage of CSF around the stylet (fig. 2). The occlusive device, suture ends, and attached string were protected by a plastic cap secured to the skin with contact adhesive.

PRODUCTION OF CEREBRAL ISCHEMIA BY MCA OCCLUSION

After recovery from the anesthesia used for implantation of the occlusive device, each cat was examined carefully for the presence of a neurological deficit related to the implantation procedure. If neurological signs were present, the cat was excluded from the study. Five to nine days were allowed for complete recovery; then, without sedation or anesthesia, the string attached to the suture was gently pulled tight. Because of the single knot in the intracranial portion of the suture, no additional stabilization was necessary to prevent reopening of the MCA.

OBSERVATION OF NEUROLOGICAL DEFICITS

Each cat was observed for seven days after MCA occlusion, or until death. The general appearance and behavior were noted, but were difficult to quantitate. Forced postural and motor activity, such as tonic deviation of the head and neck and circling movements, was graded from 0 (absent) to 4 (severe and continuous). Placing and stepping responses were tested. Weakness of the limbs opposite the occluded artery was graded from 0 (absent) to 4 (no movement during stimulation), as were disturbances of consciousness (0: normal; 1: lethargy; 2: arousal with difficulty; 3: movement on stimulation; 4: no movement on stimulation).

EXAMINATION OF THE BRAIN

Seven days after MCA occlusion each cat that survived was anesthetized with sodium pentobarbital injected intraperitoneally and killed by the intravenous injection of a saturated solution of potassium chloride. In all cats, including those that died before the end of the observation period, the left common carotid artery was exposed as soon as possible after death and 0.5 ml of India ink was injected into the artery with moderate hand pressure. The brain was removed and inspected to confirm the presence of MCA occlusion (fig. 3), then fixed in 10% formalin. Coronal sections of the fixed brain were obtained from three levels: the tips of the temporal lobes, the optic chiasm, and the posterior mamillary bodies; the sections were stained with hematoxylin and eosin for pathological examination.

Results

DEVELOPMENT AND RESOLUTION OF NEUROLOGICAL DEFICITS

The neurological deficits produced by MCA occlusion in the ten cats varied in development and resolution (table 1). However, the immediate events were similar in all cats. There were no dramatic changes, such as
collapse or seizure activity, as the artery was occluded by tightening the suture. After a few seconds to one minute, circling movements toward the side of the occluded MCA began; forced ambulation frequently was rapid, more nearly running than walking. Deviation of the head and neck toward the side of occlusion was invariable; in some cats, curvature of the trunk also was noted.

During the circling movements, weakness of the limbs opposite the occluded MCA, particularly the forelimb, became evident, and stepping and placing responses became defective. Despite the weakness, forced ambulation continued; many cats would bump into objects or the wall of a room, as if they were incoordinated. Food responses became defective. Despite the weakness, forced ambulation continued; many cats would bump into objects or the wall of a room, as if they were indifferent to obstacles or affected by a visual disturbance. The duration of forced ambulation varied, but typically circling was most pronounced five to 15 minutes after MCA occlusion, after which it gradually subsided. Deviation of the head and neck, however, persisted. Weakness of the limbs opposite the occluded MCA increased during this time.

Five to 45 minutes after MCA occlusion, active movement ceased and the cats remained sitting in one place, usually in a corner of the room. Their appearance was one of drowsiness and akinesia. Food and threatening actions were ignored. No nystagmus or unusual movements of the right eye were observed, nor was facial weakness apparent.

Two cats (Nos. 1 and 2, table 1) recovered from the apathetic or akinetic state within three to four hours and improved rapidly, such that no neurological deficit could be detected seven days after MCA occlusion. Four cats (Nos. 3 to 6; table 1) did not develop additional neurological deficits, but weakness persisted until the end of the period of observation. Two cats (Nos. 7 and 8) improved somewhat after the initial forced motor activity and akinesia, walked about for a few hours, then worsened six to ten hours after occlusion. These cats became difficult to arouse and died two to three days later. The remaining two cats (Nos. 9 and 10) never recovered from the akinetic state but developed progressive impairment of consciousness and decerebrate rigidity and died within 24 hours of occlusion.

### EXTENT AND SEVERITY OF INFARCTS

The infarcts produced by MCA occlusion inside the sealed cranium were variable; however, in all cats portions of the left caudate nucleus, internal capsule, and motor cortex were infarcted (table 1). No infarct was found in the motor cortex (parietal region) of cats Nos. 1 or 2. Two infarcts were hemorrhagic; in cat No. 4, hemorrhagic changes were confined to the caudate nucleus, but in cat No. 6 hemorrhagic changes were distributed throughout the infarct. Cat No. 10 had a moderate amount of subarachnoid blood over the surface of the left temporal lobe. Incisural and foraminial herniation were noted in cats Nos. 8, 9, and 10, but were minimal in cat No. 8.

The size and severity of the infarcts generally were related to the severity of the neurological deficits. Disturbances of consciousness were related in general to the total size of the infarct. However, there were no consistent relationships between infarction of specific regions of the brain and the maximal neurological deficits observed within 24 hours of MCA occlusion. For example, the degree of forced postural and motor activity was not consistently related to the extent of infarction of the caudate nucleus. Persistent motor disturbances, observed several days after occlusion, were related to the extent of infarction of the cortex.

### MISCELLANEOUS RESULTS

All cats tolerated the implantation procedure well and appeared healthy between the time of implantation and the time of MCA occlusion, except for cat No. 5 which was somewhat inactive because of a respiratory infection. There was no evidence of leakage of CSF.

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**TABLE 1**

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Cats are listed in order of increasing sizes of infarcts. F = forced postural and motor activity; W = focal weakness; C = disturbance of consciousness. CN = caudate nucleus; IC = internal capsule; PC = parietal cortex; TC = temporal cortex.
after implantation of the occlusive devices, and no evidence of meningitis, intracranial infection, or mechanical damage to the brain. Arachnoidal adhesions and minimal inflammatory changes were noted near the site of MCA occlusion.

Discussion

THE EXPERIMENTAL MODEL

Many experimental models for producing focal cerebral ischemia and infarction in animals have been developed, including ligation of extracranial arteries, occlusion of intracranial vessels, and intravascular injection and embolization. Each of the methods has specific disadvantages. In particular, anesthesia, an open cranium, or drainage of CSF during or just preceding the onset of focal cerebral ischemia may prevent or influence the results of clinical observations and pathophysiological and chemical determinations. With the model described here, after implantation of the device for occluding the MCA, focal cerebral ischemia and infarction can be produced easily and reliably at any time in a waking animal with an intact cranium containing CSF under pressure, without any additional anesthesia or surgical procedures.

In contrast to earlier studies in which the MCA was occluded while the cranium was open and decompressed by drainage of CSF, in the present study the cerebral cortex as well as the basal ganglia and internal capsule of the affected hemispheres was infarcted regularly. Although the extent of the infarct varied, the variability was much less than with the earlier methods for approaching and occluding the MCA. Nonetheless, the infarct was not uniform; use of this model for studies of the modification or treatment of acute focal cerebral ischemia will still require statistical analysis of results from numbers of animals. The experimental production of a cerebral infarct in animals cannot duplicate the clinical situation of a stroke in humans, but the model described here has several advantages and appears to be superior to those used previously.

The technique for implantation of the occlusive device is not difficult, and the device itself is inexpensive and easy to make. However, meticulous care must be taken to assure that the solid end of the tube carrying the suture is correctly apposed to the MCA so that the artery is not stretched or torn during occlusion; the device must be stabilized in position during the sealing of the optic foramen and orbit. Despite care, a small amount of intracranial bleeding occasionally may occur (as in cat No. 10), presumably because of displacement of the MCA and tearing of tissue or small branches during occlusion. The likelihood of this complication can be decreased by freeing the MCA from the arachnoid and mobilizing it away from the brain.

The single knot around the MCA causes the artery to be squeezed through its diameter during occlusion rather than compressed against the end of the tube carrying the suture, decreasing the likelihood of damage to the artery and hemorrhage. In addition, occlusion is maintained without the need for additional knotting, tying, or otherwise manipulating the ends of the suture or attached string.

RELATIONSHIPS BETWEEN NEUROLOGICAL DEFICITS AND PATHOLOGICAL FINDINGS

Previous reports of neurological deficits in animals with focal cerebral ischemia and infarction have been based on observations made after recovery of the animals from anesthesia and surgical procedures. The present report is the first to describe the development and resolution of neurological deficits from immediately after the onset of acute ischemia produced by MCA occlusion.

The most striking neurological signs that developed in the cats were forced postural and motor activity, particularly forced circling movements. Tonic deviation of the head and neck and similar postural disturbances also have been observed in animals with experimentally induced lesions in the caudate nucleus, regularly found to be infarcted in the present study.

Paresis of the opposite limbs was observed in each of the cats shortly after MCA occlusion. Infarcts were found in the internal capsules of all cats, but in all but the two cats that survived without a motor deficit some part of the motor cortex was infarcted as well. Thus, persistent weakness may be related to involvement of the cortex or immediately underlying white matter rather than to involvement of the internal capsule.

The severity of the early neurological deficits was not consistently related to the severity of persistent deficits: the final outcome of MCA occlusion could not be predicted from observation of the maximal deficits within the first 24 hours. Forced postural and motor activity and early weakness, therefore, might have been due to partially or completely reversible impairment of neurological function produced by ischemia, which was alleviated in part or in whole by reperfusion of ischemic regions through collateral channels. Support for this interpretation of the evolution of the neurological deficits is provided by the pathological studies, which showed that cortical regions were relatively less affected than the basal ganglia and the internal capsule. The cerebral cortex has greater potential for reperfusion after MCA occlusion, through collateral channels over the surface of the brain. Reperfusion of cerebral tissue can be accomplished despite prolonged periods of ischemia, the so-called "no-reflow phenomenon" does not appear to be an important factor in acute focal cerebral ischemia. If lessening of acute ischemic neurological deficits is due to reperfusion, it is possible that assisting reperfusion after ischemia by surgical or other therapeutic means might result in
earlier or more complete improvement of the neurological status. The times at which therapeutic intervention after acute ischemia might be effective have not yet been determined.

The neurological deficits observed in the present study suggest that two kinds of disturbance of consciousness may occur after MCA occlusion in cats. The first is the early, transient apathetic or akinetic state that develops as forced postural and motor activity decreases; the second is the progressive, persistent lethargy, stupor, and unresponsiveness that develop several hours to days later in association with large infarcts. The second type of disturbance of consciousness may be related to impairment of the function of the reticular activating system and other structures in the brain stem caused by ischemic cerebral edema, increases of intracranial pressure (ICP), and herniation.1, 7, 12, 29, 50

The mechanisms underlying the development of the first type of disturbance of consciousness are not known, but may be related to decreases of cerebral function and somatic activity causing secondary decreases of the activity of the reticular activating system. Increases of ICP cannot cause the early apathetic or akinetic state because ICP does not increase so quickly after MCA occlusion (unpublished data). Disturbances of consciousness frequently are observed in humans with acute ischemic cerebral infarcts, but the pathogenesis of such disturbances has received little comment. It has been hypothesized1,7 that coma following ischemic cerebral infarction may be related to massive damage to cortical structures, directly or indirectly, with "diaschisis" or "neural shock" disrupting the function of deeper structures; or to simultaneous ischemia of subcortical structures, particularly the midbrain, because of insufficient perfusion through the posterior communicating and posterior cerebral arteries.

In summary, the development and resolution of neurological deficits in cats after MCA occlusion occur in four stages: 1. Immediately after occlusion, forced postural and motor activity and weakness of the limbs opposite the occluded artery develop, presumably because of impaired neuronal function related to acute ischemia. The severity and persistence of these deficits may depend upon the effectiveness of reperfusion through collateral channels, and thus upon the variability of the anatomical patterns and intravascular pressure relationships of the cerebral vasculature. 2. A transient apathetic or akinetic state develops that may be related to generalized decreases of neuronal activity or to focal neuronal dysfunction. 3. Extension of ischemia and infarction, caused by cerebral edema and increases of ICP, may result in secondary impairment of consciousness and worsening of neurological deficits. 4. Herniation of cerebral structures may produce severe and irreversible impairment of brain stem functions and death. Perhaps surgical or other therapeutic measures designed to assist reperfusion in the early stages, before edema develops, may aid in the alleviation of early deficits and prevent the occurrence of secondary neuronal dysfunction.

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Useful and valuable suggestions and advice, as well as technical assistance, were provided by Margaret M. Jordan and Terry Hansen.

References

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